I) SYNTHESIS OF SMALL MOLECULES AS POTENTIAL ANTIBIOTIC AND ANTICANCER CANDIDATES

II) SYNTHESIS OF BIOACTIVE HETEROCYCLIC SCAFFOLDS

By

KEVIN MERAZ

Bachelor of Science in Chemistry
Our Lady of the Lake University
San Antonio, Texas, 2015

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
May, 2019

SYNTHESIS OF SMALL MOLECULES AS POTENTIAL ANTIBIOTIC AND ANTICANCER CANDIDATES

SYNTHESIS OF BIOACTIVE HETEROCYCLIC SCAFFOLDS

Dissertation Approved:

Dr. Richard A. Bunce

Dissertation Advisor

Dr. Kenneth D. Berlin

Dr. Jeanne Bolliger

Dr. Krishnan Gopan

Dr. Andrew Mort

ACKNOWLEDGEMENTS

First and foremost, I would like to thank God for allowing me to reach this milestone. I also want to thank Dr. Richard A. Bunce for his guidance throughout my tenure at Oklahoma State and Dr. Darrell K. Berlin for his advice and the many conversations we shared. I also wish to express my appreciation to the rest of my committee members for being helpful in every way possible. A very special thanks are also due to Dr. Krishna K. Gnanasekaran for being a tremendous mentor, friend, and individual as well as to Dr. Nathan Pickering for being a great friend and colleague.

To my aunt, Ana Avila, thank you for showing me the meaning of hard work and the true definition of perseverance and patience. A very special thank you to my mother, Claudia Rebeca Calderon for her love, support and care throughout my entire academic career. Most importantly, to my better half, Carol Fuentes, thank you for your love, devotion, and companionship during these years. Without you, none of this would have been possible.

Acknowledgements reflect the views of the author and are not endorsed by committee members or Oklahoma State University.

Name: KEVIN MERAZ

Date of Degree: MAY, 2019

Title of Study: I) SYNTHESIS OF SMALL MOLECULES AS POTENTIAL ANTIBIOTIC AND ANTICANCER CANDIDATES II) SYNTHESIS OF BIOACTIVE HETEROCYCLIC SCAFFOLDS

Major Field: ORGANIC CHEMISTRY

Abstract: The first part of this work involved the synthesis of chemical probes to the inhibiton of the BfrB/Bfd protein interaction limiting the bioavalibility of Fe^{3+} in *Pseudomonas aeruginosa* as potential antibiotic candidates Previously, our group synthesized substituted 4-aminoisoindoline-1,3-diones which exhibited promising enzymatic inhibition of the BfrB/Bfd protein interaction in the micromolar range. One of the primary goals of this project was to synthesize analogs in the nanomolar range. To achieve this, we synthesized 1- and 3-carbon linked analogs of substituted 4-aminoisoindoline-1,3-diones.

- Incorporation of new substituted benzaldehydes: This can be achieved by starting with relatively inexpensive materials. Based on molecular modeling, we previously predicted that the incorporation of these functionalities in analogs of 4-aminoisoindoline-1,3-dione would increase the protein inhibitory effect. We subsequently designed and synthesized a new series of 10 compounds incorporating various substituents on the benzaldehyde component. For the purpose of this study, the 1° and 3-carbon linkers were not altered in the synthesis.
- Altering the carbon linker BfrB/Bfd chemical probes: Other modifications to 4-aminoisoindoline-1,3-dione were also made by decreasing the 3-atom carbon linker to a 1-atom linker and incorporating a phenoxyethoxy linker. We were interested in comparing the activity data of the 1-carbon, with 3-carbon and phenoxyethoxy linked 4-aminoisoindoline-1,3-diones using similar substitution patterns in substituted benzaldehydes.

This work also involved the synthesis of anti-cancer agents. Flexible Heteroarotinoids (Flex-Hets) are a class of substituted di-aryl compounds that exhibit potent anti-cancer activity without toxicity. Previously, our group developed a sulfur containing heteroarotinoid SHetA2 (NSC 721689), which exhibited promising activity against 62 different cancer cell lines at micromolar concentration with excellent differentiation between normal and cancer cells. This work focused on modifiying the linker unit of the SHetA2 compound.

- This study also focused on the synthesis of various analogs of SHetA2 and their evaluation against ovarian cancer cell line A2780. Structural modifcations were made to the linker unit and Ring B of SHetA2 in order to improve aqueous solubility, potency and efficacy.

The second part of this work involved devising new methods for preparing bioactive heterocylic scaffolds. These methods are summarized below.

- Synthesis of naphthoates, dihydroquinolines, and naphthyridine carboxylates was accomplished *via* the Morita-Bayliss-Hillman reaction.
- A four-step synthesis to 2-fluoro-5-nitronicontinaldehyde was facilitated by reduction of an ester by DIBAL-H.
- An efficient tandem reaction was designed to synthesize 4-chromanone using 20 mol% of bismuth(III) triflate.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

Table Page

LIST OF SCHEMES

Scheme Page

LIST OF FIGURES

Figure Page

CHAPTER I

SYNTHESIS OF SMALL MOLECULES AS POTENTIAL ANTIBIOTIC AND ANTICANCER CANDIDATES

1.1 Introduction

The development of new antibiotics has always been at the forefront of medicine. As the population of the world continues to increase, scientists must formulate and improve methodologies for antibiotic development. Antibiotic-resistant bacteria have evolved into a major concern to health professionals worldwide.[1] The strict regulations set by the Food and Drug Administration (FDA) put a strain on the approval of antibiotics, causing reduced progress in pharmaceutical research.[1] During the last 21 years, only two new classes of antibiotics (Figure 1.1) have been approved by the FDA and other international drug agencies.[1] The efforts of pharmacuetical companies in antibiotic research is challenged by economical, regulatory and scientific issues.[1] It is critical to develop new classes of antibiotic candidates in an efficient manner, in order to mitigate their strict approval process.

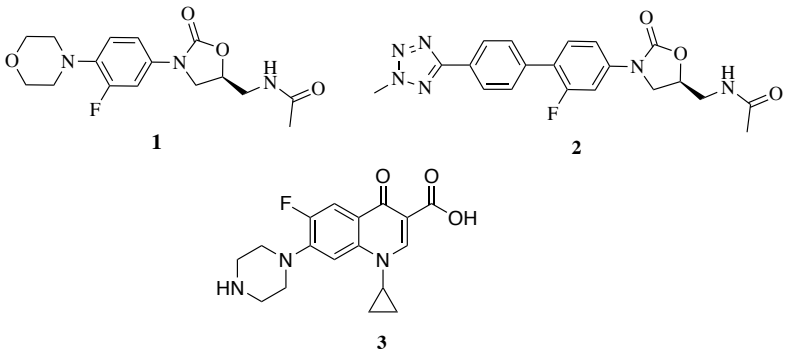


Figure 1.1 Chemical structures of antibiotics.[2]

A recent focus in our group has been dedicated to the synthesis of a series of potential antibiotic candidates which disrupt iron homeostasis in *Pseudomonas aerugionosa* cells.[3-5] Bacteria rely heavily on iron from a nutritional and chemical standpoint.[3-5] Iron typically exists in two oxidation states: Fe^{3+} greatly reduced the bioavailability due to its insolubility[4] and, Fe^{2+}, which is more soluble in an aqueous solution but can often be readily converted to Fe^{3+} via an O_2 oxidization mechanism.[4] In response to insufficient iron availability, bacteria have evolved a number of mechanisms to counter the effects of their iron-dependence.[6] An example of these mechanisms is the utilization of Fe^{2+} importers, "siderophores" which are responsible for chelating ferric ions in order to produce a ferric-siderophore complex that is utilized in the transportation of iron to the bacterial cytoplasm.[7-8] Ferric-siderophore complexes are generally produced at a higher pH, where normally, iron is present as insoluble compounds (Figure 1.2).[8] These chelating ligands have low-molecular weight, and are known to have a high affinity for Fe^{3+}.[8] Various studies have confirmed that iron levels in bacterial pathogens are crucial to their pathological activity.[8]

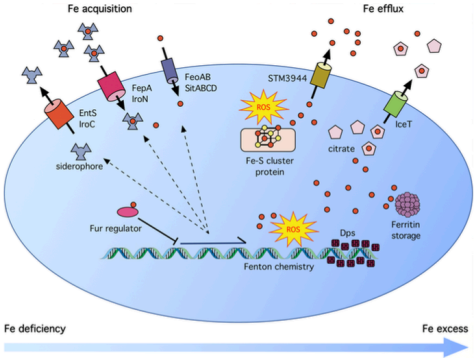


Figure 1.2 Maintenance of cellular iron homeostasis under deficient and replete conditions[9]

Several defense mechanisms of bacteria are crucial to their ability to maintain iron homeostasis. To maintain iron homeostasis, bacteria must employ various strategies surrounding the synthesis and production of iron scavenging systems.[4] Bacteria accomplish this by capturing and importing iron-scavenger complexes and maintaining proper iron storage in several iron-storage proteins.[4]

Two of the most studied iron storage proteins in *P. aeruginosa* cells are ferritins (FtnA) and heme-containing bacterioferritins (BfrB). Recently, the relationship between the iron mobilization from BfrB into ferredoxin Bfd was unclear to the scientific community.[4-6] However, recent studies suggest that the iron storage protein (BfrB) plays a key role in bacterial iron homeostasis.[5] The focus of this work is to synthesize and optimize small molecules that inhibit the BfrB:Bfd protein interaction resulting in deregulation of cytosolic iron levels in *P. aeruginosa* cells. Iron in the form of Fe^{2+} is necessary for normal growth and function of the Gram negative bacteria *P. aeruginosa*. Bacterioferritin (BfrB) is an iron storage protein that stores iron in the form of an Fe^{3+} mineral. When iron is needed by *P. aeruginosa*, bacterioferritin-associated ferredoxin (Bfd) binds to the outer shell of BfrB and facilitates the transfer of an electron from ferredoxin reductase (FPR) into BfrB to reduce the Fe^{3+} to Fe^{2+}. Interruption of this interaction deprives *P. aeroginosa* of the Fe^{2+} it needs and the bacteria die. The focus of this work is to synthesize and optimize small molecules that inhibit the BfrB:Bfd protein interaction resulting in decreased cytosolic iron levels in *P. aeruginosa* cells. This strategy exploits a new strategy for treating afflictions deriving from *P. aeruginosa.*[4-9] We are interested in improving the activity of BfrB:Bfd protein inhibitors by incorporating the following changes:

1) incorporating new substituted benzaldehydes and

2) altering the 3–carbon linker unit

Retrosynthetic analysis of potential targets **4** from **5** and **6** involving a single-and multistep syntheses are illustrated in (Figure 1.3).

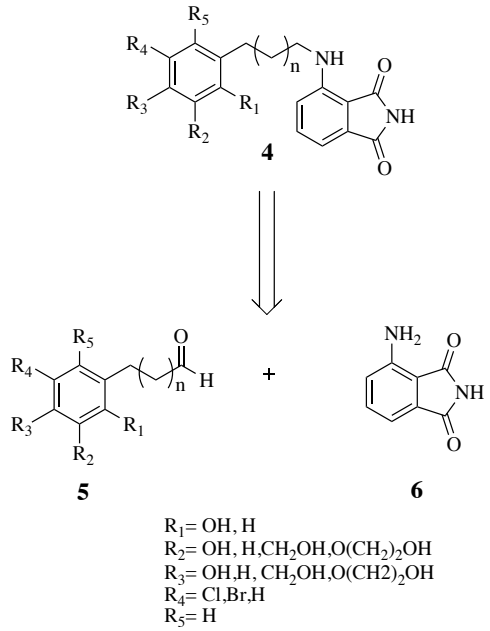


Figure 1.3 Rationale for designing substituted 4-aminoisoindoline-1,3-diones

1.2. Modification of Analogs

1.2.1 Incorporation of new substituted benzaldehydes

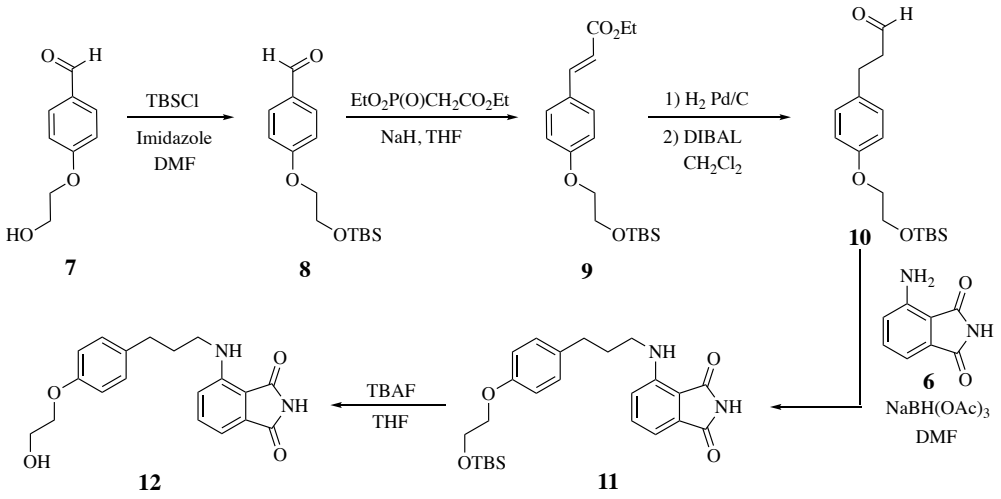
Modifications to the substituents on the benzaldehyde component have been envisioned to enhance the BfrB:Bfd protein inhibition.[4-6] Careful consideration and analysis led to utilization of chlorine and bromine substituted salicylaldehydes. Incorporation of these halogens would increase the molecular weight of our targeted molecule, and more importantly, it would allow for a "tighter" fit in the BfrB:Bfd active site, due to the presence of the larger halogen atoms. In addition, the effects of varying the position of the halogen substituents of **5** are critical to our investigation. Alternating between chlorine and hydroxyl functionalities at R_2 and R_3 may shed light on the potential inhibition effects of hydrogen bonding versus electron withdraw groups.

One of our most active compounds bears a hydroxy moiety at the R_2 position of **4**. Additional; flexibility can be added to the molecule by incorporating a CH_2OH or a $O(CH_2)_2OH$ at this position. This can be achieved by starting with relatively inexpensive materials. Based on molecular modeling, we previously predicted that the incorporation of these functionalities in analogs of **4**

would increase the protein inhibitory effect. We subsequently designed and synthesized a new series of 10 compounds incorporating various substituents on the benzaldehyde component. For the purpose of this study, the 1- and 3-carbon linkers were not altered in the synthesis. We are currently waiting on the activity assessment of these compounds, for comparison to previously synthesized analogs.

1.2.2. Results and discussion for the incorporation of new substituted benzaldehydes for BfrB/Bfd chemical probes.

The syntheses of substituted 4-aminoisoindoline-1,3-dione analogs incorporating a 1-atom linker required 1 step and analogs with a 3-atom linker required 6-8 steps (Scheme 1.1).



Scheme 1.1. Synthesis of analog **12**

tert-Butyldimethylsilyl (TBS) protection of **7** with imidazole in DMF afforded **8** in 92% after purification by silica gel chromatography.[10-15] The acrylate intermediate **8** was obtained under Horner-Wadsworth-Emmons conditions using a slight excess of triethyl phosphonoacetate (TEPA) and 60% NaH dispersed in mineral oil.[16] The addition sequence for this reaction proved to be important as an increase in yield was observed when NaH was added to a solution of TEPA in THF. The crude acrylate was taken directly to the hydrogenation step and purified by silica gel

chromatography to generate **9** in 97%. Reduction of the ester moiety using DIBAL-H can be troublesome if the temperature and mode of addition are not carefully monitored.[17] Therefore, it is imperative that the temperature does not exceed -65 ºC during the addition. Additional dry ice may be added to maintain the temperature at or below -65 ºC throughout the course of the reaction. The intermediate **10** can be isolated and characterized by ^{1}H and ^{13}C NMR. The success of the reductive amination step, between **6** and **1**catalyzed by AcOH relies heavily on the purity of the aldehyde component and the volume of DMF.[19-22] The use of excess solvent impedes formation of the imine intermediate which can further decompose upon addition of the reducing agent. Morever, it is imperative that 1.2-1.5 mL of anhydrous DMF be used for reactions of 2-3 mmol of the aldehyde component. In addition, the reactions must be strirred at 23 ºC for 1 h prior to the addition of the reducing agent.[19] The coupled product, **11** can be obtained in 12% yield after purification by column chromatogrpahy on silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone. The silyl deprotection of **11** is achieved by the addition of 2 equivalents of 1 M tetrabutylammonium fluoride (TBAF) in THF at 23 ºC. The desired analog **12** is obtained by purification using pyrone-treated silica in 78%. A similar set of reaction conditions can be used to synthesize analogs **13**, **14**, **15**, **16** and **17** (Figure 1.4).

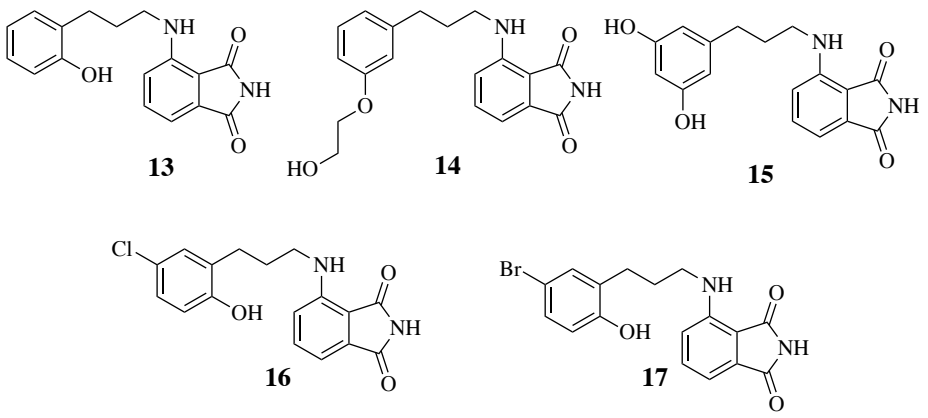
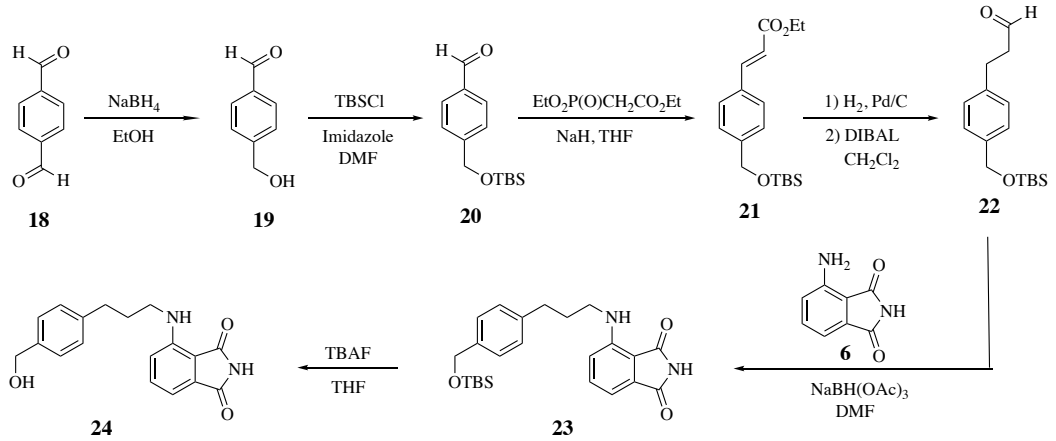


Figure 1.4 Analogs of 4-amino-isoindoline-1,3-diones with a 3 carbon linker

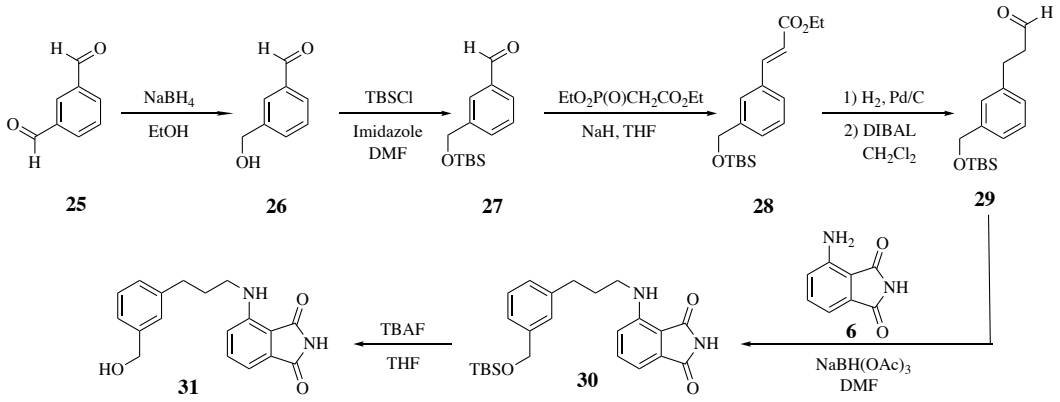
The incorporation of a hydroxymethyl substituent on the aldehyde component can achieved according to the route outlined in (Scheme 1.2).



Scheme 1.2 Synthesis of analog **24**

Reduction of **18** to **19** was achived using 0.25 equiv. of $NaBH_4$.[18] The reducing agent was added portion-wise, while simultaneously monitoring the reaction *via* TLC to minimize over reduction to the diol. Because the reaction only proceeds in 70-75%, the starting material was recycled to maximize the output of **19.** Intermediate **20** was produced *via* reaction with *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF. The corresponding acrylate **21** was synthezied using 60% NaH and TEPA in THF, and was subsequently hydrogenated and reduced with DIBAL to produce **22** in 95%. The reductive amination product was obtained by the coupling reaction of **6**

and **22** to obtain **23**. Removal of the TBS group with 1 M TBAF in THF and purification with pyrone-treated silica gel afforded **24** in 18%. A similar route to analog **31** from **25** is illustrated in (Scheme 1.3).



Scheme 1.3 Synthesis of analog **31**

1.3. Altering the carbon linker of BfrB/Bfd chemical probes

Other modifications to **4** were also made by decreasing the 3-atom carbon linker to a 1-atom linker and incorporating a phenoxyethoxy linker is illustrated in (Figure 1.5).

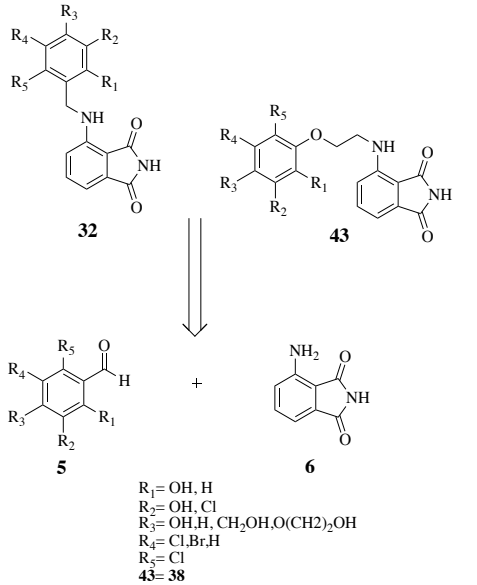
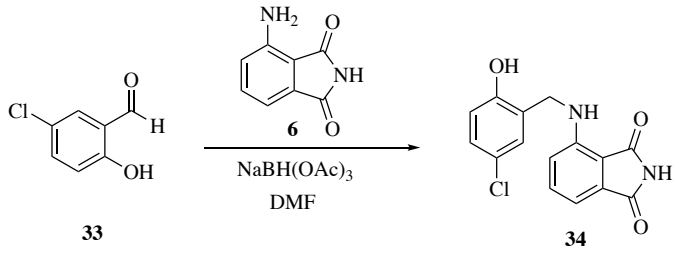


Figure 1.5 Rationale for altering carbon linker in 4-amino-isoindoline-1,3-diones

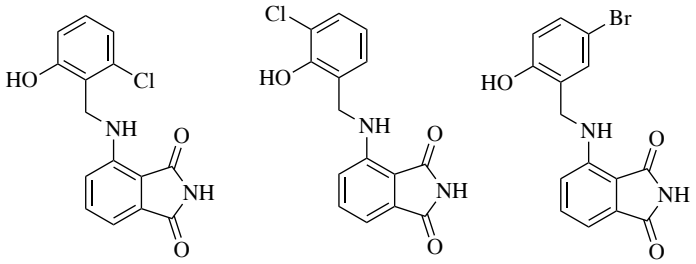
We were interested in comparing the activity data of the 1-carbon and phenoxyethoxy-linked 4-aminoisoindoline-1,3-diones using similar substitution patterns in **5**. A probable route to a 1-carbon linker analog is shown in (Scheme 1.4).



Scheme 1.4 Synthesis of analog **34**

1.3.1. 1 **Results and Discussion for the 1-carbon linker BfrB/Bfd chemical probes**

Reaction between **33** and **6** did not proceed at room temperature.[19] Initial trial runs using our previously mentioned conditions failed to afford **34** in good yield. Therefore, in order to maximize the converstion to **34**, the reaction between of **6** and **33** in DMF and AcOH required heating at 90 ºC for no more than 2 h. This can be attributed to the decrease in reactivity of **33** toward the nucleophilic attack of **6**.[19,23] Addition of **6** to **33** formed a thick slurry, which then turned clear once the reaction reached 90 ºC. Allowing the reaction to proceed at 90ºC for longer than 2 h did not improve the outcome. After allowing the reaction to proceed for 2 h at 90 ºC, it was then cooled to 0 ºC prior to the portion-wise addition of the reducing agent.[19] The expected product **35** was obtained after purification by column chromatography. A similar set of reaction conditions was used to synthesize analogs **35, 36** and **37** (Figure 1.6).

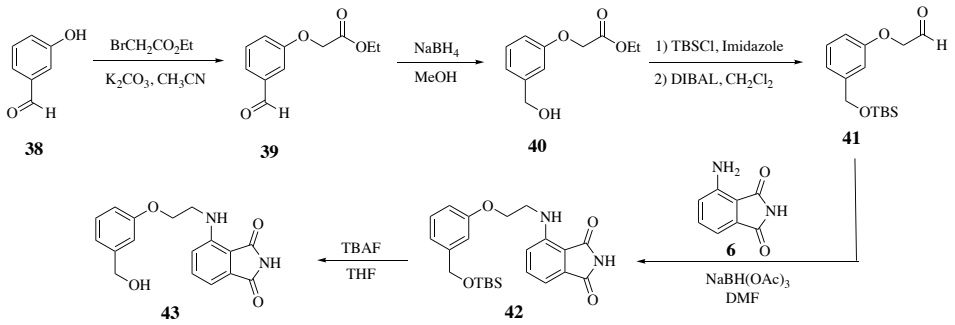


35 **36** **37**

Figure 1.6 Analogs of 4-aminoisoindoline-1,3-diones with a 1 carbon linker

1.3.2. Results and discussion for the phenoxyethoxy linker analogs.

The synthesis of **43** began with *O*-alkylation of **38** with ethyl bromoacetate in CH_3CN with K_2CO_3 (Scheme 1.5). This proceeeded in 95% yield following purification by silica gel chromatography.[25-28] Treatment of **39** with $NaBH_4$ afforded **41** without further purification in 63%. Protection of **40** with *tert*-butyldimethylsilyl chloride in the presence of imidazole led to the TBS-protected intermediate, which was subsquently reduced to **41** with DIBAL in CH_2Cl_2 at -78 ºC in 83% yield. The reductive amination sequence between **41** and **6** proceeded after chromatographic purification on pre-treated silica to gel provide **42** in 15% yield. Removal of the TBS protecting groups with 1 M TBAF in THF at 23 ºC proceeded to give **43** in 72%.



Scheme 1.5 Synthesis of analog **43**

A similar set of reaction conditions was used to synthesize analogs **44 and 45.**

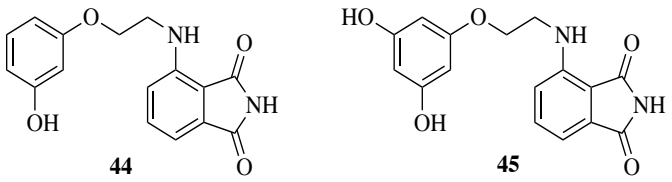


Figure 1.7 Analogs of 4-aminoisoindoline-1,3-diones with a phenoxyethoxy linker

1.4 Anticancer agents

In addition to the synthesis of BrfB/Bfd chemical probes, this study also focused on the synthesis of various analogs of SHetA2 and their evaluation against the A2780 ovarian cancer cell line.[31-33] Structural modifcations were made to the linker unit and Ring B of SHetA2 (Figure 1.8) in order to improve aqueous solubility, potency and efficacy.

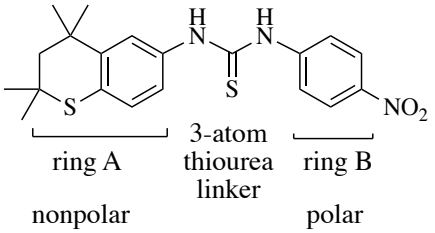


Figure 1.8 Anticancer agent SHetA2

Previously, our group synthesized a handful of second-generation flexible heteroarotinoids differentiating the linker unit by incorporating cinnamamide linked to the sulfur-containing heterocycle found in SHet-A2.[30] (Figure 1.9)

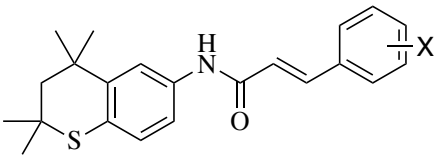


Figure 1.9 Acrylamide modification in SHetA2

While several structural modifications were made to the linker unit, the biological activity data of the synthesized compounds failed to compare to that of SHetA2.[30] In addition, last year our group finalized the synthesis of oxygen containing analogs, which proved to be more potent against ovarian cancer than SHetA2.[34]

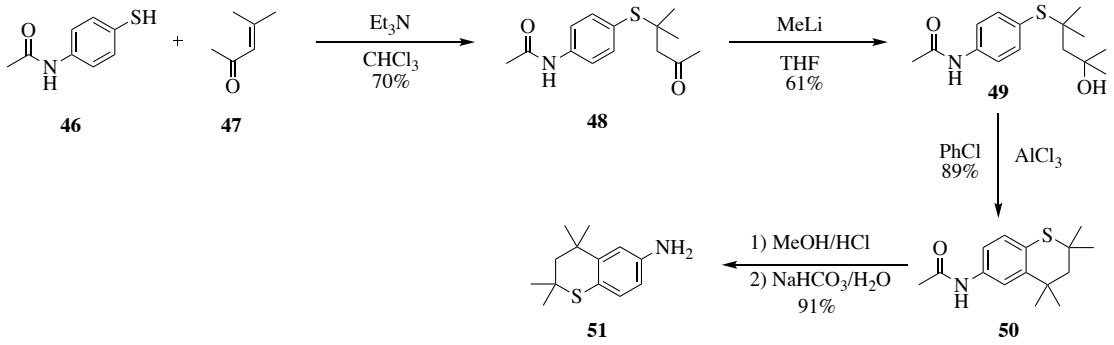
1.4.1 Altering the linker unit of SHetA2

Increasing the 3-atom linker unit in SHetA2 was envisioned to enhance potency and hydrogen bonding capabilities. Recent studies by our collaborators indicated that SHetA2 interacts with

mortalin (HSPA9).[33] This interaction prohibits the binding of mortalin to p53 and bcl-2, two proteins that regulate apoptosis of cells.[33] Our lead compound SHetA2 displaces the protein p53 and bcl-2 from mortalin causing programmed apoptosis.[32,33] Based on these observations, the focus of this work was to increase hydrogen bonding capabilities to potentiate this interaction further.

1.4.2. Results and discussion for altering the linker unit of SHet-A2

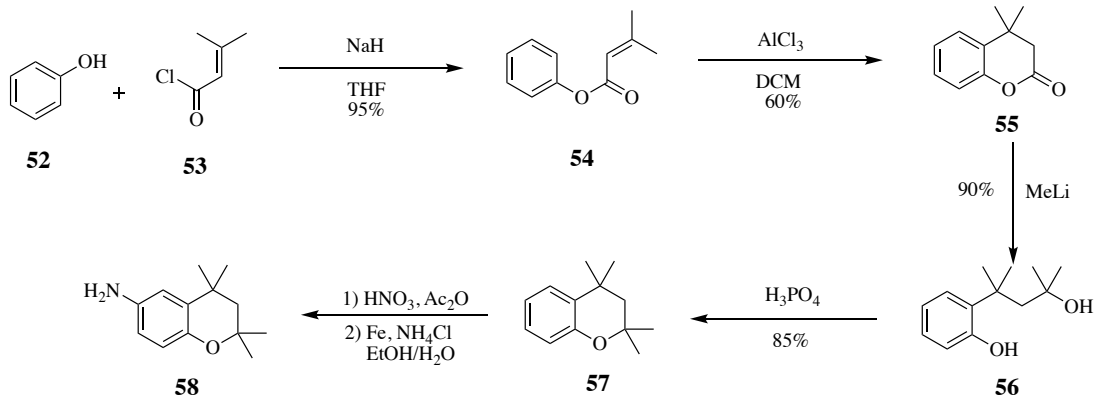
The synthesis of the SHetA2 analogs was performed in 5-8 steps according to the following procedures[30,34] outlined in (Scheme 1.6)



Scheme 1.6 Synthesis of thiochroman heterocycle **51**

Initially, 4-acetamidothiophenol **46** underwent a Michael addition with mesityl oxide **47** in the presence of triethylamine. The reaction was optimized by using a two-fold excess of **47** and triethylamine and adding the reagents in a dropwise fashion.[30] Intermediate **48** was treated with 3 equivalents of MeLi at -45 ºC to afford the tertiary alcohol **49**. A Friedel-Craftscyclization of **49** with $AlCl_3$ in chlorobenzene produced the desired thiochroman derivative **50** in 89% yield. The acetyl group was then removed by action of 6 M HCl in MeOH to produce the hydrochloride amine salt, which was neutralized by the addition of $NaHCO_3$ in water to afford **(51)** as a brown oil in 91% yield.

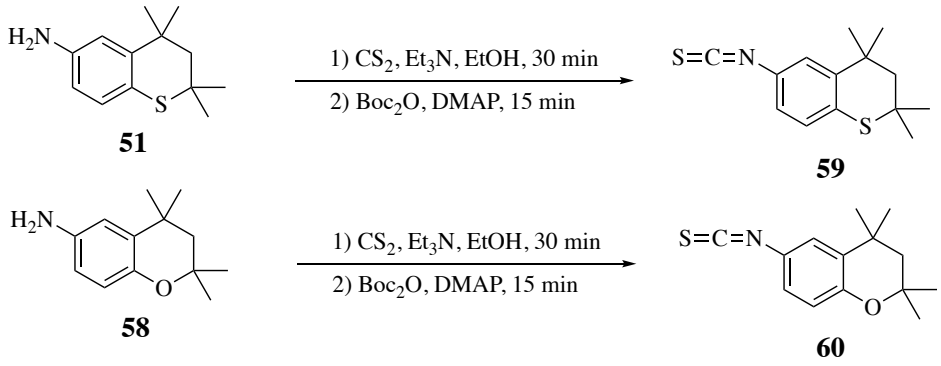
The synthesis of the oxygen chroman heterocycle was performed in a 6-step reaction sequence as outined in Scheme 1.7.



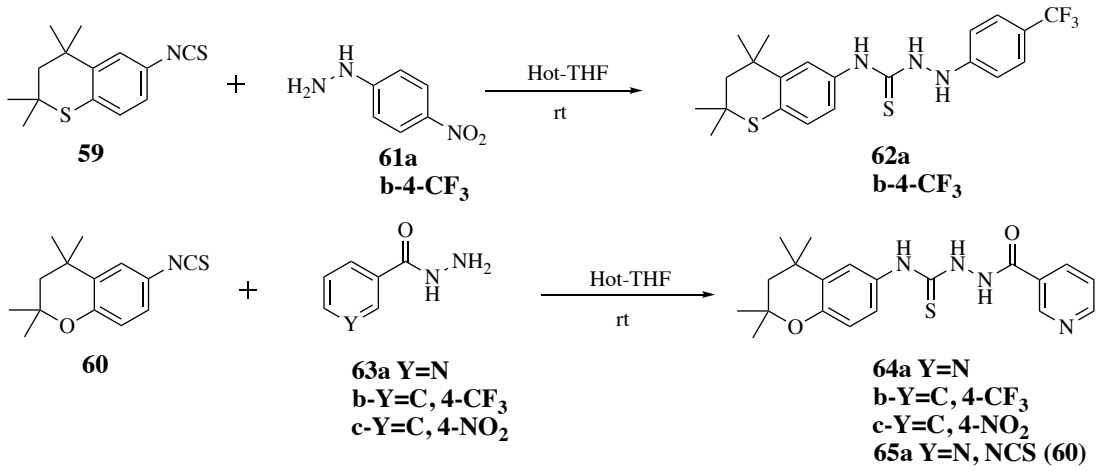
52 **53** **54** **55** **56** **57** **58**

Scheme 1.7 Synthesis of chroman heterocycle **58**

The synthesis of **54** was achieved by following a procedure similar to that described by Dawson and coworkers.[35] Phenol **52** was added dropwise to an oil-free suspesion of NaH in THF at 0 ºC. After stirring the reaction mixture for 15 minutes, 3-methylbut-2-enoyl chloride (**5**) was added dropwise, and the reaction mixture was allowed to gradually warm to room temperature. Work-up and purification by silica gel chromatography generated **54** as a colorless oil in 95% yield. The aryl ester **54** was treated with $AlCl_3$ in DCM to afford the desired chromanone **55**. Subsequent treatment with MeLi at 0 ºC afforded the diol **56** as a white solid in 90% yield. The chroman derivative **57** was obtained by a cyclodehydration sequence using concentrated phosphoric acid at 100 ºC. The chroman derivative **57** was nitrated using nitric acid in acetic anhydride at -15 ºC (ice/methanol bath) to produce the 6-and 8-nitro isomers which were carried on to a reduction promoted by iron powder and ammonium chloride in aqueous ethanol.[36] The target **58** was obtained after purification by silica gel chromatography.[33]Compounds **51** and **58** were converted to their respective isothiocyanates according to the known procedure[37] (Scheme 1.8) and were combined with substituted benzhydrazides (Scheme1.9) to generate the carbothioamides.



Scheme 1.8 Synthesis of aryl isothiocyanates **59** and **60.**



Scheme 1.9 Synthesis of 3- and 4-atom linker targets

These synthesized analogs were screened to identify structural features important for cancer cell inhibition activity. SHetA2 was used as a standard for comparison. The biological effects of the compounds were assessed using a cytotoxicity assay on the human A2780 ovarian cancer cell line (Table 1.1).

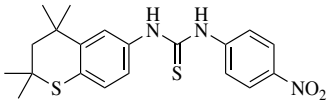
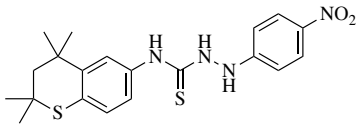
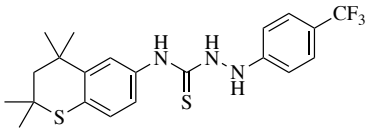
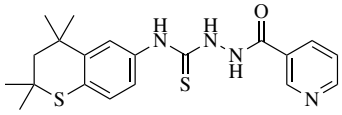
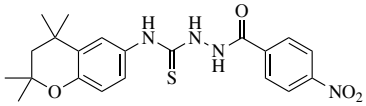
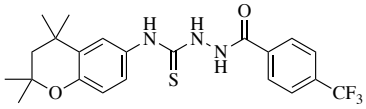
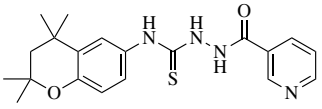
Compound	IC_{50} (μM)	Efficacy	% Growth Inhibition
 **SHetA2**	**3.17**	**100**	**93.17 ± 2.37**
 **63a**	**7.63**	**94.68**	**76.61 ± 4.99**
 **63b**	**8.12**	**14.45**	**11.67± 2.24**
 **64a**	**6.38**	**22.31**	**18.02 ± 1.81**
 **64b**	**6.04**	**19.29**	**15.58 ± 1.55**
 **64c**	**5.33**	**8.39**	**6.78 ± 1.69**
 **65**	**7.24**	**6.40**	**5.17 ± 3.49**

Table 1.1. Activity data for analogs **64a-b, 65a-c** and **66**

Of the synthesized analogues, compound **63a** proved most active demonstrating 77% cancer cell growth inhibition compared to that of SHetA2 (93%). However, the addition of the hydrazine group in the linker unit seemed to reduce the overall potency. All of the other derivatives were found to be less active only showing 5-18% of cancer cell growth inhibtion.

1.5. Conclusion

In summary, we have synthesized various compounds as potential antibiotic and anti-cancer candidates.

1.5.1 Incorporation of new substituted benzaldehydes

In this study, we have successfully prepared new analogs of **4** from substituted benzaldehydes. The syntheses of these analogs were performed in a 5-8 steps. Our interests lie in the results of the incorporation of various substituents on the benzaldehyde component and their inhibition of the BfrB/Bfd protein interaction.

1.5.2 Altering the carbon linker in BfrB/Bfd chemical probes

In an effort to further block the BfrB/Bfd protein interaction, the synthesis of a single carbon linker analogs was achieved with improved yields. Our interests lie in comparing the activity between our 3-carbon linker and 1-carbon linker chemical probes. Moreover, the addition of polar groups to the linker unit could increase the solubility and hydrogen bonding potential of our analogs to surrounding amino acid residues.[4-9] We are anxiously waiting the activity data pertaining to substitution effects on the pertubation of the BfrB/Bfd protein interaction.

1.5.3 Synthesis of Anticancer agents

In this study, we attempted to synthesis analogs of SHetA2 with extended linker units. Unfortunately, only one analog **63a** demonstrated comparable cancer cell inhibition to that of SHetA2. It would be a worthy endevaour to alter the thiourea component of **63a** to a urea, as well as synthesizing a similar compound incorporating the oxygen heterocyclic system. Further explorations into the synthesis of 4-5 atom linkers are ongoing in our group.

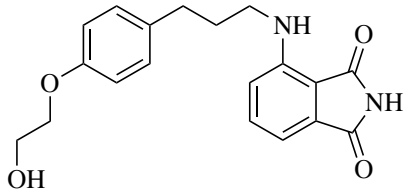
1.6 Chemistry

1.6.1 Incorporation of substituted benzaldehydes in BfrB/Bfd chemical probes

General procedure for pyrone treated silica gel: A 3-L sintered-glass funnel suspended on an O-ring was charged with one-kilogram of silica gel (Sorbent Technologies CA# 40940-25). The silica gel was treated with a solution of 3-hydroxy-2-methyl-4-pyrone (20 mg) in 1 L of MeOH. The initial wash (yellow-orange coloring) was discarded. Additionally, the silica gel was washed with 500 mL of recycled MeOH (old washings). An additional 1.5 L of fresh MeOH was used to rinse the silica gel. The silica gel was transferred to a tray, covered with aluminum foil (poked holes to let silica breathe) and was set to air dry at room temperature overnight. Subsequently, the silica gel was dried in the oven at 90 °C in 3 h increments.

General methods: Commercial anhydrous *N,N*-dimethylformamide was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and then distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations for final compounds were performed by column chromatography on silica gel (Davisil®, grade 62, 60 - 200 mesh) pre-treated with 3-hydroxy-2-methyl-4-pyrone mixed with UV-active phosphor (Sorbent Technologies No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

Synthesis of (12)



4-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)benzaldehyde 8. A stirred solution of 4-(2-hydroxyethoxy)benzaldehyde **7** (1.44 g, 8.65 mmol) in DMF (10 mL) was cooled to 0 ºC under nitrogen atmosphere and imidazole (1.18 g, 17.3 mmol) was added. The resulting solution was stirred for 20 min and *tert*-butyldimethylsilyl chloride (1.64 g, 10.4 mmol) was added dropwise as a solution in DMF (10 mL) was added dropwise over a period of 15 min. The reaction mixture was warmed to room temperature (23 ºC) and stirred until TLC analysis indicated the complete conversion of the phenolic compound. The crude reaction was poured into water (50 mL), extracted with ether (3 × 40 mL), and the combined organic layers were washed with saturated NaCl (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography to afford (2.42 g, 92%) of 4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)benzaldehyde **8** as a colorless oil. IR: 2951, 2931, 2857, 1692, 1600, 1507, 1258, 908.61 cm^{-1}; ^1H NMR ($CDCl_3$): δ; 9.88 (s, 1H), 7.83 (dd, *J* = 6.9 Hz, 1.9 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.14 (t, *J* = 4.9, 2H), 4.00 (t, *J* = 5.2 Hz, 2H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 190.8, 164.1, 131.9, 129.9, 114.87, 69.6, 61.8, 25.9, -5.2.

Ethyl (*E*)-3-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)acrylate (9). To a stirred, ice-cold solution of triethylphosphonoacetate (1.92 g, 1.70 mL, 8.5 mmol) in THF (5.0 mL) was added a 60% NaH dispersed in mineral oil (340 mg, 8.5 mmol) and the mixture was stirred for 15 min. To the resulting reaction mixture was added dropwise TBS protected 4-(2-hydroxyethoxybenzaldehyde (**8,** 2.00 g, 7.14 mmol) in THF (15 mL) and the stirred reaction was allowed warmed to 23 ºC. After the TLC analysis indicated the complete consumption of starting material, the reaction mass was cooled and quenched by dropwise addition of ice-cold water. The

product was extracted into ether (2 × 25 mL), and the organic layer was washed with saturated NaCl (15 mL), dried (Na_2SO_4) and evaporated to afford acrylate **9** (2.11 g, 82%) as a colorless oil. This compound was carried forward without further purification.

E**thyl 3-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)propanoate. (9a)** A solution of ethyl (*E*)-3-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)acrylate **9** (2.01 g, 5.74 mmol) in ethanol (15 mL) was flushed twice with nitrogen and 10% Pd/C (211 mg, 50% wet) was added. The reaction was stirred at room temperature under H_2 (1 atm) for 18 h. The reaction mass was filtered through a Celite® bed and washed with ethanol (2 × 40 mL). The filtrate was concentrated under vacuum and purified by silica gel column chromatography to afford ethyl 3-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)propanoate (1.97 g, 97%) as a colorless oil. IR: 2957, 2931, 2859, 1734, 1310 , 1248, 915 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.02 (t, *J* = 4.7 Hz, 2H), 3.96 (t, *J* = 4.9 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 173.0, 157.4, 137.7, 129.9, 129.2, 114.6, 69.3, 62.1, 60.4, 36.3, 30.2, 25.9, 14.2, -5.2.

3-(4-(2-hydroxyethoxy)phenyl)propanal (10). The ester **9a** (1.40 g, 4.0 mmol) prepared above was dissolved in dicholoromethane (DCM, 10 mL) and cooled to –78 ºC. The solution was treated by dropwise addition of 1.5 M DIBAL-H in toluene (2.63 mL, 4.0 mmol) over a period of 30 min. Stirring was continued for 2 h at –78 ºC until TLC analysis indicated the complete absence of starting material. The reaction was quenched at –70 ºC by dropwise addition of methanol (10 mL), followed by the dropwise addition of 1 M HCl (15 mL). The aqueous layer was separated and extracted with DCM (2 × 50 mL). The combined organic layers were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 3-(4-(2-hydroxyethoxy)phenyl)propanal (1.15 g, 95%) as a colorless oil. IR: 1723, 1508, 1244, 914 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.81 (t, *J* = 1.5 Hz, 1H), 7.10 (dd, *J* = 6.6 Hz, 2.2 Hz, 2H), 6.83 (dd, *J* = 6.6,

2.1 Hz, 2H), 3.99 (d, *J* = 5.1 Hz, 2H), 3.97 (dd, *J* = 5.1, 1.7 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.75 (td, *J* = 8.5, 7.8, 2H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR: δ 201.8, 157.5, 132.4, 129.9, 129.8, 129.3, 129.2, 114.7, 114.4, 69.3, 62.81, 45.6, 27.3, 25.9, 20.5,

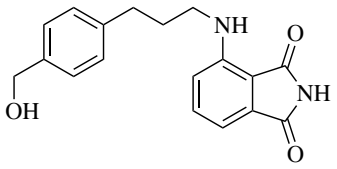
-5.2.

4-((3-(4-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)phenyl)propyl)amino)isoindoline-1,3-dione (11) To a solution of 3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanal (0.96 g, 3.44 mmol) in DMF (1.5 mL) was added AcOH (0.8 mL) and the solution was stirred for 10 min. To this reaction mixture, 4-aminophthalimide **6** (0.28 g, 1.72 mmol) was added and stirring was continued at 23 ºC for 1 h. An additional 1 mL of DMF was added bringing the volume to 2.5 mL. The reaction was cooled to 0 ºC and $NaBH(OAc)_3$ (1.13 g, 5.16 mmol) was added subsequently portion-wise to the reaction. Stirring was continued at this temperature for 30 min, and then the reaction was gradually warmed to 23 ºC and stirred for 18 h. The crude reaction mixture was poured into de-ionized water, extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 mL) and saturated NaCl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 1 mL of EtOH and the solution was heated at 50 ºC for 10 min under N_2. The resulting solid was filtered and washed with EtOH (2 × 10 mL). The filtrate was concentrated under vacuum and subjected to chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluting with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **11** (266 mg, 18%) as a yellow solid, mp 211-212 ºC. ^{1}H NMR (DMSO-d_6): δ; 11.0 (s, H), 7.53 (dd, 8.3, 7.4 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 7.01 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.50 (t, *J* = 6.2 Hz, 1H), 3.97 (t, *J* = 4.4 Hz, 2H), 3.89 (t, *J* = 4.4 Hz, 2H), 3.25 (q, *J* = 6.7 Hz, 2H), 2.60 (t, *J* =7.4 Hz, 2H), 1.84 (quintet, *J* = 7.3 Hz, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (DMSO-d_6): δ; 170.8, 168.7, 156.1, 145.6, 135.3, 132.7, 128.6, 115.8, 113.7, 110.1, 109.2, 68.4, 61.1, 40.7, 29.9, 25.2,

17.4, -5.8.

4-((3-(4-(2-Hydroxyethoxy)phenyl)propyl)amino)isoindoline-1,3-dione (12). A solution of the 2-hydroxyethoxysilyl ether (0.22 g, 0.48 mmol) in 7 mL of THF was stirred under N_2 at 23 ºC and 1.0 M TBAF in THF (0.95 mL, 0.96 mmol) was added. When TLC analysis indicated the complete consumption of the silyl ether, de-ionized water (5.0 mL) was added and the THF was evaporated under vacuum. The crude mixture was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with saturated NaCl (50 mL), dried (Na_2SO_4), and concentrated under vacuum. The product was purified by column chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluted with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **12** (127 mg, 78%) as a yellow solid, mp 165-166 ºC. IR; 1753, 1710, 1377, 1149 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.9 (s, 1H), 7.51 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.50 (t, *J* = 5.9 Hz, 1H), 4.83 (t, *J* = 5.5 Hz, 1H), 3.94 (t, *J* = 5.2, Hz 2H), 3.69 (q, *J* = 5.2 Hz, 2H), 3.26 (q, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.85 (quintet, *J* = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 171.1, 168.9, 156.5, 145.8, 135.5, 133.2, 132.7, 128.8, 116.0, 113.9, 110.3, 109.4, 68.9, 59.2, 40.9, 31.0, 30.1.

Synthesis of (24)



4-(Hydroxymethyl)benzaldehyde (19). A 100-mL round-bottomed flask was charged with terephthalaldehyde **18** (1.34 g, 7.66 mmol) in 10 mL of MeOH under N_2. The solution was cooled to 0 °C, $NaBH_4$ (72 mg, 1.92 mmol) was added portion-wise over a 5-min period. The mixture was gradually warmed to 23 ºC and stirred for 5 h. After 5 h, the reaction was deemed completed at which time, the solvent was removed and the residue was taken up with DCM and transferred to a separatory funnel. The organic layer was washed with H_2O (25 mL), NaCl (25 mL) and dried

(Na_2SO_4). The product was purified by silica gel chromatography using 20% ether/hexane to yield the hydroxyaldehyde **19** (1.04 g, 75%) as a colorless oil. IR: 3402, 1691, 1606, 1579, 1211 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.01 (s, 1H), 7.89 (dd, *J* = 6.6, 1.6 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 4.81 (s, 2H), 1.85 (br s, 1H); ^{13}C NMR: ($CDCl_3$): δ 192.0, 147.7, 135.7, 130.0, 126.9, 64.6.

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)benzaldehyde (20). A stirred solution of 4-(hydroxymethyl)benzaldehyde (**19**, 1.15 g, 8.5 mmol) in DMF (10 mL) was cooled to 0 ˚C under N_2 and imidazole (1.16 g, 16.9 mmol) was added. The resulting solution was stirred for 20 min and TBS chloride (1.53 g, 10.2 mmol) as a solution in DMF (10 mL) was added dropwise over a period of 15 min. The reaction mixture was warmed to 23 ºC and stirred until TLC analysis indicated the complete absence of the phenol. The crude reaction was poured into water (50 mL), extracted with ether (3 × 40 mL), and the combined organic layers were washed with saturated NaCl (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography to afford 4-(((*tert*-butyldimethylsilyl)oxy)methyl)benzaldehyde **20** (1.73 g, 82%) as a colorless oil. IR: 1703, 1610, 1466, 913 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.00 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 4.82 (s, 2H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 192.1, 148.7, 135.3, 129.8, 126.2, 64.5, 25.9, 18.4, -5.3.

Ethyl (*E*)-3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)acrylate (21). To a stirred, ice-cold solution of triethylphosphonoacetate (1.42 mL, 7.14 mmol) in THF (10 mL) was added a 60% dispersion of NaH in mineral oil (286 mg, 7.14 mmol) and the reaction was stirred for 15 min. To the resulting tan solution was added dropwise 4-(((*tert*-butyldimethylsilyl)oxy)methyl)benzaldehyde (**20** 1.5 g, 6.0 mmol) in THF (15 mL) and the mixture was warmed to 23 ºC. After the TLC analysis indicated the complete absence of starting material, cooled the reaction mass and quenched by dropwise addition of ice-cold water. The product was extracted into ether (2 × 25 mL), and the combined organic layers were washed with saturated NaCl

(15 mL), dried (Na_2SO_4) and evaporated to afford the acrylate **21**, (1.82 g, 97%) as a colorless oil. This compound was carried forward without further purification.

Ethyl 3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanoate (21a). A solution of ethyl (*E*)-3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)acrylate **21** (1.82 g, 5.7 mmol) in ethanol (25 mL) was flushed twice with N_2 and 10% Pd/C (192 mg, 50% wet) was added. The reaction was stirred at room temperature under H_2 (1 atm) for 18 h, then filtered through Celite, the bed was washed with ethanol (2 x 40 mL) and the filtrate was concentrated under vacuum and purified by silica gel column chromatography to afford the propanoate ester **21a** (1.14 g, 62%) as a colorless oil. IR:2856, 1736.5, 1254., 1088 , 914 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 4.71 (s, 2H), 4.13 (q, J =7.1 Hz, 2H), 2.94 (t, J = 5.1 Hz, 2H), 2.60 (t, J =8.1 Hz, 2H), 1.2.3 (t, J = 7.5 Hz, 3H), 0.94 (s, 9H), 0.09 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 179.7, 139.4, 139.2, 128.2, 126.3, 64.8, 60.4, 36.0, 30.7, 25.9, 18.4, 14.2, -5.2

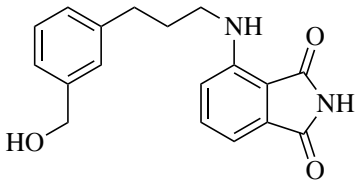
3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)propanal (22). The propanoate ester **21a** prepared above (1.0 g, 3.1 mmol) was dissolved in DCM (10 mL) and cooled to –78 ºC under N_2. The solution was treated dropwise with 1.5 M solution of DIBAL-H (2.07 mL, 3.1 mmol) in toluene over a period of 30 min. Stirring was continued for 2 h at –78 ºC until TLC analysis indicated the complete conversion of starting material. The reaction was quenched by dropwise addition of methanol (10 mL), followed by dropwise addition of 1 M HCl (15 mL). The aqueous layer was separated and extracted with DCM (2 × 50 mL). All of the combined organic layers were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanal **22**, (0.96 g, 99%) as a colorless oil. IR: 1725, 1250, 913cm^{-1} ; ^1H NMR ($CDCl_3$): δ 9.82 (t, J = 1.3 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.71 (s, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.8 (t, J = 7.9, 2H), 0.94 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 201.7, 166.8, 139.5, 138.9, 128.1, 126.4, 128.1, 126.4, 64.7, 45.4, 27.8, 25.9, -5.2.

4-((3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)propyl)amino)isoindoline-1,3-dione (23). To a solution of 3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanal (**22,** 0.96 g, 3.44 mmol) in DMF (1.5 mL) was added AcOH (0.8 mL) and the solution was stirred for 10 min. To this reaction mixture, 4-aminophthalimide **6** (0.28 g, 1.72 mmol) was added and stirring was continued at 23 ºC for 1 h. An additional 1 mL of DMF was added bringing the volume to 2.5 mL. The reaction was cooled to 0 ºC and $NaBH(OAc)_3$ (1.13 g, 5.16 mmol) was added portion-wise to the reaction. Stirring was continued at this temperature for 30 min, and the reaction was gradually warmed to 23 ºC and stirred for 18 h. The crude reaction mixture was poured into de-ionized water, extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 mL) and saturated NaCl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 1 mL of EtOH and the solution was heated at 50 ºC for 10 min under N_2. The resulting solid was filtered and washed with EtOH (2 × 10 mL). The filtrate was concentrated under vacuum and subjected to chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluting with 20% EtOAc/hexane to afford the isoindoline-1,3-dione (**23** 266 mg, 18%) as a yellow solid, mp 211-212 ºC. ^{1}H NMR (DMSO-d_6): δ 10.93 (s, 1H), 7.51 (dt, J = 8.2, 6.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.96 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 4.66 (s, 2H), 3.26 (t, J = 6.6 Hz, 2H), 6.52 (t, J = 5.8 Hz, 1H), 2.64 (t, J = 7.7 Hz, 2H), 1.86 (quintet, J = 7.5 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 171.9, 169.8, 146.7, 140.5, 139.1, 136.3, 128.6, 128.5, 126.7, 111.3, 110.3, 64.6, 41.8, 32.5, 30.8, 26.3, -4.7.

4-((3-(4-(Hydroxymethyl)phenyl)propyl)amino)isoindoline-1,3-dione (24). A solution of 4-hydroxymethyl silyl ether **23** (0.27 g, 0.63 mmol) in 7 mL of THF was stirred under nitrogen at 23 ºC and 1.0 M TBAF in THF (1.25 mL 1.25 mmol) was added. When TLC analysis indicated the complete conversion of the silyl ether, de-ionized water (5.0 mL) was added and the THF was evaporated under vacuum. The mixture was extracted with ethyl acetate (3 × 40 mL) and the

combined organic layers were washed with saturated NaCl (50 mL), dried (Na_2SO_4), concentrated under vacuum. The crude product was purified by column chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluting with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **24** (155 mg 79%) as a yellow solid, mp 131-132 °C. ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 7.1 Hz, 1H) 6.52 (t, J = 5.7 Hz, 1H), 5.09 (t, J = 5.7 Hz, 1H), 4.46 (d, J = 5.7 Hz, 2H) 3.28 (q, J = 6.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.87 (quintet, J = 7.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.2, 168.7, 14.6, 139.4, 139.1, 135.3, 132.9, 127.3, 126.0, 155.8, 110.2, 109.2, 62.1, 40.7, 31.4, 29.8.

Synthesis of (31)



3-(Hydroxymethyl)benzaldehyde (26). A 100-mL round-bottomed flask was charged with isophthalaldehyde **25** (5.0 g, 37.31 mmol) in 30 mL of MeOH under N_2. The solution was cooled to 0 °C, $NaBH_4$ (295 mg, 7.8 mmol) was added portion-wise over a 5 min period. The mixture was gradually warmed to 23 °C and stirred for 5 h. After 5 h, the reaction was deemed completed (by TLC) at which time, the solvent was removed and the residue was taken up with DCM and transferred to a separatory funnel. The organic layer was washed with H_2O (25 mL), NaCl (25 mL) and dried over (Na_2SO_4). The product was purified by silica gel chromatography using 20% ether/hexane to yield the hydroxyaldehyde (**26**, 3.42 g, 70%) as a colorless oil. IR: 3425, 2923, 2736, 1697, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.08 (s, 1H), 7.90 (d, J = 0.5 Hz, 1H), 7.82 (dt, J = 7.6 Hz, 1H), 7.66 (dd, J = 7.6, 0.5 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 4.80 (s, 2 H); ^{13}C NMR: ($CDCl_3$): δ 192.3, 142.0, 136.7, 132.8, 129.3, 129.1, 127.8, 64.5.

3-(((*tert*-butyldimethylsilyl)oxy)methyl)benzaldehyde (27) A stirred solution of 3-(hydroxymethyl)benzaldehyde (**26**, 1.92 g, 14.6 mmol) in DMF (15 mL) was cooled to 0 ˚C under N_2 and imidazole (2.01 g, 29.3 mmol) was added. The resulting solution was stirred for 20 min and TBS chloride (2.65 g, 17.6 mmol) as a solution in DMF (15 mL) was added dropwise over a period of 15 min. The reaction mixture was warmed to 23 ºC and stirred until TLC analysis indicated the complete absence of the phenol. The crude reaction was poured into water (50 mL), extracted with ether (3 × 40 mL), and the combined organic layers were washed with saturated NaCl (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography to afford 3-(((*tert*-butyldimethylsilyl)oxy)methyl)benzaldehyde (**27**, 3.30 g, 90%) as a colorless oil. IR: 2856 , 2720, 1703, 1591, 1144, 1466, 1103, 1255, 1080 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.0 (s, 1H), 7.83 (d, J = 6.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 4.81 (s, 2H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR; 192.5, 142.7, 136.4, 132.1, 128.9, 128.4, 127.2, 64.3, 25.9, 18.4, -5.3.

Ethyl (*E*)-3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)acrylate (28) To a stirred, ice-cold solution of triethylphosphonoacetate (2.84 mL, 14.3 mmol) in THF (10 mL) was added a 60% dispersion of NaH in mineral oil (572 mg, 14.3 mmol) and stirred for 15 min. To the resulting tan solution was added dropwise TBS protected 3-(((*tert*-butyldimethylsilyl)oxy)-methyl)benzaldehyde (**27,** 3.0 g, 12.0 mmol) in THF (15 mL) and the mixture was warmed to 23 ºC. After the TLC analysis indicated the complete absence of starting material, the reaction mixture was cooled and quenched by dropwise addition of ice-cold water. The product was extracted into ether (2 × 25 mL), washed the organic layer with saturated NaCl (15 mL), dried and evaporated to afford the acrylate **28** (2.80 g, 73%) as a colorless oil. This compound was carried forward without further purification.

Ethyl 3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanoate (28a) A solution of ethyl (*E*)-3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)acrylate **(28**, 2.80 g, 8.8 mmol) in ethanol (25 mL) was flushed twice with N_2 and 10% Pd/C (320 mg, 50% wet) was added. The reaction was stirred at room temperature under H_2 (1 atm) for 18 h, and then filtered through a Celite®. The bed was washed with ethanol (2 × 40 mL) and the filtrate was concentrated under vacuum and purified by silica gel column chromatography to afford the propanoate ester (**28a**) (2.40 g, 84%) as a colorless oil. IR: 1735, 1591, 1372, 1253, 1158 cm^{-1}; ^1H NMR: ($CDCl_3$): δ 7.20 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.02 (dd, *J* = 7.8, 4.9 Hz, 1H) 4.72 (s, 2H), 4.12 (dq, *J* = 6.3, 0.8 Hz,, 2H) 2.93 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* =7.6 Hz, 2H), 1.24(t, *J* = 6.7 Hz, 3H) 0.94 (s, 9H), 0.10 (s, 6H);^{13}C NMR; ($CDCl_3$): δ 173.0, 141.6, 140.5, 128.4, 126.9, 126.0, 124.0, 65.0, 60.4, 35.9, 30.9, 25.9, 14.2, -5.2.

3-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)propanal (29). The propanoate ester **28a** prepared above (1.4 g, 5.03 mmol) was dissolved in DCM (10 mL) and cooled to –78 ºC under N_2. The solution was treated dropwise with a 1.5 M solution of DIBAL-H (3.36 mL, 5.03 mmol) in toluene over a period of 30 min. Stirring was continued for 2 h at –78 ºC until TLC analysis indicated the complete conversion of starting material. The reaction was quenched by drop-wise addition of methanol (10 mL), followed by the drop-wise addition of 1 M HCl (15 mL). The aqueous layer was separated and extracted with DCM (2 × 50 mL). All of the combined organic layers were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanal (**29,** 1.20g, 89%) as a colorless oil. This compound was carried forward without further purification.

4-((3-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)propyl)amino)isoindoline-1,3-dione (30). To a solution of 3-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)propanal (**29**, 1.20 g, 4.32 mmol) in DMF (1.5 mL) was added AcOH (0.8 mL) and the solution was stirred for 10 min. To this reaction mixture, 4-aminophthalimide (**6**, 0.35g, 2.16 mmol) was added and stirring was

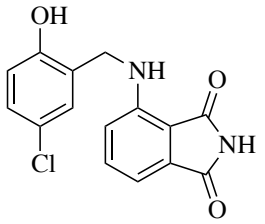
continued at 23 ºC for 1 h. An additional 1 mL of DMF was added bringing the volume to 3.3 mL. The reaction was cooled to 0 ºC and $NaBH(OAc)_3$ (1.42 g, 6.50 mmol) was added portion-wise to the reaction. Stirring was continued at this temperature for 30 min, and then the reaction was gradually warmed to 23 ºC and stirred for 18 h. The crude reaction mixture was poured into de-ionized water, extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 mL) and saturated NaCl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 1 mL of EtOH and the solution was heated at 50 ºC for 10 min under N_2. The resulting solid was filtered and washed with EtOH (2 × 10 mL). The EtOH solution was concentrated under vacuum and subjected to chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluted with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **30** (385 mg, 21%) as a yellow solid, mp 223-224 ºC. This compound was carried forward without further purification

4-((3-(3-(Hydroxymethyl)phenyl)propyl)amino)isoindoline-1,3-dione (31). A solution of 3-hydroxymethyl silyl ether **30** (0.37 g, 0.88 mmol) in 7 mL of THF was stirred under nitrogen at 23 °C and 1.0 M TBAF in THF (1.75 mL, 1.75 mmol) was added. When TLC analysis indicated the complete conversion of the silyl ether, de-ionized water (5.0 mL) was added and the THF was evaporated under vacuum. The mixture was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with saturated NaCl (50 mL), dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluted with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **31** (121 mg 72%) as a yellow solid mp 147-149 ºC. IR (nujol); 3378, 1758 1623, 1213, 972 cm^{-1} ; ^1H NMR (DMSO-d_6): δ 10.93 (s,1H), 7.53 (t, J = 7.7 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.15 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 6.54 (t, J = 5.9 Hz, 1H), 5.11 (t, J = 5.7 Hz, 2H), 4.45 (d, J = 5.7 Hz, 2H), 3.28 (t, J = 6.7 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 1.86 (quintet, J = 7.1 Hz, 2H). ^{13}C NMR

(DMSO-d_6): δ 171.9, 169.8, 146.7, 143.1, 136.4, 134.1, 133.7, 128.5, 127.1, 126.8, 124.5, 116.9, 111.2, 110.3, 63.4, 41.9, 32.8, 30.8.

1.6.2 One carbon linker in BfrB/Bfd chemical probes

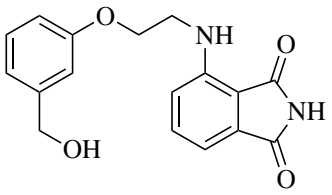
Synthesis of (34)



4-((5-Chloro-2-hydroxybenzyl)amino)isoindoline-1,3-dione(34). To a solution of 5-chlorosalicylicaldehyde (**33**, 0.52 g, 3.34 mmol) in DMF (1.5 mL) was added AcOH (0.8 mL) and the solution was stirred for 10 min. To this reaction mixture, 4-aminophthalimide **6** (0.27 g, 1.67 mmol) was added and stirring was continued at 23 ºC for 1 h. An additional 1 mL of DMF was added bringing the volume to 3.3 mL. The reaction was heated to 90 ºC for 2 h, and then cooled to room temperature. $NaBH(OAc)_3$ (1.1 g, 5.01 mmol) was added portion-wise to the reaction at 0 ºC. Stirring continued at this temperature for 30 min, and then the reaction was gradually allowed to attain 23 ºC and stirred for 18 h. The crude reaction mixture was poured into de-ionized water, extracted with EtOAc (3 × 75 mL), and the combined organic layers were washed with $NaHCO_3$ (2 × 50 mL) and NaCl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 1 mL of EtOH and the solution was heated at 50 ºC for 10 min under N_2. The resulting solid was filtered and washed with EtOH (2 × 10 mL). The EtOH solution was concentrated under vacuum and subjected to chromatography (using silica gel pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluted with 20% EtOAc/hexane to afford the isoindoline-1,3-dione **34** as an orange solid (210 mg, 58%), mp 235-236 ºC. ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 10.4 (s, 1H) 7.58 (dd, J = 8.4, 7.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.93 (dd, J = 8.1, 0.9 Hz, 1H), 6.86 (dd, J = 8.1, 0.9 Hz, 1H)

6.75 (t, J = 6.2 Hz, 1H), 4.55 (d, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 172.0, 169.7, 157.2, 146.4, 136.4, 134.5, 130.2, 122.9, 120.5, 117.1, 114.9, 111.7, 110.8, 40.6.

Synthesis of (43)



Ethyl 2-(3-formylphenoxy)acetate (39). To a solution of 3-hydroxybenzaldehyde (**38**, 1.0 g, 8.2 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in 10 mL of CH_3CN was added ethyl bromoacetate (906 μL, 8.2 mmol) under N_2. The mixture was heated at 90 ºC for 4 h. After cooling the reaction mass to room temperature, the solution was poured into water and extracted with EtOAc (3 × 50 mL). All of the combined organic layers were washed with saturated NaCl and dried over (Na_2SO_4). The solvent was evaporated and the residue was subjected to silica-gel chromatography using 10% EtOAc/hexane to afford (1.53 g, 90%) of ethyl 2-(3-formylphenoxy)acetate **39** as a colorless oil. IR: 1750, 1695,1587, 1481, 1199, 912 cm^{-1}; ^{1}H NMR (CDCl3): δ 9.97 (s, 1H), 7.52 (dt, J = 8.7, 7.5, 2.6 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.38 (dd, J = 3.7, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ; 191.8, 168.4, 158.4, 137.8, 130.3, 124.2, 122.1, 112.9, 65.4, 61.6, 14.2.

Ethyl 2-(3-(hydroxymethyl)phenoxy)acetate(40). A solution of ethyl 2-(3-formylphenoxy)acetate **39** (1.53 g, 7.4 mmol) in 10 mL of EtOH was treated portion-wise with $NaBH_4$ (0.28 g, 7.4 mmol) at 0 ºC. The mixture was gradually warmed to room temperature and stirred for an additional 30 min. The EtOH was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with 100 mL of a 1:1 DCM/ether mixture. The organic layer was washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent afforded ethyl 2-(3-(hydroxymethyl)phenoxy)acetate (**40,** 0.98 g, 63%) as a colorless oil. IR: 3279, 1743, 1589, 1487, 1204, 1155, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.28 (d, J = 7.9 Hz, 1H), 6.95 (d, J

= 2.3 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.83 (dd, *J* = 8.1, 2.4 Hz, 1 H), 4.66 (d, *J* = 4.6 Hz, 2H), 4.63 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.73 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ; 168.2 158.7, 142.7, 129.7, 120.1, 113.9, 113.1, 65.4, 65.1, 61.4, 14.2.

Ethyl 2-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenoxy)acetate (41) A stirred solution of ethyl 2-(3-(hydroxymethyl)phenoxy)acetate (**40,** 0.98 g, 4.7 mmol) in DMF (10 mL) was cooled to 0 ºC under N_2 and imidazole (0.63 g, 9.3 mmol) was added. The resulting solution was stirred for 20 min and the TBS chloride (0.84 g, 5.6 mmol) as a solution in DMF (10 mL) was added dropwise over a period of 15 min. The reaction mixture was warmed to room temperature and stirred until TLC analysis indicated the complete absence of the phenolic compound. The crude reaction was poured into water (50 mL), extracted with ether (3 × 40 mL), and the combined organic layers were washed with saturated NaCl (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography to afford ethyl 2-(3-(((*tert* butyldimethylsilyl)oxy)methyl)phenoxy)acetate (**40** ,1.24 g, 83%) as a colorless oil. IR: 1762, 1739, 1593, 1468, 1560, 1203, 1164, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.24 (d *J* = 7.9 Hz, 1H), 6.94 (t, *J* = 2.5 Hz, 2H), 6.78 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.71 (s, 2H), 4.62 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.5, 158.4, 143.8, 129.8, 119.7, 113.6, 112.6, 65.9, 61.8, 26.4, 18.9, 14.6, -4.8.

1.6.3 Anticancer Agents

***N*-(4-(2-Methyl-4-oxopentan-2-yl)thio)phenyl)acetamide (48)**. To a stirred solution of acetamidothiophenol **46** (25.0 g, 149.7 mmol) in dry chloroform (200 mL) was added triethylamine (21.0 mL, 149.7 mmol), followed by addition of mesityl oxide **47** (17.0 mL, 149.7 mmol). The resulting slurry was heated to reflux (bath temperature 70 ºC). Two additional portions of triethylamine (10.5 mL, 74.5 mmol) and mesityl oxide (8.6 mL, 74.5 mmol) were added at regular intervals of 4 h, and the resulting solution was refluxed for 16 h after the final addition. The resulting reaction mixture was cooled, filtered through Celite and washed with chloroform (2 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous NaCl,

dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil. The crude reaction mixture was then purified by silica gel column chromatography and eluted with DCM:ethyl acetate (1:1) to afford **48** (27.8 g, 70%) as a pale yellow solid, mp 49-51 ºC. IR: 3310, 1699, 1676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (br s, 1H), 7.53 (d, 1H, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 2.65 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 206.9, 168.6, 139.0, 138.3, 126.2, 119.6, 54.3, 47.0, 32.1, 28.0, 24.5.

***N*-(4-((4-Hydroxy-2,4-dimethylpentan-2-yl)thio)phenyl)acetamide (49).** To a stirred solution of methyllithium in ether (198 mL, 316.5 mmol, 1.6 M) in tetrahydrofuran (300 mL) at -50 ºC was added dropwise **48** (28 g, 105.5 mmol) in tetrahydrofuran (200 mL) over 30-45 min. The reaction mixture formed a white precipitate, which was slowly warmed to room temperature over a period of 3 h and stirred at this temperature for 1 h. The reaction mass was then cooled to 0 ºC, and the mixture was quenched by dropwise addition to ice water (150 mL). After adjusting the solution to pH 6-7 by addition of 6 M aqueous HCl, the solution was extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were washed with saturated NaCl (1 × 150 mL), dried ($MgSO_4$), and concentrated under vacuum to afford a dark brown liquid. To the crude mixture was added chloroform (60 mL) with cooling to 0 ºC for 1 h, which afforded a yellow solid. The solid was filtered and dried under vacuum to afford **49** (18 g, 61%) as a pale yellow solid, mp 141-142 ºC. IR: 3400, 3303, 1676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68 (br s, 1H), 7.52 (m, 4H), 3.50 (br s, 1H), 2.19 (s, 3H), 1.77 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.4, 138.8, 138.1, 126.3, 119.6, 72.0, 52.0, 49.2, 32.2, 30.8, 24.6.

***N*-(2,2,4,4-Tetramethylthiochroman-6-yl)acetamide (50)**. To a stirred solution of **49** (18 g, 63.9 mmol) in chlorobenzene (125 mL) at room temperature was added portion-wise anhydrous aluminum chloride (10.2 g, 76.7 mmol) over a period of 45 min, and reaction mixture was refluxed for 90 min. The reaction mixture was cooled to 23 ºC and quenched with ice cold water (150 mL) to give a thick suspension. The solid was removed by filtration through Celite and washed with

ethyl acetate (2 × 100 mL). The layers were separated, and the aqueous layer was extracted with additional ethyl acetate (2 × 100 mL). The combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil. The crude product was purified on a silica gel column using hexanes:ethyl acetate (1:1) to afford the product **50** (15.0 g, 89%) as a pale yellow solid, mp 105-107 ºC. IR: 3295, 1662 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 (br s, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 2.16 (s, 3H), 1.92 (s, 2H), 1.39 (s, 6H), 1.35 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.3, 143.4, 135.1, 128.4, 128.2, 118.7, 118.2, 54.4, 42.0, 35.7, 32.4, 31.4, 24.4.

2,2,4,4-Tetramethylthiochroman-6-amine hydrochloride (51). To a stirred solution of **50** (15.0 g, 56.9 mmol) in methanol (75 mL) was added 6 M aqueous HCl (75 mL). The reaction mixture was heated to 90 ºC for 1 h, followed by cooling to room temperature. The reaction was concentrated to 1/4 of its initial volume. The resulting mixture was cooled to 0 ºC and maintained at this temperature for 1 h to yield a solid. This material was filtered and dried under vacuum to afford **51** as a white solid (14.0 g, 95%), mp 208-209 ºC. IR: 2922, 2853 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.08 (s, 2H), 7.48 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 1.94 (s, 2H), 1.42 (s, 6H), 1.40 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 144.2, 132.0, 130.0, 129.1, 122.0, 121.2, 53.5, 42.6, 35.8, 32.6, 31.6.

Phenyl 3-methylbut-2-enoate (54). To an oil-free suspension of NaH (1.34 g, 56.0 mmol) in anhydrous THF (20 mL) at 0 ^{o}C (ice bath) was added over a 5-min period with stirring a solution of phenol **52** (5.0 g, 53 mmol) in THF (55 mL). The solution was stirred for 10 min and treated with a solution of 3-methylbut-2-enoyl chloride **53** (7.0 g, 59 mmol) in THF (25 mL) over a 5-min period at 0 ºC, and was then allowed to warm to 23 ºC for 3 h. The white suspension was transferred to a separatory funnel containing water (150 mL) and acetic acid (1 mL) and was gently shaken. The mixture was extracted with ether (150 mL), and the extract was washed with saturated NaCl (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to give a light yellow oil. The product was

purified on a 40-cm x 2.5-cm silica gel column eluted with 10% ether in hexanes to give **54** (8.4 g, 89%) as a colorless oil. IR: 1738, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ d 7.38 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.91 (m, 1H,), 2.22 (d, *J* = 1.8 Hz, 3H), 1.96 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (CDCl3): δ 164.9, 159.9, 150.7, 129.3, 125.5, 121.8, 115.3, 27.6, 20.5.

4,4-Dimethylchroman-2-one (55). Into a 500-mL, three-necked, round-bottomed flask equipped with a stir bar, an addition funnel and a condenser (drying tube) was placed DCM (164 mL) to which was added $AlCl_3$ (9.87 g, 74.0 mmol). The resulting suspension was stirred and cooled to 0 ^{o}C , and a solution of **54** (7.4 g, 42.0 mmol) in DCM (40 mL) was added dropwise. The reaction was gradually warmed to room temperature, and stirring was continued for 72 h. The resulting brown solution was added to a mixture of ice and saturated NaCl, the layers were separated, and the aqueous layer was extracted with DCM (100 mL). The combined organic layers were washed with saturated NaCl (2 × 75 mL), dried ($MgSO_4$), filtered, and concentrated to give a brown oil, which was purified by silica gel chromatography using 10% ether in hexanes to give **55** (5.00 g, 68%) as a colorless oil. IR: 1769 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.25 (td, *J* = 7.9, 1.7 Hz, 1H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 7.05 (dd, *J*= 8.0, 1.4 Hz, 1H), 2.62 (s, 2H, CH_2), 1.36 (s, 6H, 2 CH_3); ^{13}C NMR ($CDCl_3$): δ 168.1, 150.6, 131.7, 128.2, 124.8, 124.4, 117.1, 45.6, 33.2, 27.6.

2-(4-Hydroxy-2,4-dimethylpentan-2-yl)phenol (56). A solution of **55** (2.5 g, 14.2 mmol) in dry ether (40 mL) was placed in a 250-mL, three-necked, round-bottomed flask equipped with a stir bar, a septum, and a condenser. The solution was cooled to -45 ^{o} C (dry ice/acetonitrile bath), and an ether solution of methyllithium (1.6 M, 22.2 mL, 35.5 mmol) was added over 20 min. The reaction was stirred for 18 h with gradual warming to room temperature. The reaction was carefully poured into a mixture of ice and saturated NH_4Cl and shaken. The layers were separated, and the aqueous layer was washed with ether (2 × 50 mL). The combined ether layers were washed with

saturated NH_4Cl and water, dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting oil solidified on standing at room temperature. The solid was triturated with 1% ether in pentane and filtered to give **56** (2.72 g, 92%) as a white solid, mp 86-88 °C. IR: 3540, 3259, 1372, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.07 (td, *J* = 7.7, 1.7 Hz, 1H,), 6.88 (td, *J*=7.5, 1.4 Hz, 1H,), 6.65 (br s, 1H, phenol OH), 6.62 (dd, *J* = 7.9, 1.4 Hz, 1H), 2.22 (s, 2H, CH_2), 1.74 (br s, 1H, OH), 1.48 (s, 6H, $2CH_3$), 1.12 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 154.9, 134.4, 127.8, 127.5, 120.7, 117.5, 73.2, 52.4, 37.5, 31.0, 30.9.

2,2,4,4-Tetramethylchroman (57) A 100-mL, one-necked, round-bottomed flask was charged concentrated phosphoric acid (10 mL). The acid was heated to 100 °C, **56** (2.08 g 10 mmol) was added, and the mixture was stirred for 1 h. The crude reaction mixture was cooled, diluted with water, and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$),filtered, and concentrated under vacuum. The resulting oil was passed through a column of silica gel using hexanes as the eluent to give **57** (1.81 g, 95%) as a colorless oil. IR: 1367, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.99 (td, *J* = 7.9, 1.4 Hz, 1H) , 6.83 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 1.76 (s, 2H, CH_2), 1.28 (s, 6H, $2CH_3$), 1.27 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 152.5, 131.5, 127.0, 126.8, 120.6, 117.9, 74.3, 49.3, 32.8, 30.8, 28.6.

2,2,4,4-Tetramethyl-6-nitrochroman and 2,2,4,4-tetramethyl-8-nitrochroman A 25-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, and a nitrogen inlet was charged with **57** (1.00 g, 5.3 mmol) and freshly distilled acetic anhydride (1 mL). The solution was cooled to -15 °C (ice/methanol bath), and a cold solution of concentrated nitric acid (577 μL) in acetic anhydride (1 mL) was added dropwise over 15 min. The reaction was stirred at -5 °C for 30 min and then diluted with DCM and washed with saturated $NaHCO_3$. The $NaHCO_3$ wash was back-extracted with 20 mL of DCM, and the combined organic layers were washed with

water and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum to give 1.2 g of the crude product which was taken directly to the reduction step.

2,2,4,4-Tetramethylchroman-6-amine (58). A 100-mL-round bottomed flask, equipped with a condenser and stir bar was charged with the nitro compound prepared above. To this solution, Fe powder (0.86 g, 15.3 mmol) and NH_4Cl (0.27 g, 5.10 mmol) were added in a 4:1 mixture of $EtOH/H_2O$. The mixture was heated to 80 ^{o}C for 3 h, and then it was filtered through Celite®. The filter cake was rinsed with $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaCl and dried over (Na_2SO_4). Removal of the solvent and purification by silica gel chromatography afforded **58**, the 6-isomer as a yellow oil (the 8-isomer eluted first) IR: 3435, 3358, 3221, 1627, 1498 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1H,), 6.61 (d, J = 7.8 Hz, 1H,), 6.47 (dd, J = 7.8, 2.7 Hz, 1H,), 3.50 (br s, 2H, NH_2), 1.78 (s, 2H), 1.31 (s, 6H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 145.4, 139.5, 132.3, 118.3, 114.9, 113.4, 73.8, 49.3, 32.6, 31.0, 28.4.

6-Isothiocyanato-2,2,4,4-tetramethylthiochroman (59). A 100-mL, one–necked, round bottomed flask equipped with a condenser and a stir bar was charged with 2,2,4,4-tetramethylthiochroman-6-amine (**58**, 0.258 g, 1 mmol), Et_3N (140 µL, 1mmol) and CS_2 (604 µL, 10 mmol) under N_2. After stirring for 10 minutes, 5 mL of ethanol was added, and stirring was continued for 1 h. The solution was then cooled to 0 ºC, and solutions of di-*tert*-butyl dicarbonate (0.20 g, 0.9 mmol) and 4-dimethylaminopyridine (4 mg, 3 mol%) in 1 mL of ethanol were added consecutively. The resulting mixture was gradually warmed to room temperature over 30 min. The solvent was then removed on the rotary evaporator to provide **59** (0.24 g, 90%) as a thick yellow oil. IR: 2961, 2920, 2113 (NCS), 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.32 (d, J= 2.2 Hz, 1H), 7.07 (d, J = 8.31 Hz, 1H), 6.92 (dd, J = 8.3, 2.2 Hz, 1H), 1.93 (s, 2H), 1.41 (s, 6H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$) : δ 144.79, 133.5, 129.4, 129.3, 128.0, 124.7, 123.8, 54.3, 42.9, 36.2, 32.8, 32.0.

6-Isothiocyanato-2,2,4,4-tetramethylchromane (60). A 100-mL, one–necked, round-bottomed flask equipped with a condenser and a stir bar was charged 6-isothiocyanato-2,2,4,4-tetramethylchroman **58** (0.21 g, 1 mmol), Et_3N (140 μL, 1.0 mmol) and CS_2 (604 μL, 10 mmol) under N_2. After stirring for 10 min, 5 mL of ethanol was added, and stirring was continued for 1 h. The solution was then cooled to 0 ºC, and two separate solutions of di-*tert*-butyl dicarbonate (0.20 g, 0.9 mmol) and 4-dimethylaminopyridine (4 mg, 3 mol%) in 1 mL of ethanol were added consecutively. The resulting mixture was gradually warmed to room temperature over 30 min. Then the solvent was then removed on the rotary evaporator to provide **60** (0.23 g, 94%) as a thick yellow-orange oil. IR: 2971, 2120 (NCS), 1487 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.15 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 8.6, 2.5 Hz, 1H), 6.92 (d, J = 8.6, 1H), 1.82 (s, 2H), 1.36 (s, 6H), 1.33 (s, 6H) ; ^{13}C NMR ($CDCl_3$): δ 152.4, 150.2, 133.3, 125.0, 123.7, 119.5, 75.6, 49.1, 33.1, 28.9.

General procedure for the synthesis of carbothioamides (62a-b, 64a-c and 65):A 50-mL, round bottomed flask was charged with **61a-b** or **63a-c** in 5 mL of hot THF under N_2. The resulting solution was cooled to 0 °C, and **58** or **60** in 5 mL of hot THF was added dropwise over a 20 min. The solution was gradually warmed to room temperature with continued stirring overnight. Upon completion, the solution was concentrated under vaccum, and the residue was taken up in water and extracted with EtOAc (3×). The combined organic layers were washed with brine and dried (Na_2SO_4) and concentrated. The resulting oil was dissolved in an ether/pentane mixture, which produced a precipitate of the compounds **62a-b, 64a-c** or **65**.

***N*-2-(4-Nitrophenyl)-*N*-(2,2,4,4-tetramethylthio-chroman-6-yl)hydrazine-1-carbothioamide (62a).** Tan solid, mp 181-183 °C, (0.142 g, 50%). IR (nujol): 15780, 1356, 1242 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.90 (s, 2H), 9.19 (s, 1H), 8.16 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 8.3, 1.7 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 9.1 Hz, 2H), 1.91 (s, 2H), 1.36 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 154.6, 152.5, 142.3, 139.5, 136.4, 128.6, 127.2,

126.3, 124.4, 112.2, 53.9, 42.4 35.9, 32.7, 31.6. Anal. Calcd for $C_{20}H_{24}N_4O_2S_2$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.71; H, 5.92, N, 13.31.

***N*-(2,2,4,4-Tetramethylthiochroman-6-yl)-2-(4-(trifluoromethyl)phenyl)hydrazine-1-carbothioamide (62b).** White solid, mp 163-165 °C (0.183 g, 71%). IR (nujol): 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.83 (s, 1H), 9.78 (s, 1H), 8.60 (s, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.4, 2.2 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 1.91 (s, 2H), 1.36 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 151.9, 142.7, 136.7, 128.3, 127.1, 126.7, 126.2 124.3 (q, J = 272.2 Hz) 123.6, 112.9, 53.9, 42.4, 35.7, 32.8, 31.7. Anal. Calcd for $C_{21}H_{24}F_3N_3S_2$: C, 57.38; H, 5.50; N, 9.56. Found: C, 57.15; H, 5.49, N, 9.29.

2-Nicotinoyl-*N*-(2,2,4,4-tetramethylchroman-6-yl)hydrazine-1-carbothioamide (64a)

White solid, mp 123-125 °C (0.133 g, 41%). IR (nujol): 1785, 1601 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.70 (s, 1H), 9.69 (s, 2H), 9.10 (d, J= 2.0 Hz, 1H), 8.75 (dd, J = 4.7, 1.7 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H) 7.55 (dd, J = 7.8, 4.9 Hz, 1H), 7.29 (s,1H), 7.10 (d, J = 7.2 Hz, 1H) 6.68 (d, J = 8.6 Hz, 1H), 1.81 (s, 2H), 1.29 (s, 12H); ^{13}C NMR (DMSO-d_6): δ 165.3, 151.6, 147.9, 142.9, 136.1, 134.7, 127.8, 126.9, 126.5, 123.1, 61.5, 42.8, 36.1, 32.5, 31.4. Anal. Calcd for $C_{20}H_{24}N_4O_2S$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.37; H, 6.29, N, 14.23.

2-(4-Nitrobenzoyl)-*N*-(2,2,4,4-tetramethylchroman-6-yl)hydrazine-1-carbothioamide (64b). White solid, mp 171-172 °C (0.124 g, 43%). IR (nujol): 1782, 1575, 1354 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.73 (s, 2H), 8.34 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H), 7.29 (s, 1H), 7.11 (dd, J = 8.5, 1.8 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 1.81 (s, 2H), 1.29 (s, 12H); ^{13}C NMR (DMSO-d_6): δ 178.5, 164.5, 149.5, 138.4, 131.7, 130.5, 129., 123.4, 116.8, 74.2, 48.2, 32.5, 30.6, 28.1. Anal. Calcd for $C_{21}H_{24}N_4O_4S$: C, 58.86; H, 5.65; N, 13.08. Found: C, 58.77; H, 5.71, N, 13.05.

***N*-(2,2,4,4-Tetramethylchroman-6-yl)-2-(4-(trifluoromethyl)benzoyl)hydrazine-1-carbothioamide (64c).** White solid, mp 118-119 °C (0.152 g, 52%). IR (nujol): 1745 cm^{-1};

^{1}H NMR: (DMSO-d_6): δ 10.7 (s, 1H), 9.70 (s, 2H), 8.15 (d, J = 8.2 Hz, 2H), 7.91(d, J = 8.3 Hz, 2H) 7.29 (s, 1H), 7.12 (dd, J = 8.6, 2.1 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 1.81 (s, 2H), 1.30 (s, 6H), 1.29 (s, 6H) ^{13}C NMR: (DMSO-d_6): δ 178.6, 163.2, 156.1, 144.2., 142.9, 138.9, 136.1, 129.5, 127.1, 125.7, 123.3, 122.7, 119.4 (q, J= 270.2 Hz), 118.8, 113.4, 53.9, 42.4, 40.4, 35.7, 32.7, 31.6. Anal. Calcd for $C_{22}H_{22}F_3N_3O_2S$: C, 58.52; H, 5.36; N, 9.31. Found: C, 58.38; H, 5.47, N, 9.35.

2-nicotinoyl-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)hydrazine-1-carbothioamide (65).

White solid, mp 151-153 °C (0.113 g, 55%). IR (nujol): 1778 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 9.77 (s, 2H), 9.10 (d, J = 2.2 Hz, 1H), 8.75 (dd, J = 4.7, 1.5 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 7.56 (dd, J = 7.8, 4.9 Hz, 2H), 7.19 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 1.92 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 177.6, 164.7, 152.4, 148.9, 141.9, 136.2, 135.7, 135.6, 128.2, 126.9, 126.8, 123.4, 53.5, 41.9, 35.2, 32.3, 31.2. Anal. Calcd for $C_{20}H_{24}N_4OS_4$: C, 59.97; H, 6.04; N, 13.99. Found: C, 59.78; H, 6.09, N, 13.89.

CHAPTER II

SYNTHESIS OF BIOACTIVE HETEROCYCLIC SCAFFOLDS

2.1 Introduction

The need for synthesis and optimization studies to efficiently prepare biologically active heterocyclic scaffolds has increased. Synthetic chemists look for the most viable and cost-effective routes to simplify the total synthesis of various targets. More importantly, recent efforts in drug discovery have amplified the need to develop high atom economy and eco-friendly ways to access heterocyclic frameworks. In past years, the use of transition metal catalysts to access carbon-carbon bonds has dominated organic chemistry and has been a central topic in the synthesis of heterocyclic scaffolds. However, utilizing transition metal catalysts in late-stage drug synthesis requires the use of special purification techniques to remove them from the final target.

Common purification methods such as filtration through Celite or silica gel chromatography may not always free the final product of these toxic metals. Therefore, it is crucial to formulate simple, transition metal-free methodologies to prepare heterocyclic scaffolds through carbon-carbon bond forming reactions. Zolpidem, a sedative, was previously synthesized in a 4-step fashion from 4-methylacetophenone in 66% yield.[38] However, the synthesis of Zolpidem was improved and obtained in 96% from 2-aminopyridines and Morita-Bayliss-Hillman acetates of nitroalkenes.[39]

Our research group is primarily involved in developing new drug molecules as antibiotic and anti-cancer candidates. Additionally, we strive to develop cost-effective, high atom economy synthetic methodology to important heterocyclic scaffolds such as quinazolinones, dihydroquinolines, indoles, naphthyridines, and chromanones. As an extension of this dissertation work, new methods have been developed to synthesize, 7-nitro-2-naphthoates, 6-nitro-1,2-dihydroquinolines

carboxylates, 1,8-naphthyridine carboxylates, and 4-chromanones as well as an efficient synthesis of 2-fluoro-5-nitronicotinaldehyde.

2.1.2 A Mortia-Bayliss-Hillman inspired synthesis of heterocyclic scaffolds

The Morita-Bayliss Hillman (MBH) reaction has proven to provided access to a wide variety of pharmaceuticaly important scaffolds.[40] Since it was first introduced in 1941, the scope of the reaction has broadened dramatically (Figure 2.1) and its versatility has been exploited extensively by synthetic chemists.[41-44]

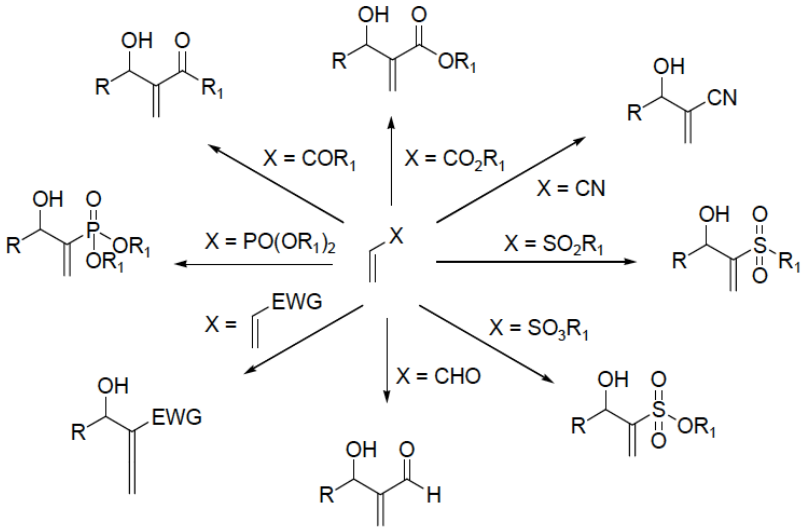


Figure 2.1 Scope of Morita-Bayliss-Hillman Reaction

The MBH reaction is a carbon-bond forming reaction resulting in allylic alcohols or (MBH adducts) from electrophiles and activated alkenes.[41-44] The reaction is promoted by the addition of a tertiary amine or phosphine catalyst. In addition, these adducts, and their acetates have proven to be attractive synthons in building toward more complex molecular frameworks.[41-44] Recently, Reddy and co-workers published a thorough review on the impact and importance of the MBH reaction in medicinal chemistry.[42] In addition, synthetic chemists have been able to

access biologically active heterocyclic systems such as imidazopyridines[38], isoxazoles[43], and acridines[45] exhibiting anti-malarial activity.

2.2 Results and discussion.

2.2.1 Naphthoates, dihydroquinolines carboxylates and naphthyridine carboxylates from MBH acetates.

The current study was pursued with the goal of providing attractive heterocyclic scaffolds from MBH acetates. One of these scaffolds is naphthalene, which is the simplest bicyclic aromatic ring, and is frequently found in the molecular frameworks of anticancer agents (Figure 2.2).[45]

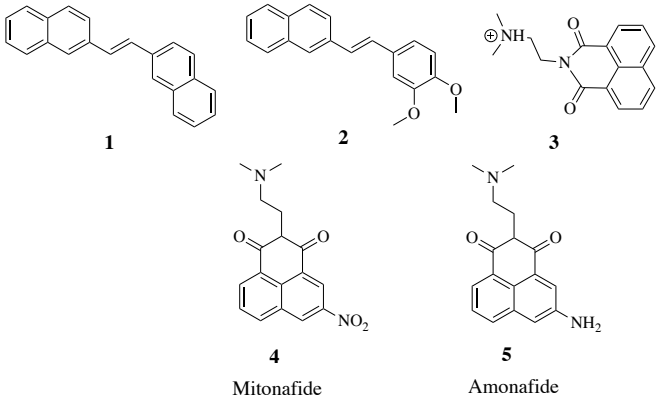
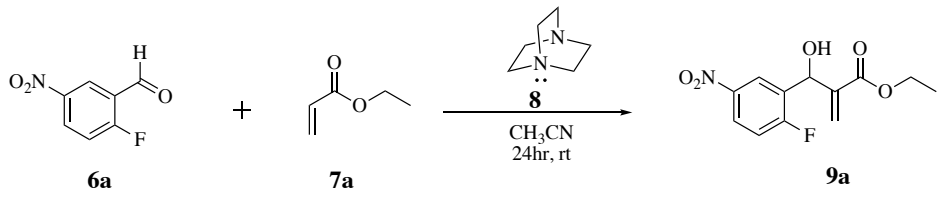


Figure 2.2 Naphthalene containing anticancer agents

Some of the methods for the synthesis of naphthalene-containing molecules involve transition metal catalysts such as $PdCl_2$, $GaCl_3$ and $TiCl_4$ which may require some type of purification step to limit metal contamination in the final products.[46-48] Our strategy to prepare highly substituted naphthalene containing compounds originated from the MBH reaction between 2-fluoro-5-nitrobenzaldehyde **6a** and ethyl acrylate **7a** in the presence of DABCO **8** to afford the desired MBH adduct **9a** (Scheme 2.1).



Scheme 2.1 Reaction rationale toward substituted naphthalenes

Originally, the reaction was performed at 23 ˚C using equimolar equivalents of **6a**, **7a** and **8.** Extractive work-up and ^{1}H NMR analysis of the product, revealed the presence of **9a**. One of the goals of this study was to afford a clean conversion of the MBH adducts and minimize purification steps enroute to our target compounds. Current methods involve the use of **7a** as a solvent and reactant, but still require purification by column chromatography.[49] More commonly however, the reaction is performed in a polar aprotic solvent using an excess of the activated alkene component.[50] This work focused on including electron withdrawing groups at C5 of an aromatic electrophile (Figure 2.3), which proved crucial in achieving maximum conversion to the corresponding adducts.[51]

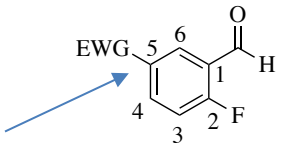
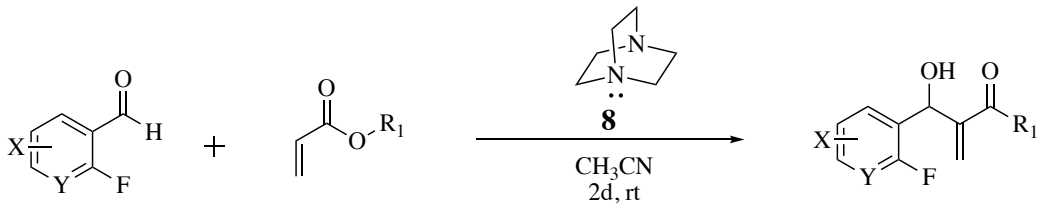


Figure 2.3 Illustration of C5 on electrophiles

With these guidelines in hand, we were able to broaden the scope of the reaction (Scheme 2.2) and synthesize new MBH adducts at 23˚C in excellent purity from their respective electrophiles and activated alkenes (Table 2.1) using 1.2 equivalents of **8** (Figure 2.4).



6a-c **7a-d** **9a-h**

X=NO_2, F, H
Y=C, N

R_1= OMe, OEt, CN, CF_3

Scheme 2.2 Reaction scope of MBH adducts

X	Entry	Alkene	MBH Adduct/ Yield (%)
NO_2	**Y=C, 6a**	**7a, R_1=OEt**	**9a (97%)**
NO_2	**Y=C, 6a**	**7b, R_1=OMe**	**9b (92%)**
NO_2	**Y=C, 6a**	**7c, R_1=OCF_3**	**9c (82%)**
NO_2	**Y=C, 6a**	**7d, R_1=CN**	**9d (80%)**
F	**Y=C, 6b**	**7a, R_1=OEt**	**9e (83%)**
F	**Y=C, 6b**	**7b, R_1=OMe**	**9f (99%)**
H	**Y=N, 6c**	**7a, R_1=OEt**	**9g (99%)**
H	**Y=N, 6c**	**7b, R_1=OMe**	**9h (96%)**

Table 2.1 Entries for MBH reaction

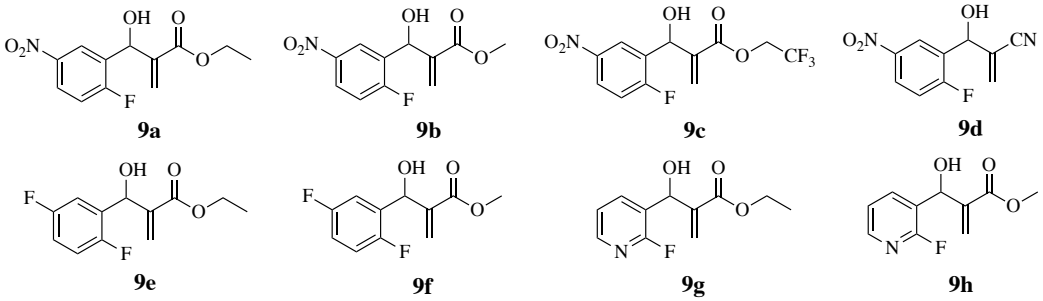


Figure 2.4 Synthesized MBH adducts

The mechanism of the MBH reaction has been reviewed extensively.[39,43-48,52] A plausible mechanism pertaining to our work is shown in (Figure 2.4).

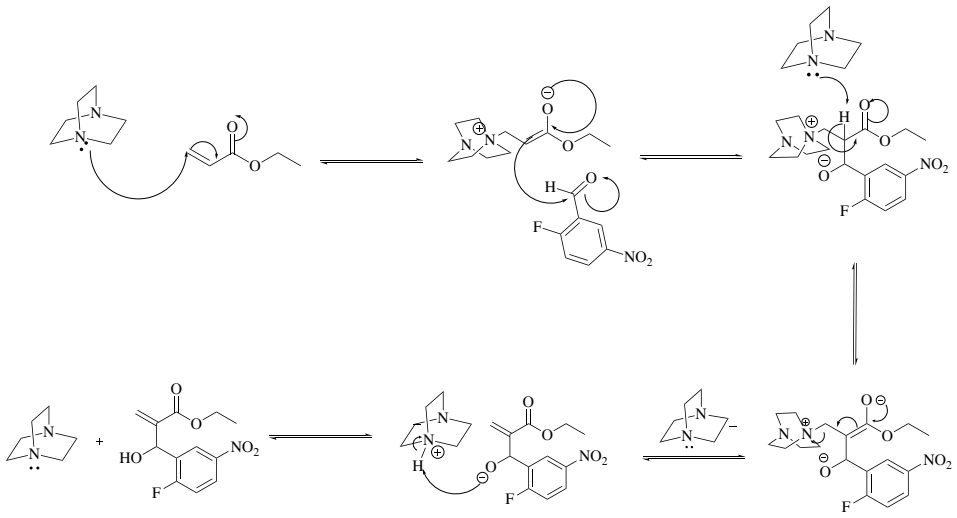
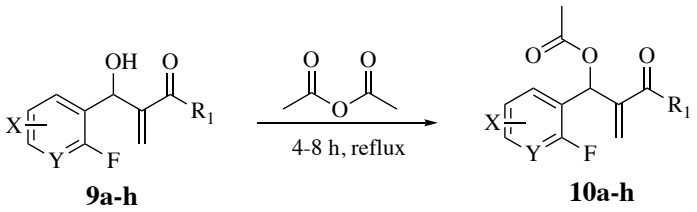


Figure 2.5 A plausible mechanism for MBH reaction

In order to furnish our desired naphthalene precursors, the MBH adducts **9a-h** were converted to their respective acetates. Common acylation methods of MBH acetates include the utilization of acetyl chloride or acetic anhydride in dichloromethane with pyridine as a base.[40-49] Acylation of MBH adducts greatly enhance their reactivity toward Michael reactions.[40-49] To our delight, the acetylation step proceeded cleanly by simply refluxing the corresponding adducts **9a-h** in 2 mL of acetic anhydride for 4-8 h. However, failure to remove excess acetic anhydride affected the next

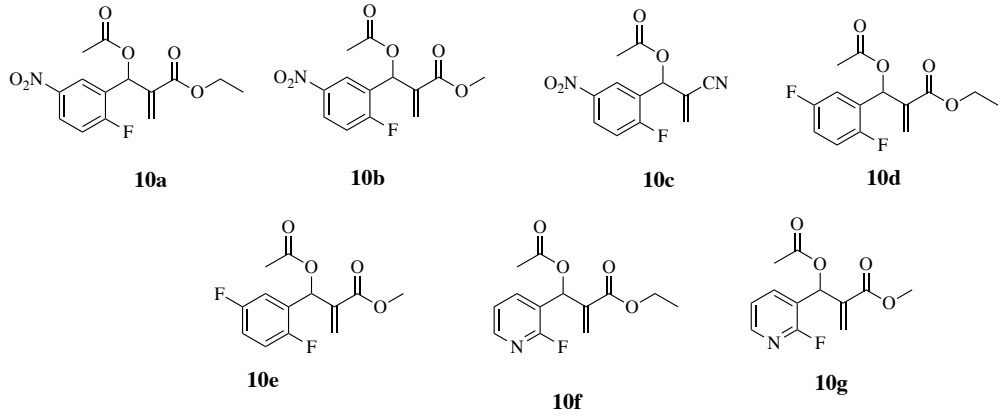
step in our synthesis. Therefore, all acetates were purified by column chromatography after extractive work-up furnishing the acetates (Figure 2.5) **10a-h** (Scheme 2.3) in 75-95% yield.



9a-h **10a-h**

Scheme 2.3 Synthesis of MBH acetates

Finally, our targeted naphthalene compounds were synthesized *via* a Michael elimanation-S_NAr from **10a-h** and active methylene compounds, e.g. ethyl cyanoacetate, ethyl nitroacetate and methyl phenylsulfonylacetate. The desired 7-nitro-2-naphthoates **11a-c** were synthesized (Scheme 2.4) in the presence of K_2CO_3 in 1 mL of DMF in excellent purity after extractive work-up. This was made

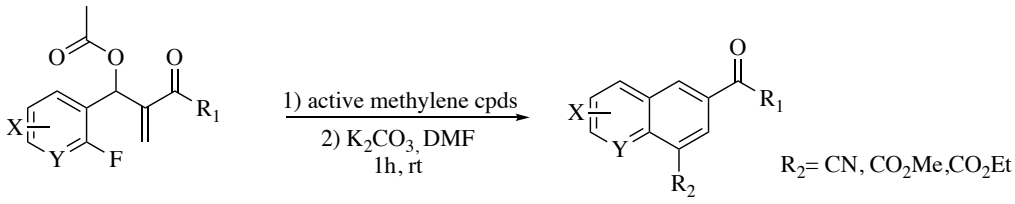


10a **10b** **10c** **10d**

10e **10f** **10g**

Figure 2.6 MBH acetates

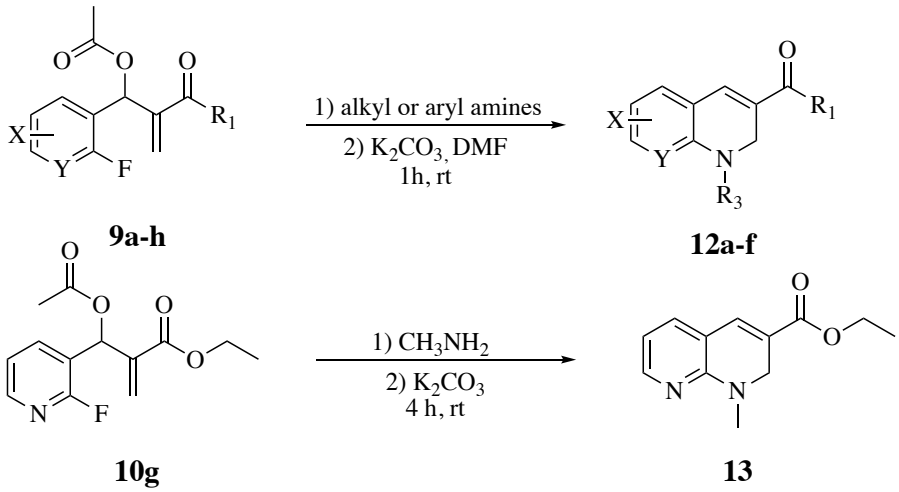
possible by using electrophiles bearing the fluorine atom at the C2 of the aromatic electrophile. The smaller fluorine atom is more reactive toward a S_NAr reaction.[49,53] This reactivity is enhanced by the nitro group para to the fluorine atom. The order of reactivity for a S_NAr reaction is as follows: fluoride > chloride > bromide > iodide.[53]



10a-h **11a-c**

Scheme 2.4 Synthesis of naphthoates

In addition to the synthesis of substituted naphthoates, we were able to synthesizee dihydroquinolines and naphthyridines from MBH acetates **10a-h** (Y=N**)** and aryl and alkyl amines in good to excellent yields without column chromatography. (Scheme 2.5).



9a-h **12a-f**

10g **13**

Scheme 2.5 Synthesis of dihydroquinoline and naphthyridine carboxylates

Previous methods involving the aza-Michael elimanation-S_NAr reaction between **10a-h** and amine components failed to provide the desired heterocyclic compounds without silica gel chromatography, even in the presence of excess amine.[50-53] In our case, through an acid-base work-up, any unreacted amine component was washed away, furnishing compounds **12a-f**. In the case of **13**, methylamine in water (12.1 M) was used as the solvent and reactant, and led to desired naphthyridine in 89%.

2.2.2 Conclusion

In summary, we were able to synthesize several bioactive heterocyclic systems by implementation of the MBH reaction, in good to excellent yields. The products were formed by a procedure that eliminated high temperatures, strong bases, and metal catalysts. Also, all products were obtained without the need for column purification, further establishing the versatility and elegance of our method.

2.2.3 Synthesis of 2-fluoro-5-nitronicontinaldehyde

Pyridines are present in a wide variety of compounds ranging from natural products, vitamins, and active pharmaceutical ingredients. The pyridine moiety, though hard to synthesize, is a vital scaffold (Figure 2.6) in drug discovery, which is why its synthesis has been so thoroughly investigated by orgnanic chemists.[54-57] Due to their small molecular size and high stability, pyridines can serve as bioisosteres for benzenes, amines and amides.[54] Recent procedures for pyridine synthesis include reactions between *N*-oxides and Grignard reagents,[55-57] cross-coupling reactions with transition metal catalysts [58-60] and multicomponent reactions.[61]

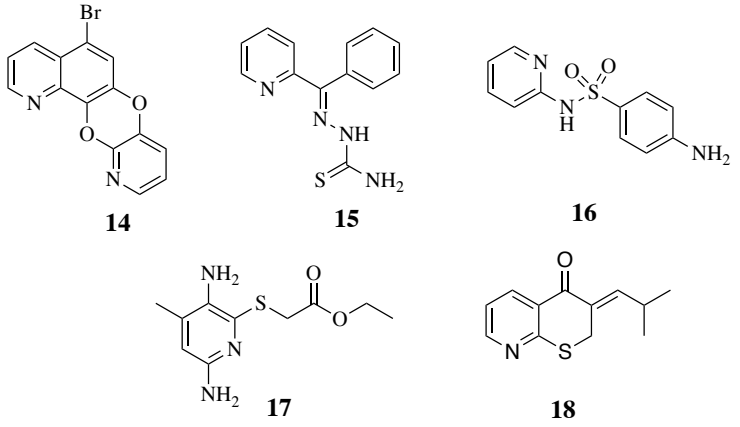
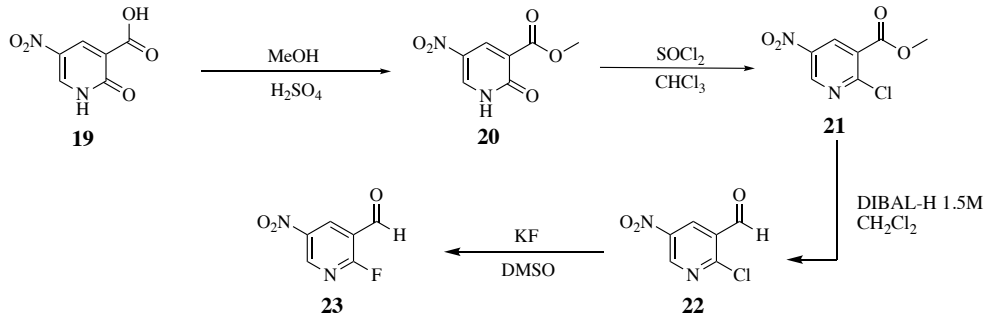


Figure 2.7 Anticancer and antimicrobial drugs bearing the pyridine moiety

This work was directed towards synthesizing an essential pyridine building block that could serve as the next pharmaceutically important scaffold. Coincidentally, our group strives to develop synthetic methodology geared toward the discovery and utilization of heterocyclic systems in drug

synthesis. By preparing 2-fluoro-5-nitronicotinaldehyde **23** from **19** (Scheme 2.6) we have simultaneously established a synthetic route to two unknown pyridine compounds and broken through the next frontier of accessible scaffolds.



Scheme 2.6 Synthesis of 2-fluoro-5-nitronicotinaldehyde (23)

Compound **19** was synthesized in excellent yield according to literature methods.[58-59] The esterification of **19** was achieved by refluxing in MeOH using a catalytic amount of H_2SO_4 to provide **20** in excellent yield as a white solid. The chlorination sequence of **20** was performed by using an excess of $SOCl_2$ in $CHCl_3$ to afford **21**. Several attempts were made to synthesize **22** by a reduction-oxidation sequence in the presence of the nitro functional group. Trial experiments with $LiAlH_4$, $NaBH_4$ failed in our system. An aromatic nitro group is readily reduced to an amine in the presence of LAH. On the other hand ,$NaBH_4$ is not known to be potent enough to efficiently reduce aromatic esters. The reduction of **21** to **22,** however, was successful achieved by using a slight excess of DIBAL-H (1.5 M/PhMe) at -78˚C (dry ice/acetone) bath. The hydride reagent was added dropwise over a 30-minute period. Failure to maintain the addition rate and low temperature resulted in an impurity (mixture of reduced alcohols) that was uncharacterizable by ^{1}H NMR. The reaction was quenched by the dropwise addition of a saturated aqueous solution of Rochelle's salt (potassium sodium tartrate solution) at -70˚C.[17] After extractive work-up and silica gel chromatography, the desired aldehyde was furnished as a yellow oil. Displacement of the chlorine substituent on **22** was conducted with KF (spray dried) in DMSO at 70˚C for 2 h. The fluorinated

compound **23** was obtained as a white solid after purification by column chromatography in 82%. The goal of this particular work was to synthesize nicontinaldehyde derivatives that were not previously known in the literature. As a result, we were able to synthesize two derivatives, **22** and **23,** which can serve as a starting point for building small molecule libraries or be used as potential starting points for future projects.

2.2.4 Conclusion

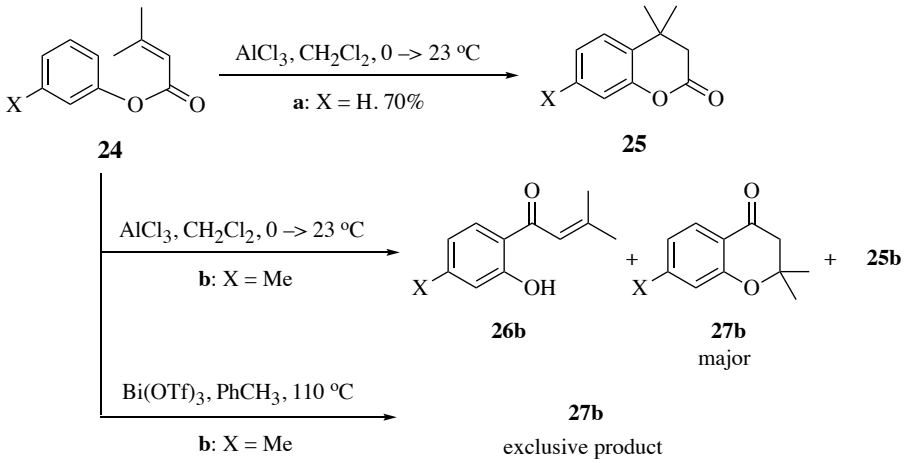
The synthesis of 2-fluoro-5-nitronicotinaldehyde was completed using a four-step sequence. In addition, because of the commercial availability of the reagents and starting material, this process was inexpensive and could easily be reproduced on a gram scale. Future investigations focusing on implementing 2-fluoro-5-nitronicotinaldehyde as a starting point for potential projects is ongoing in our group.

2.2.5 A bismuth (III) trifluoromethanesulfonate catalyzed route to 4-chromonones

Efficient methods to produce oxygen heterocycles for use as building blocks in natural product and drug synthesis is a worthy endeavor. Among the heterocyclic scaffolds containing oxygen, 4-chromanones are widely dispersed in nature and constitute valuable substrates for drug synthesis.[62-63] Various derivatives of this system also exhibit a wide range of pharmacological activities such as anti-bacterial[64], anti-HIV[65], anti-cancer[66] and anti-fungal[64]. Common methods for the synthesis of 4-chromanones have utilized a wide range of reaction protocols. One of the first generated 7-hydroxy-2,2-dimethyl-4-chromanone from highly activated resorcinol with 3,3-dimethylacrylic acid in the presence of $SbCl_3$.[66] More commonly, a number of chromanone derivatives were synthesized from chalcones, via an intramolecular Wittig strategy.[67] A more common method involved the acylation of *o*-hydroxyacetophenone with an aromatic acid chloride resulting in an aromatic ester, which was treated by base, undergoing a Baker-Venkataraman rearrangement to a 1,3-diaryl-1,3-diketone. The diarylketone then gave the a

2-arylchromanoe after a cyclocondensation reaction with acyl compounds.[68] Our approach involved the reaction of phenols bearing additional activating groups with 3,3-dimethylacrylic acid or crotonic acid to give a variety of tetra- and trisubstituted 4-chromanones, respectively. This was achieved by utilizing bismuth(III) trifluoromethanesulfonate to catalyze a one-pot conversion involving a tandem esterification–Fries rearrangement–oxa-Michael sequence.

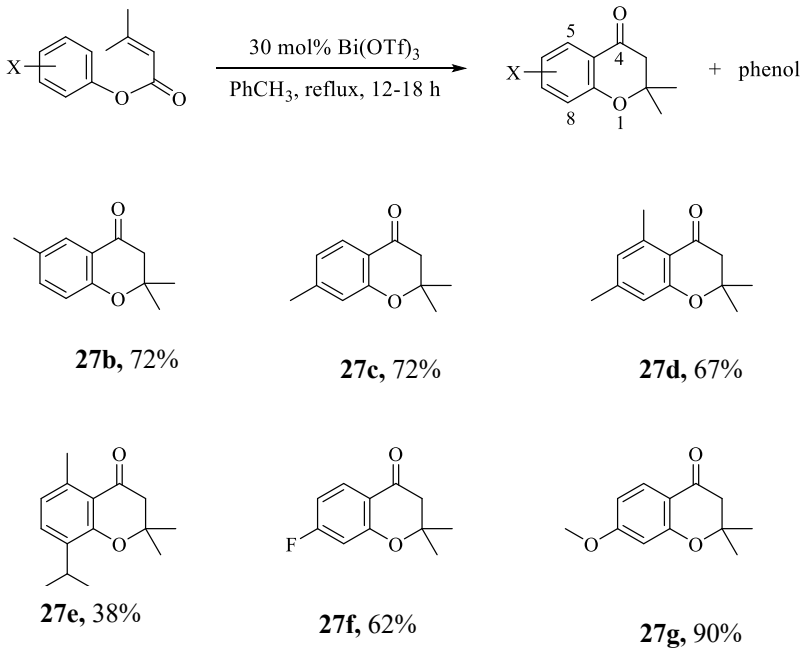
Initially, we attempted the Friedel–Crafts ring closure of phenyl 3,3-dimethylacrylate (**24**a, X = H) to other phenol-derived acrylate esters. Cyclization of **24**a is reported to give 4,4-dimethyl-2-chromanone (**25**) in >70% yield using 1.7 equiv of aluminum chloride in dichloromethane,[35] and we have successfully employed this procedure to access drug precursors for one of our projects.[34] Attempts to perform this reaction with esters incorporating more activated aryl groups, however, led to mixtures of several products. For example, **24b** (X = Me) produced 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**26b**, 18%) and 2,2,7-trimethyl-4-chromanone (**27**c, 65%) in addition to a small amount of **25b** (2%) the undesired product (Scheme 2.7).



Scheme 2.7. Friedel-Crafts reaction of aryl ester of 3,3-dimethylacrylic acid

After careful consideration, it was determined that the 4-chromanone product is likely derived from a Lewis acid promoted tandem esterification-Fries rearrangement-oxa Michael reaction. As a

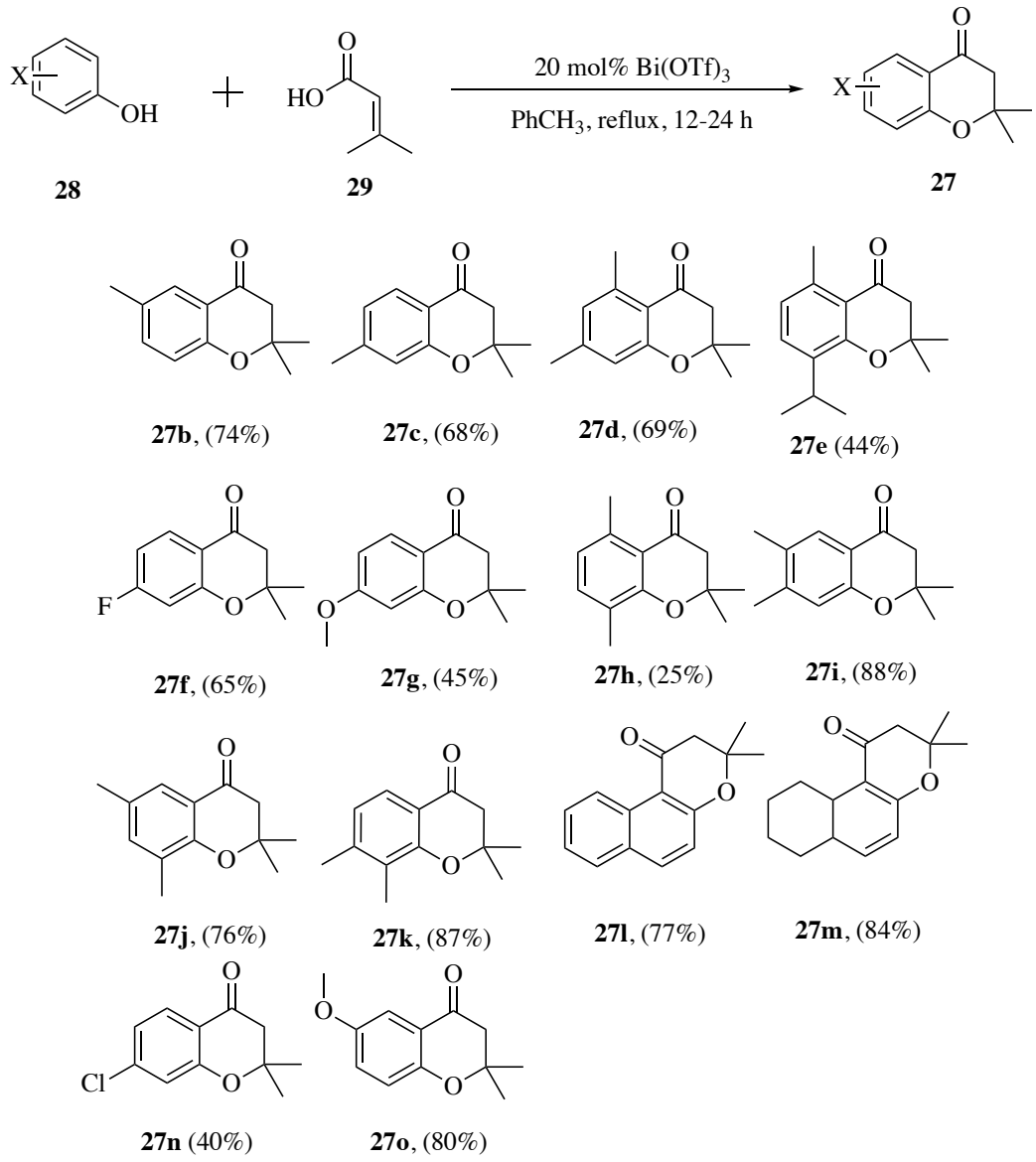
control experiment, this reaction with aluminum chloride resulted in mixtures of **25**, **26** and **27**. As a result, we carried out several investigations to selectively synthesize 4-chromanone derivatives. Our research group had previously described the use of bismuth(III) trifluoromethanesulfonate as a catalyst for Friedel-Crafts cyclizations of tertiary alcohols to produce chromans as well as a variety of other heterocycles.[69] Attempting to use the similar strategy with ester **24c** revealed that the reaction of activated aryl esters with bismuth(III) trifluoromethanesulfonate afforded >70% of **27c** as the exclusive cyclized product, along with *ca.* 10% of the phenol from acid catalyzed cleavage of the starting ester. Additional examples showed that this process appeared to be broadly applicable to many substrates (Scheme 2.8).



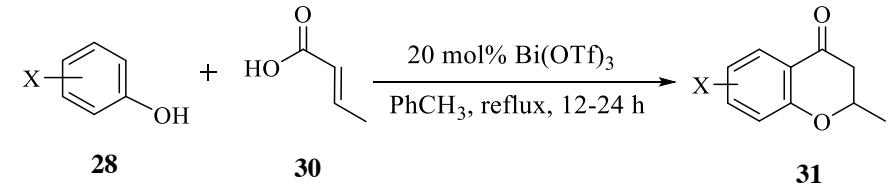
Scheme 2.8 4-Chromanones from aryl esters of 3,3-dimethylacrylic acid

We were primarily interested in developing an efficient, approach toward the preparation of 4-chromanones. Rather than include another step by preparing the corresponding esters from relatively expensive 3,3-dimethylacryloyl chloride, we attempted to prepare the 4-chromanones directly from the corresponding phenol and 3,3-dimethylacrylic acid using bismuth(III)

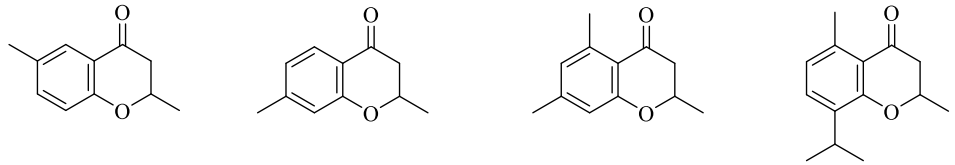
trifluoromethanesulfonate. This route selectively provided 4-chromanones in fair to excellent yields with none of the 2-chromanone products. Throughout the course of our investigation, the only substrates that failed to provide a clean conversion to the 4-chromanones were phenol and 2-methylphenol. Additionally, we were also successful in expanding this process to cyclizations with crotonic acid. To our displeasure, attempts to further expand this reaction for ring closures of *trans*-cinnamic acid gave uncharacterizable mixtures with poor yields of the desired products. The results of our study of cyclizations using 3,3-dimethylacrylic acid and crotonic acid are shown in (Schemes 2.9 and 2.10), respectively.



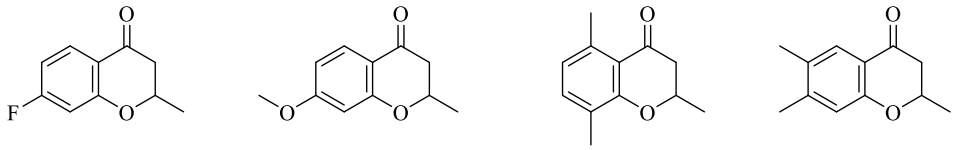
Scheme 2.9 4-Chromonnes from 3,3-dimethylacrylic acid



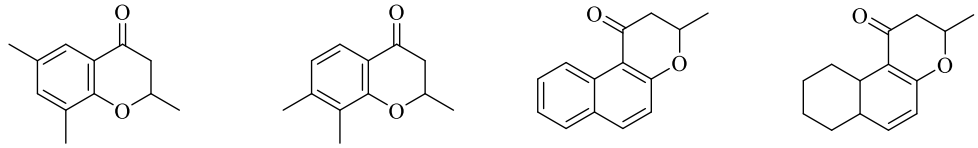
28 **30** **31**



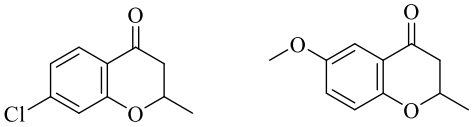
31b, (65%) **31c,** (52%) **31d,** (84%) **31e,** (33%)



31f, (71%) **31g,**(55%) **31h,** (45%) **31i,** (45%)



31j, (36%) **31k,** (80%) **31l,** (45%) **31m,** (52%)

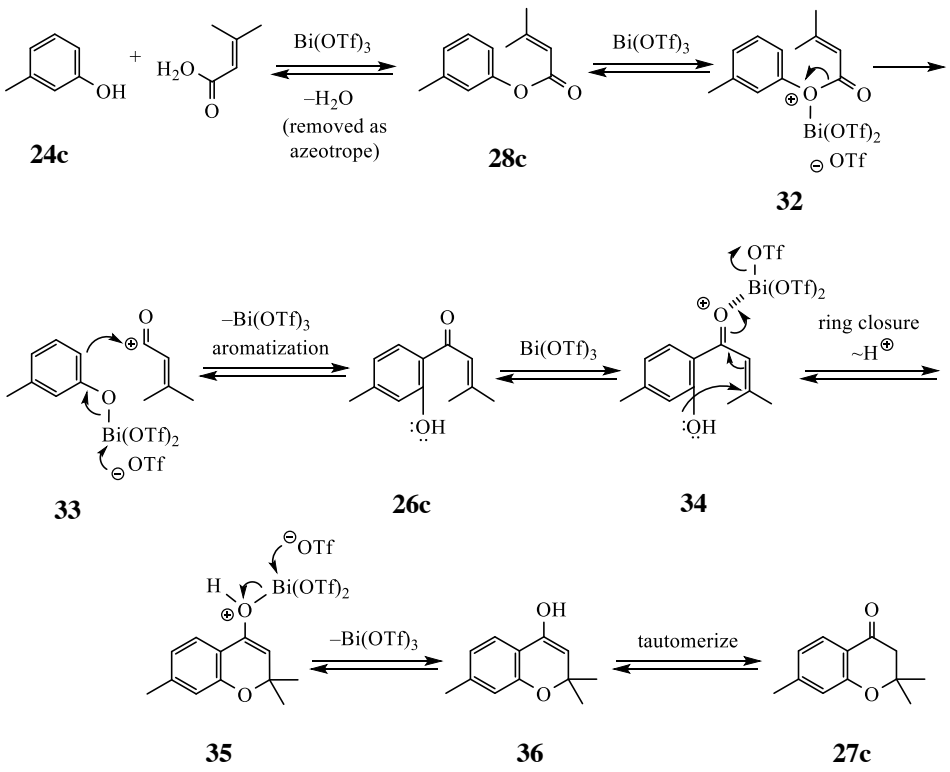


31n, (36%) **31o,** (52%)

Scheme 2.10 4-Chromanones from *trans*-crotonic acid

All of the reactions were performed in toluene at reflux using a 1:1 ratio of phenol to carboxylic acid and 30 mol% of bismuth(III) triflate. The mixtures were refluxed for 12-18 h while monitoring by TLC. When maximum conversions were attained, the reactions were cooled, concentrated under

vacuum and the crude products, diluted with a small amount of chloroform, were applied to preparative thin layer chromatography (PTLC) plates. Elution 3-4 times with 5% ether in hexane (8-10% ether in hexane was used for the methoxy-substituted products) yielded 2-3 bands. In each case, the bright fluorescent blue band was the 4-chromanone, while others contained unreacted phenol or the aryl ester of the acid. Our reaction proceeded in fair to high yields and tolerated a broad range of substrates. The 4-chromanone products were easily purified by preparative thin layer chromatography. Good yields were achieved with nearly all of the methyl-substituted derivatives, and in 3-substituted phenols where the two ortho carbons were unsubstituted, closure occurred toward the less hindered position. Only 2-methylphenol failed to undergo a clean reaction, and this could derive from steric hindrance at the hydroxyl group as well as the fact that the single methyl substituent would exert only a minimal activating effect at the aromatic carbon that will attack the acylium electrophile during the Fries rearrangement. Lower yields were also observed with 2,5-disubstituted phenols (entries **e** and **f**), which were sterically hindered and also tended to sublime into the condenser. Lower yields were also observed with 3-chlorophenol (entry **m**), which could be attributed to the deactivating effect of the substituent. On the contrary, the fluoro-substituted phenol (entry **l**) was unique in having an electron-withdrawing group while still providing a good yield of the desired chromanone product. This could be attributed to that fact fluorine-substituted aromatics show high reactivity in the para position relative to the fluorine.[70-71] In 3-fluorophenol, the fluorine is para to the position that accepts the acylium ion during the Fries rearrangement, providing a much cleaner conversion was than expected. However, the yields of 4-chromanones were slightly lower for reactions involving crotonic acid, as might be predicted for a substrate with an impaired ability to stabilize the acylium ion intermediate. A plausible mechanism to the desired 4-chromanone product is illustrated in (Scheme 2.11)



24c **28c** **32** **33** **26c** **34** **35** **36** **27c**

Scheme 2.11. A plausible mechanism for the $Bi(OTf)_3$ catalyzed synthesis of 4-chromanones

Through careful monitoring by thin layer chromatography, the first intermediate in the process was identified the aryl ester **28c**. The reason we chose toluene as a solvent, is to remove an equivalent of water produced in the reaction by azeotropic distillation into the condenser. The corresponding aryl ester would then undergo a Fries rearrangement to give 1-(2-hydroxy-4-methylphenyl)-3-methylbut-2-en-1-one **26c**. The failure of **26c** to completely cyclize under the aluminum chloride conditions likely resulted from strong coordination of both the phenol and side chain ketone functions by the excess Lewis acid. This coordination would diminish the nucleophilicity of the ortho-hydroxyl group and slow the oxa-Michael addition to the enone double bond. Once ring closure occured in the bismuth(III) catalyzed reaction, proton transfer to generate **35**, disengagement of the catalyst to give enol **36**, and tautomerization would lead to the final product **27c**.

2.2.6 Conclusion

We were able to develop an efficient bismuth(III) triflate catalyzed tandem reaction to prepare substituted 4-chromononones from a wide range of substituted phenols and 3,3-dimethylacrylic acid or *trans*-crotonic acid. The procedure was convenient to perform, product purification was straightforward, and the target heterocycles were isolated in fair to excellent yields. A reasonable selection of substrates was surveyed to define the scope of the reaction. Limitations were predictably associated with deactivating groups on the aromatic nucleus and steric hindrance toward reattachment of the acyl group to the aromatic ring during the Fries rearrangement. Additionally, experiments confirmed that the sequence of events during the reaction involved (1) esterification of the acid by the phenol, (2) Fries rearrangement of the 2-butenyl acylium fragment to the less hindered ortho position and (3) oxa-Michael ring closure of the phenolic OH to the side chain enone of the Fries product.

2.3 Chemistry

General Methods: All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech, No. 21521). Preparative separations were performed by one of the following methods: (1) preparative thin layer chromatography (PTLC) on 20-cm × 20-cm silica gel GF plates (Analtech, No. 02015) or (2) column chromatography on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies, No. UV-05) packed into quartz columns. Band elution for all chromatographic methods was monitored using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on NaCl disks or as nujol mulls. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using $(CH_3)_4Si$ as the internal standard; coupling constants (*J*) are given in Hertz. Low-resolution mass spectra (electron impact/direct probe) were obtained at 70 eV. Elemental analyses (±0.4%) were performed by Atlantic Microlabs, Inc., Norcross, GA 30071.

2.3.1 Naphthoates, dihydroquinolines carboxylates and naphthyridine carboxylates from MBH acetates.

General Procedure for the synthesis of Morita-Bayliss-Hillman Adducts (9a-h): To a stirred solution of aldehyde **6a-e** (1 equiv) and DABCO (1.5 equiv) in CH_3CN (8 mL) under N_2 was added the corresponding acrylate **7a-d** (2 equiv) at room temperature. After 2 days, the solution was partitioned between H_2O and EtOAc. The organic layer was washed with 1M HCl (2×) and saturated $NaHCO_3$. The combined aqueous layers were back extracted with EtOAc (3×). All of the combined organic layers were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent resulted in pure MBH adducts **9a-h**, which were used without further purification.

Ethyl 2-((2-fluoro-5-nitrophenyl)(hydroxy)methyl)acrylate (9a): Yield 0.45g (97%) as a colorless oil; IR:1748, 1725, 1632, 1532, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.20 (ddd, *J* = 8.9, 4.2, 2.9 Hz, 1H), 7.20 (t, *J* = 8.9 Hz, 1H), 6.88 (s, 1H), 6.51 (s, 1H), 5.96 (br d, *J* = 1.0 H_3, 1H), 3.71 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 164.5 (d, *J* = 238.4 Hz) 144.5, 139.8, 130.4 (d, *J* = 15.4 Hz), 127.2 (d, *J* = 1.15 Hz), 125.4(d, *J* = 10.3 Hz), 124.7(d, *J* = 5.9 Hz), 116.5, 116.2, 66.9, 61.5, 14.0.

Methyl2-((2-fluoro-5-nitrophenyl)(hydroxy)methyl)acrylate(9b): Yield 0.35g (92%) as a yellow-orange oil; IR: 3477, 1716, 1629, 1531, 1351 cm^{-1}, ^1H NMR ($CDCl_3$): δ 8.47 (dd, *J* = 6.2, 2.9 H, 1H), 8.21 (ddd, 9.0, 4.3, 2.9 Hz, 2H), 7.19 (t, *J* = 9.0 Hz, 1H), 6.41(s, 1H), 5.89 (br d, *J* = 2.4 Hz), 5.81 (s, 1 H), 3.79 (s, 3H); OH not observed, poss 3.48; ^{13}C NMR ($CDCl_3$): δ 171.2, 166.4 (d, *J* = 240.2 Hz,), 155.9, 139.6, 130.4 (d, *J* = 15.4 Hz), 127.4, 125.4 (d, *J* = 10.3 Hz), 124.6 (d, *J* = 5.9 Hz), 116.6, 116.3 (d, *J* = 2.7 Hz), 66.8, 60.4, 52.3, 21.1, 14.2.

2,2,2-trifluoroethyl 2-((2-fluoro-5-nitrophenyl)(hydroxy)methyl)acrylate (9c) : Yield 0.25g (82%) as a light-gren oil; IR- 3341, 1746, 1545, 1368 cm^{-1};^1H NMR ($CDCl_3$): δ 8.44 (dd, *J* = 6.2, 2.8 Hz, 1H), 8.23-8.21 (complex, 1H), 7.21 (t, *J* 8.9 Hz, 1H), 6.58 (s, 1H), 6.06 (s, 1H), 5.94 (s, 1H), 4.53 (dq, *J* = 6.4 Hz, 2H), ^{13}C NMR ($CDCl_3$): δ 176.0, 164.3 (d, *J*= 242.2 Hz), 140.2, 138.8,

131.9, 129.4, 125.7 (d, J = 10.5 Hz), 124.6 (d, J = 5.8 Hz), 124.0 (d, J = 10.9 Hz), 121.2 (q, J = 269.2 Hz) 116.7 (d, J = 4.7 Hz), 66.4 (d, J = 2.9 Hz), 61.0, 60.6.

2-((2-fluoro-5-nitrophenyl)(hydroxy)methyl)acrylonitrile (9d): Yield 0.30g (80%) as a yellow oil; IR: 3451, 2232, 1636, 1530, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.51 (dd, J = 6.1, 2.8 Hz, 1H), 8.29 (ddd, J = 9.0, 4.4, 2.9 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 7.24 (s, 1H), 6.22 (t, J = 0.9 Hz, 1H), 6.15 (d, J = 0.9 Hz, 1H), 5.72 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 163.0 (d, J = 258.7 Hz), 144.8 (d, J = 2.9 Hz), 131.60 , 128.4 (d, J = 15.3 Hz), 126.3 (d, J = 10.4 Hz), 124.2 (d, J = 8.4 Hz), 116.9, 116.7, 115.9, 67.4.

Ethyl 2-((2,5-difluorophenyl)(hydroxy)methyl)acrylate (9e): Yield 0.42g (83%) as yellow oil; IR: 3451, 1713, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$); δ 7.21 (ddd, J = 8.7, 6.0, 3.0 Hz, 1H), 7.03-6.92 (complex, 2H), 6.35 (s, 1H), 5.80 (s, 1H), 5.73 (br d, J = 2.6 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); OH not observed; ^{13}C NMR ($CDCl_3$): δ 166.3, 158.9 (dd, J = 242.7, 2.4 Hz) 155.8 (dd, J = 242.7, 2.4 Hz) 140.4, 130.1 (dd, J = 16.9, 7.3 Hz), 126.6 (d, J = 0.9 Hz), 116.3 (dd, J = 24.6, 8.5 Hz)115.8 (dd, J = 24.6, 8.6 Hz), 114.8 (dd, J = 25.2, 4.2 Hz), 67.0, 61.3, 14.0.

Methyl 2-((2,5-difluorophenyl)(hydroxy)methyl)acrylate (9f) : Yield 0.54g (99%) as a yellow oil; IR: 3432, 1717, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.21 (ddd, J = 8.7, 5.8, 3.0 Hz, 1H), 7.03-6.92 (complex, 2H), 6.35 (s, 1H), 5.83 (br d, J = 2.7 Hz, 1H), 5.74 (q, J = 0.7 Hz, 1H), 3.78 (s, 3H), 3.33 (d, J = 4.8 Hz, 1H); ^{13}C NMR; δ 166.7, 158.9 (dd, J = 242.5, 1.3 Hz), 155.7 (dd, J = 242.7, 2.5 Hz), 140.2, 130.0 (dd, J = 16.0, 7.3 Hz), 126.9, 116.4 (dd, J = 24.7, 8.5 Hz), 115.8 (dd, J = 24.2, 8.6 Hz), 114.8 (dd, J = 25.2, 4.3 Hz), 67.0, 52.9.

Ethyl 2-((2-fluoropyridin-3-yl)(hydroxy)methyl)acrylate (9g): Yield 0.50g (99%) as a colorless oil; IR: 3399, 1714, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.16 (dt, J = 4.9, 1.6 Hz, 1H), 7.97 (ddd, J = 9.5, 7.5, 1.9 Hz), 7.23 (ddd, J = 7.0, 4.9, 1.7 Hz, 1H), 6.35 (s, 1H), 5.78 (m, 1H), 5.76 (br d, J = 3.3 Hz, 1H), 4.21 (qd, J = 7.1, 0.9 Hz, 2H), 3.56 (d, J = 5.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 161.7 (d, J = 239.4 Hz), 159.3, 146.9 (d, J = 2.2 Hz), 139.9 (d, J = 1.14 Hz),

139.1 (d, J = 2.5 Hz) 127.6, 123.7 (d, J = 1.9 Hz), 123.4 (d, J = 2.0 Hz), 121.7 (d, J =4.2 Hz), 67.5, 61.3, 14.0.

Methyl 2-((2-fluoropyridin-3-yl)(hydroxy)methyl)acrylate (9h): Yield 0.44g (96%) as a yellow oil; IR: 3336, 1714, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.16 (dt, J = 4.9, 1.3 Hz, 1H), 7.97 (dddd, J = 9.6, 7.5, 1.9, 0.6 Hz, 1H), 7.24 (ddd, J = 7.5, 4.9, 1.7 Hz, 1H), 6.38 (s, 1H), 5.79 (brs, 1H), 5.77 (d, J = 6.3 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.5, 161.5 (d, J = 239.2 Hz), 146.7 (d, J = 14.9 Hz) 139.4, 138.8 (d, J = 4.6 Hz) 127.2, 123.3 121.5 (d, J = 4.2 Hz), 67.4, 52.1.

General Procedure for the synthesis of Morita-Bayliss-Hillman Acetates (10a-g): The corresponding MBH Adduct **9a-h** was treated with 2 mL of acetic anhydride. The mixture was refluxed until complete consumption of the starting material. Excess acetic anhydride was removed under vacuum. The crude mixture was diluted with 20 mL of DCM and washed with 3 equal portions of saturated $NaHCO_3$. Aqueous layers were back extracted with DCM (3×). The combined organic layers were washed with H_2O, saturated NaCl and dried (Na_2SO_4). Removal of the solvent and purification by silica gel chromatography afforded the pure acetates **10a-g**.

Ethyl 2-(acetoxy(2-fluoro-5-nitrophenyl)methyl)acrylate (10a): Yield 0.40g (85%) as a colorless oil; IR: 1751, 1723, 1639, 1532, 1351 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ; 8.26 (dd, J = 6.0, 2.8 Hz, 1H), 8.23 (ddd, J = 8.9, 4.3, 2.9 Hz, 1H), 7.22 (t, J = 8.9 Hz, 2H), 6.91 (s, 1H), 6.54 (s, 1H), 4.18 (qd, J = 7.1, 1.3 Hz, 2H), 2.15 (s, 3H), 1.25 (q, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 182.6, 169.0, 164.22 (d, J = 232.5 Hz), 144.2, 137.4, 127.4, 126.0 (d, J = 10.2 Hz), 125.2 (d, J = 5.2 Hz), 116.9, 116.7, 66.6, 61.4, 20.9, 13.9.

Methyl 2-(acetoxy(2-fluoro-5-nitrophenyl)methyl)acrylate (10b): Yield 0.43g (82%) as a colorless oil;IR: 1748, 1725, 1632, 1532, 1351 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ; 8.23 dd, J = 6.1, 2.9 Hz, 1H), 8.20 (ddd, J = 8.9, 4.2, 2.9 Hz, 1H), 7.20 (t, J = 8.9 Hz, 1H), 6.88 (s, 1H), 6.51 (s, 1H), 5.96 (br d, J = 1.0 Hz, 1H), 3.71 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.3, 165.4, 165.0 (d, J =

237.2 Hz) 144.6, 137.5, 128.0, 127.7 (d, J = 15.6 Hz), 126.4 (d, J = 10.4 Hz), 125.4 (d, J = 5.4 Hz), 117.4, 117.11, 66.9, 61.6, 52.5, 21.1.

2-cyano-1-(2-fluoro-5-nitrophenyl)allyl acetate (10c): Yield 0.30g (84%) as a colorless oil; IR: 2256, 1716, 1642, 1523 , 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.43 (dd, J = 6.1, 2.8 Hz, 1H), 8.31 (ddd, J = 9.0, 4.4, 2.8 Hz, 1H), 7.29 (t, J = 9.0 Hz, 1H), 6.63 (s, 1H), 6.19 (s, 1H), 6.18 (s, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.8, 164.4 (d, J = 262.1 Hz), 144.7, 133.7, 126.9 (d, J = 10.4 Hz), 125.4 (d, J = 15.1 Hz), 124.1 (d, J = 4.9 Hz), 120.9, 117.3, 117.0, 115.2, 67.8, 20.8.

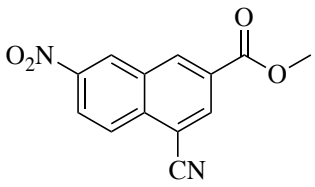
Ethyl 2-(acetoxy(2,5-difluorophenyl)methyl)acrylate (10d): Yield 0.46g (88%) as a colorless oil; IR- 1752, 1723, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.05-6.95 (complex, 3H), 6.88 (s, 1H), 6.47 (s, 1H), 5.82 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.12 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 169.1, 164.5 (d, J = 242.2 Hz), 158.5 156.2, 148.8, 138.2, 133.5, 126.9, 116.7 (ddd, 24.7, 24.7, 8.5 Hz), 115.4 (dd, J = 25.0, 3.8 Hz), 62.0, 61.2, 20.9, 14.0.

Methyl 2-(acetoxy(2,5-difluorophenyl)methyl)acrylate (10e): Yield 0.42g (94%) as a colorless oil; IR- 1751, 1728, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ7.06-6.95 (complex, 3H), 6.88 (s, 1H), 6.47 (s, 1H), 5.84 (s, 1H), 3.74 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.1, 165.0, 159.8 (dd, J = 242.7, 2.4. Hz), 157.4 (dd, J = 245.6, 2.4 Hz), 155.0 (d, J = 2.6 Hz), 137.8, 127.3, 126.9 (d, J = 7.4 Hz), 126.7 (d, J = 7.3 Hz), 117.0 (d, J = 8.5 Hz), 116.7 (dd, J = 8.6, 2.6 Hz), 116.5 (d, J = 8.6 Hz), 115.5 (d, J = 3.7 Hz), 115.2 (d, J = 3.7 Hz), 67.1 (dd, J = 2.9, 0.84 Hz), 52.2, 20.9.

Ethyl 2-(acetoxy(2-fluoropyridin-3-yl)methyl)acrylate (10f): Yield 0.30g (80%) as a colorless oil; IR: 1749, 1721, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ; 8.19 (d, J = 4.9 Hz, 1H), 7.81 (ddd, J = 9.3, 7.6, 1.7 Hz, 1H), 7.19 (ddd, J = 7.6, 4.9, 1.4 Hz, 1H), 6.80 (s, 1H), 6.50 (s, 1H), 5.92 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 169.1, 164.4, 161.0 (d, J = 242.1 Hz), 147.6 (d, J = 14.9 Hz), 140.1 (d, J = 4.4 Hz), 137.5, 127.2, 121.4 (d, J = 4.4 Hz), 120.5 (d, J = 30.4 Hz), 67.8, 61.2, 20.9, 14.0.

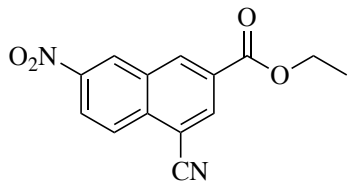
Methyl 2-(acetoxy(2-fluoropyridin-3-yl)methyl)acrylate (10g): Yield 0.25g (75%) as a colorless oil;IR:1745, 1726, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.19 (dt, *J* = 4.9, 1.3 Hz, 1H), 7.82 (ddd, *J* = 9.4, 7.5, 1.9 Hz, 1H), 7.20 (ddd, *J* = 7.5, 4.9, 1.9 Hz, 1H), 6.79 (s, 1H), 6.50 (s, 1H), 5.95 (s, 1H), 3.73 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.1, 164.9 (d, *J*= 242.2 Hz) 162.2, 159.8, 147.7 (d, *J*= 14.9 Hz), 137.2, 127.6, 121.4 (d, *J* = 4.4 Hz), 120.5, 120.3 67.9 (d, *J*= 4.42 Hz) 52.2, 20.9.

General Procedure for the synthesis of cyclization with Morita-Bayliss-Hillman Acetates and active methylene compounds: A 50-mL, round-bottomed flask equipped with a condenser, stir bar and vacuum adapter, was charged with MBH acetate **10a** (1 equiv) in 1 mL of DMF under N_2. The corresponding active methylene compound (1.5 equiv) and K_2CO_3 (1.5 equiv) were added at room temperature with continued stirring. TLC indicated complete consumption of the starting material after 1 h. The solution was poured into 15 mL of de-ionized water, and extracted with EtOAc (3×). The combined organic layers were washed with NaCl and dried (Na_2SO_4). Removal of the solvent and trituration with 5% ether/pentane and filtration afforded the pure naphthalene carboxylates **11a-c**.



(11a)

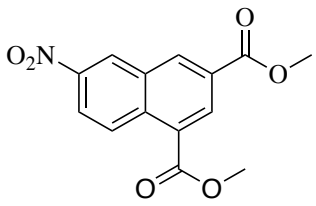
Ethyl 4-cyano-7-nitro-2-naphthoate (11a) from 10a and ethyl cyanoacetate: Yield: .70 mg (85%) as a tan solid m.p. 77-79 ºC; IR: 1716, 1628, 1536, 1349, 1289, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.91 (d, *J* = 2.3 Hz, 2H), 8.60 (d, *J* = 1.6 Hz 1H), 8.48 (dd, *J* = 9.2, 2.3 H_Z, 1H), 8.36 (d, *J* = 9.2 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 163.9, 147.1, 136.8, 136.2, 135.2, 131.5, 129.7, 127.4, 126.2, 124.0, 116.1, 111.6, 62.4, 14.3.



(11b)

Methyl 4-cyano-7-nitro-2-naphthoate (11b) from 10b and ethyl cyanoacetate:

Yield: 55 mg (81%) as a light brown solid m.p. 81-82 ºC ; IR: 1720, 1531, 1440, 1349, 1293, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ; 9.01 (d, *J* = 2.2 Hz, 2H), 8.70 (d, *J* = 1.5 Hz, 1H), 8.58 (dd, *J* = 9.2, 2.2 Hz, 1H), 8.47 (d, *J* = 9.2 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.3, 146.7, 137.7, 135.6, 135.3, 131.4, 128.6, 127.0, 126.8, 124.5, 118.2, 110.3, 53.0.

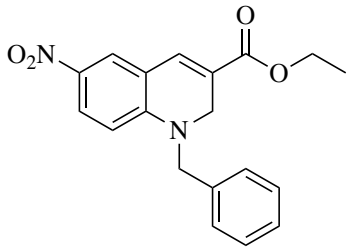


(11c)

Dimethyl 6-nitronaphthalene-1,3-dicarboxylate (11c) from 10b and methyl phenylsulfonyl acetate; Yield: 70 mg (96%) as na off-white solid m.p. 97-99 ºC; IR:1720, 1625, 1532, 1379, 1302, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.22 (d, *J* = 9.5 Hz, 1H), 8.96 (d, *J* = 1.6 Hz, 1H), 8.94 (d, *J* =2.4 Hz, 2H), 8.46 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.07 (s, 3H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.4, 165.4, 146.6, 139.0, 137.1, 135.8, 133.0, 128.6, 128.2, 127.9, 125.9, 123.0, 52.9, 52.8.

General Procedure for the of cyclization with Morita-Bayliss-Hillman Acetates with alkyl or aryl amines: A 50-mL, round-bottomed flask equipped with a condenser, stir bar and N_2, was charged with the MBH acetate **10a-b** (1 equiv) in 1 mL of DMF under N_2. The corresponding amine (1.5 equiv) and K_2CO_3 (1.5 equiv) were added at room temperature with continued stirring. TLC indicated complete consumption of the starting material after 1-4 h. The solution was poured into

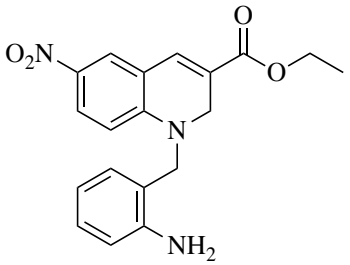
15 mL of DI water, and extracted with EtOAc (3×). The organic layer was washed with 1M HCl (2×) and saturated $NaHCO_3$ (2×). The combined organic layers were washed with NaCl and dried (Na_2SO_4). Removal of the solvent and trituration with 5% ether/pentane and filtration afforded the pure dihydroquinoline carboxylates **12a-f**.



(12a)

Ethyl 1-benzyl-6-nitro-1,2-dihydroquinoline-3-carboxylate from 10a and benzylamine

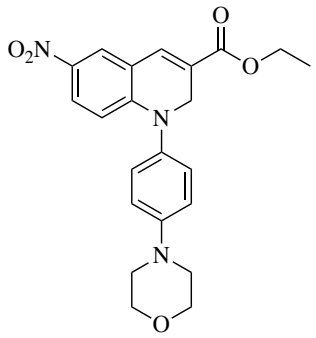
Yield: 51 mg (80%) as a yellow solid m.p. 197-199 °C; IR:1705, 1574, 1322 cm^{-1};^{1}H NMR (DMSO-d_6): δ; 8.09 (d, J = 2.7 Hz, 1H), 7.91 (dd, J = 9.3, 2.7 Hz, 1H), 7.51 (s, 1H), 7.40-7.27 (complex, 5H), 6.68 (d, J = 9.4 Hz, 1H), 4.66 (s, 2H), 4.52 (d, J = 1.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 164.0, 150.9, 136.5, 135.4, 133.3, 128.9, 128.3, 127.4, 126.9, 125.8, 122.5, 118.1, 109.9, 60.6, 52.9, 49.7, 14.1.



(12b)

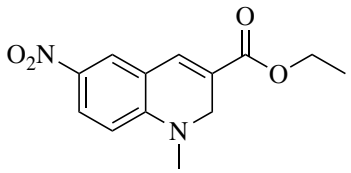
Ethyl 1-(2-aminobenzyl)-6-nitro-1,2-dihydroquinoline-3-carboxylate

from 10a and 2-aminobenzylamine: Yield: 64 mg (83%) as na organge solid : m.p. 140-141 ºC; IR: (nujol): 3469, 3372, 1706, 1654, 1596, 1335 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.08 (d, J = 2.7 H_3, 1H), 7.92 (dd, J = 9.3, 2.7 Hz, 1H), 7.52 (s, 1H), 7.00 (t, J = 7.9 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 7.9 H_3, 1H), 6.53 (t, J = 7.5 Hz, 1H), 6.45 (d, J = 9.3 Hz, 1H), 5.01 (s, 2H), 4.49 (s, 2H), 4.39 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ172.6, 150.8, 146.4, 136.2, 133.1, 127.6, 125.4, 122.4, 117.9, 116.9, 115.3, 113.6, 112.8, 109.5, 60.4, 57.6, 49.5, 13.9.



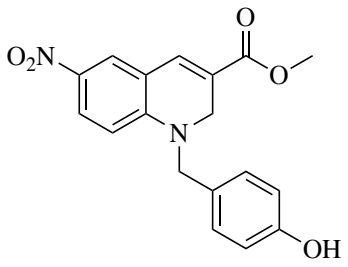
(12c)

Ethyl 1-(4-morpholinophenyl)-6-nitro-1,2-dihydroquinoline-3-carboxylate from (10a) and 4-morpholinoaniline: Yield 82 mg asan organge solid, (72%) m.p. 181-183 ºC; IR: (nujol): 1707, 1654, 1598, 1319, 1292 cm^{-1};^{1}H NMR (DMSO-d_6): δ; 8.14 (d, J = 2.7 Hz, 1H), 7.84 (dd, J = 9.3, 2.7 Hz, 1H), 7.56 (s, 1H), 7.28 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 6.17 (d, J = 9.3 Hz, 1H), 4.69 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.75 (t, J = 4.7 Hz, 4H), 3.17 (t, J = 4.7 Hz, 4H), 1.24 (q, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 164.4, 151.7, 150.7, 137.6, 134.7, 133.5, 128.3, 127.3, 126.2 ,123.1, 119.2, 116.8, 112.1, 66.5, 61.1, 52.0, 48.5, 14.6.



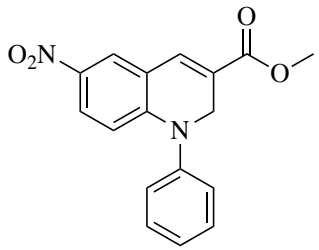
(12d)

Ethyl 1-methyl-6-nitro-1,2-dihydroquinoline-3-carboxylate (12d) from 10a and methyl amine: Yield: 160mg (93%) as s yellow solid m.p. 117-118 ºC; IR: (nujol) 1692, 1593, 1317 cm^{-1};^{1}H NMR (DMSO-d_6): δ; 8.01 (d, J = 2.7 Hz, 1H), 7.95 (dd, J = 9.2, 2.7 Hz, 1H), 7.42 (s, 1H), 6.60 (d, J = 9.2 Hz, 1H), 4.45 (brd, J = 1.1 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.92 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 164.5, 151.9, 136.7, 133.9, 128.9, 125.8, 123.1, 118.6, 109.8, 66.0, 51.3, 37.9, 14.6.



(12e)

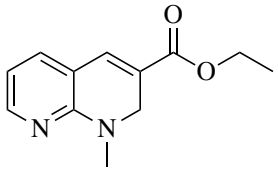
Methyl 1-(4-methoxybenzyl)-6-nitro-1,2-dihydroquinoline-3-carboxylate (12d) from 10b and 4-hydroxy benzylamine: Yield: 130 mg (91%) as an orange solid m.p. 235-237 ºC ; IR: (nujol); 1704, 1656, 1596, 1326 $cm^{-1;}$^{1}H NMR (DMSO-d_6): δ 9.42 (s, 1H), 8.06 (d, J = 2.4 Hz, 1H), 7.92 (dd, J = 9.3, 2.4 Hz, 1H), 7.48 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H and s, 1H), 4.51 (s, 2H), 4.46 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 165.0, 157.3, 151.4, 136.7, 134.0, 128.9, 128.8, 126.3, 125.7, 122.6, 118.5, 116.1, 110.4, 52.9, 52.4, 49.8.



(12f)

Methyl 6-nitro-1-phenyl-1,2-dihydroquinoline-3-carboxylate (12f) from 10b and aniline

Yield: 120 mg (60%) as an organge m.p. 112-113 ºC; IR: (nujol): 1711, 1652, 1567, 1374 cm^{-1};^{1}H NMR (DMSO-d_6): δ; 8.20 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 9.2, 2.4 Hz, 1H), 7.62 (s, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 6.30 (d, J = 9.3 Hz, 1H), 4.74 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 164.8, 151.0, 143.7, 138.2, 133.6, 130.9, 128.2, 128.1, 127.9, 126.3, 126.2, 123.2, 112.6, 52.5, 51.3.



Synthesis of (13)

The MBH adduct **10g** (80 mg, .3 mmol) was suspended in 1 mL of methyl amine (12.1 M) under N_2. The resulting fluorescent solution was treated with K_2CO_3 (620 mg, 0.45mmol) with continued stirring for 1 h. Then, the solution was cooled to 0 ºC and treated with 5 mL of water resulting in the formation of a bright yellow solid. The product was filtered and dried under vacum to afford **13** (58 mg, 88%) as a fluorescent yellow solid m.p. 65-66 ºC; IR: 1701, 1646, 1556, 1395, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, J = 5.1, 1.8 Hz, 1H), 7.23 (t, J = 1.3 Hz, 1H) 7.10(dd, J = 7.2, 1.8 Hz, 1H) 6.42 (dd, J = 7.2, 2.1 Hz, 1H) 4.48 (d, J = 1.2 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.0 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.1, 156.7, 150.1, 135.9, 134.5, 122.1, 114.6,

112.5, 60.8, 51.1, 35.2, 14.3.

2.3.2 Synthesis of 2-fluoro-5-nitronicotinaldehyde (23)

Methyl 2-hydroxy-5-nitronicotinate (20)

A 100-mL, round-bottomed flask, equipped with a stir bar, reflux condenser and a $CaCl_2$ drying tube, was charged with 2-hydroxy-5-nitronicotinic acid[71,72] **19** (2.0 g, 10.9 mmol) in 25 mL of MeOH and 2-3 drops of conc. H_2SO_4. The mixture was heated to reflux for 8 hrs. After the allotted time period, the mixture was cooled to room temperature resulting in the formation of a white precipitate. The solid was filtered and washed with 20 mL of cold MeOH and dried under vacuum to afford (2.0 g, 93%) of methyl 2-hydroxy-5-nitronicotinate as a white solid, m.p. 242-244°C; IR (nujol): 1726, 1655, 1576.4 1357, 1283 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.2 (s, 1H), 8.9 (d, J = 3.3 Hz, 1H), 8.6 (d, J= 3.3 Hz, 1H), 3.8 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 163.3, 158.3, 142.1, 137.7, 128.8, 118.2, 52.1.

Methyl 2-chloro-5-nitronicotinate (21)

A 100-mL round-bottomed flask equipped with a stir bar, reflux condenser and a $CaCl_2$ drying tube, was charged with methyl 2-hydroxy-5-nitronicotinate (**20**, 2.0 g, 10.1 mmol) in 10 mL of $CHCl_3$. Thionyl chloride (7 mL) and DMF (0.5 mL) were added at room temperature. The solution was heated to 100°C for 6 h. The solution was cooled, and the volatiles were removed under vacuum. The resulting solution was treated with 25 mL of MeOH at 0 °C and stirred for 30 min. The solution was poured into 100 mL of H_2O and extracted with EtOAc (150 mL). The organic layer was washed with H_2O, saturated NaCl and dried (Na_2SO_4). Removal of the solvent afforded methyl 2-chloro-5-nitronicotinate (**21)** as a yellow crystalline solid (2.05 g, 93%), m.p 63-65°C IR: 3080, 2954, 1744, 1600, 1567, 1438, 1351, 1271, 1063 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.30 (d, J=2.8 Hz, 1H), 8.92 (d, J= 2.7 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.8, 155.5, 146.8, 142.7, 135.3, 127.1, 53.6.

2-Chloro-5-nitronicotinaldehyde (22)

A three-neckED, 100-mL round-bottomed flask, equipped with a stir bar, reflux condenser and two-rubber septa was charged with methyl 2-chloro-5-nitronicotinate (**21,** 1.05 g, 4.84 mmol) in 15mL of CH_2Cl_2 under N_2. The solution was cooled to -78°C and DIBAL-H (1.5 M, 3.5 mL, 5.3 mmol) was added dropwise over a 30-minute period. The mixture was stirred at -75°C for 1 h after which TLC analysis indicated the complete absence of starting material. The mixture was quenched at -70°C by the dropwise addition of 15 mL of saturated Rochelle's salt (sodium potassium tartrate) solution. The ice bath was removed and the resulting orange solution was stirred for 10 min and poured into a separatory funnel and extracted with 30 mL of DCM (3×). The combined organic layers were washed with saturated NaCl and dried over (Na_2SO_4). Removal of the solvent and purification by silica gel chromatography using 5% EtOAc/Hex afforded 2-chloro-5-nitronicotinaldehyde **(22)** as a yellow oil (795 mg, 88%). IR: 2876 1694, 1597, 1567, 1347, 1241, 1072 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.51 (s, 1H) 9.40 (d, *J* =2.8 Hz, 1H), 8.91 (d, *J* = 2.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$): δ 186.8, 157.8, 148.7, 143.9, 132.9, 128.8.

2-Fluoro-5-nitronicotinaldehyde (23)

To a solution of 2-chloro-5-nitronicotinaldehyde (**22** , 532 mg, 2.9 mmol) in 15 mL of dry DMSO, was added KF (331 mg, 5.7mmol) under N_2. The solution was heated at 70 °C for 2 h, then cooled to room temperature and poured into 50 mL of water. The aqueous layer was extracted (3×) with 30 mL of EtOAc. The combined organic layers were washed with saturated NaCl and dried (Na_2SO_4). Removal of the solvent and purification by silica gel chromatography using 5% EtOAc/hex afforded 2-fluoro-5-nitronicotinaldehyde (**23**, 400 mg, 82%) as a white solid m.p. 50-52°C IR: 2886, 1702, 1615, 1584, 1446, 1355 1238, 913.4 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.4 (s, 1H) 9.34 (dd, *J* = 2.9, 1.2 Hz, 1H), 9.15 (dd, *J* = 7.5, 2.9 Hz, 1H) ; ^{13}C NMR ($CDCl_3$): δ 183.9, 166.6 (d, *J* = 257.1 Hz), 149.1(d, *J* = 19.4 Hz), 143.3, 135.3 (d, *J* = 5.1 Hz), 118.4 (d, *J* = 24.5 Hz); ^{19}F NMR ($CDCl_3$): δ -64.3 (d, *J* = 6.9 Hz)

2.3.3 A bismuth (III) trifluoromethanesulfonate catalyzed route to 4-chromonones

Representative procedure for the preparation of aryl 3,3-dimethylacrylates.[35] To an oil free suspension of NaH (0.60 g, 25.0 mmol) in 10 mL of anhydrous THF, a solution of the phenol (2.2g, 23.1 mmol) in of THF (30 mL) was added over a 5-min period with stirring at 0 °C (ice bath). The solution was stirred for 10 min and then treated with a solution of 3-methyl-2-butenoyl chloride (2.78 g, 23.3 mmol) in THF (15 mL) over a 5-min period at 0 °C. The reaction was then allowed to warm to room temperature over a 3-h period. The white suspension was transferred to separatory funnel containing water (75 mL) and acetic acid (0.5 mL) and was gently shaken. The mixture was extracted with ether (2 × 50 mL), and the extract was washed with saturated NaCl (3 × 50 mL), dried ($MgSO_4$), and concentrated to give a light-yellow oil. The product was purified on a 40-cm × 2.5-cm silica gel column eluted with 10% ether in hexanes to give the pure ester.

Phenyl 3-methyl-2-butenoate (24a): Yield: 3.61 g (20.6 mmol, 89%) as a colorless oil. IR: 1738, 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.91 (m, 1H), 2.22 (d, *J* = 1.8 Hz, 3H), 1.96 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (100 $CDCl_3$): δ 164.9, 159.9, 150.7, 129.3, 125.5, 121.8, 115.3, 27.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; Found: 177.0910.

4-Methylphenyl 3-methyl-2-butenoate (24b): Yield**:** 4.30 g (22.6 mmol, 98%) as a colorless oil; IR: 1738, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.90 (s, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.1, 159.6, 148.4, 135.1, 129.8, 121.5, 115.3, 27.6, 20.9, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; Found: 191.1073.

3-Methylphenyl 3-methyl-2-butenoate (24c): Yield: 4.25 g (22.4 mmol, 97%) as a colorless oil; IR: 1739, 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.24 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 5.90 (s, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.1, 159.7, 150.6, 139.5, 129.1, 126.3, 122.4, 118.8, 115.3, 27.7, 21.3, 20.5; HRMS

(ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1062.

3,5-Dimethylphenyl 3-methyl-2-butenoate (24d): Yield: 4.23 g (20.7 mmol, 89%) as a colorless oil; IR: 1734, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.84 (s, 1H), 6.97 (s, 2H), 5.89 (s, 1H), 2.30 (s, 6H), 2.22 (s, 3H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.2, 159.5, 150.6, 139.1, 127.3, 119.4, 115.3, 27.6, 21.2, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; Found: 205.1222.

2-Isopropyl-5-methylphenyl 3-methyl-2-butenoate (24e): Yield: 5.19 g (22.3 mmol, 96%) as a colorless oil; IR: 1738, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.83 (s, 1H), 5.95 (apparent sextet, J = 1.3 Hz, 1H), 2.99 (d septet, J = 6.8, 1.3 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 1.99 (s, 3H), 1.19 (dd, J = 8.0, 1.9 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 165.2, 159.5, 147.8, 137.2, 136.4, 126.8, 126.3, 123.0, 115.2, 27.6, 27.1, 23.1, 20.8, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{20}O_2 + H]^+$: 233.1542; Found: 233.1548.

3-Fluorophenyl 3-methyl-2-butenoate (24f): Yield: 4.07 g (21.0 mmol, 90%) as a colorless oil; IR: 1739, 1648, 1123 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.34 (AB pattern, J = 7.8 Hz, 1H), 6.95-6.84 (complex, 3H), 5.89 (s, 1H), 2.23 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.4, 162.9 (d, J = 247.0 Hz), 160.8, 151.6 (d, J = 10.8 Hz), 130.0 (d, J = 9.5 Hz), 117.6 (d, J = 3.3 Hz), 114.8, 112.5 (d, J = 21.0 Hz), 109.9 (d, J = 24.1 Hz), 27.7, 20.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}FO_2 + H]^+$: 195.0821; found: 195.0825.

3-Methoxyphenyl 3-methyl-2-butenoate (24g): Yield: 4.61 g (22.4 mmol, 96%) as a colorless oil; IR: 2838, 1740, 1648 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 (t, J = 8.2 Hz, 1H), 6.77 (ddd, J = 8.2, 2.3, 0.7 Hz, 1H), 6.70 (ddd, J = 8.0, 2.3, 0.7 Hz, 1H), 6.66 (t, J = 2.3 Hz, 1H), 5.91 (s, 1H), 3.79 (s, 3H), 2.23 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.8, 160.4, 160.0, 151.7, 129.7, 115.2, 114.1, 111.4, 107.7, 55.4, 27.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; Found: 207.1017.

Reaction of 3-methylphenyl 3-methyl-2-butenoate with aluminum chloride: A 250-mL three-necked, round-bottomed flask , equipped with a stir bar, an addition funnel and a condenser (with a drying tube) was charged with DCM (40 mL) and $AlCl_3$ (1.19 g, 8.95 mmol). The resulting suspension was stirred and cooled to 0 ºC (ice bath), and a solution of **24c** (1.00 g, 5.26 mmol) in DCM (10 mL) was added dropwise. The reaction was gradually warmed to room temperature and stirring was continued for 65 h. The resulting brown solution was added to a mixture of ice and saturated aq NaCl, the layers were separated, and the aqueous layer was extracted with DCM (40 mL). The combined organic extracts were washed with saturated NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated to give a brown oil, which was purified on a 30 cm × 2.5 cm silica gel column eluted with increasing concentrations (2-10%) of ether in hexanes to give four bands: band 1 (highest R_f), 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**26c**, 181 mg, 0.95 mmol, 18%) as a yellow oil; band 2, 3-methylphenyl 3-methyl-2-butenoate (**24c**, 51 mg, 0.26 mmol, 5%); band 3, 2,2,7-trimethyl-4-chromanone (**27c**, 648 mg, 3.41 mmol, 65%) as a white solid, m.p. 69-70 ºC; and band 4, 4,4,7-trimethyl-2-chromanone (**25c**, 21 mg, 0.011 mmol, 2%) as a yellow oil. The spectral data were as follows:

Band 1 (**26c**): IR: 3200-2700 (broad), 1640, 1583 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.9 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 2.34 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 195.8, 163.4, 157.1, 147.3, 126.8, 120.1, 119.8, 118.5, 118.4, 28.2, 21.9, 21.3; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; Found: 191.1065.

Band 2 (**24c**) recovered starting material): The spectral data matched those reported for **1c** above.

Band 3 (**27c**): The spectral data matched those reported for **27c** below.

Band 4 (**25c**): IR: 1772, 1625, 1581 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (d, J = 7.8 Hz, 1H), 6.96 (dd, J = 7.8, 1.7 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H), 2.60 (s, 2H), 2.33 (s, 3H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.5, 150.5, 138.5, 128.7, 125.5, 124.2, 117.5, 43.8, 33.0, 27.8, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; Found: 191.1069.

General procedure for the preparation of 4-chromanones from aryl 3,3-dimethylacrylates:A solution of the aryl 3,3-dimethylacrylate (**24**, 1.00 mmol) and bismuth(III) trifluoromethanesulfonate (131 mg, 20 mol%) in 8 mL of toluene was boiled for 12-24 h while monitored by TLC. Each reaction was worked up by cooling, removing the solvent, diluting with 1 mL of $CHCl_3$, and applying the crude product mixture directly to a 20 cm × 20 cm PTLC plate. After the $CHCl_3$ had been evaporated, the plate was eluted with 5% ether in hexanes (8-10% ether in hexanes for the methoxy-substituted products) to give three major bands. The bright blue fluorescent band (the 4-chromanone) was accompanied by small amounts of the starting ester (a faster moving band) and the corresponding phenol (a slower moving band). For 2-isopropyl-5-methylphenol, the 4-chromanone (40%) was accompanied by larger quantities of aryl 3,3-dimethylacrylate (12%) and phenol (30%). The spectra for all of the 4-chromanones and some of the aryl esters isolated are listed below.

Conversion of Fries product 26c to 4-chromanone 27c. A toluene (8 mL) solution of 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**26c**, 60 mg, 0.31 mmol) and bismuth(III) trifluoromethansesulfonate (41 mg, 0.06 mmol, 20 mol%) was heated at reflux for 15 min. The solvent was removed under vacuum and the remaining oil was filtered through a short plug of silica gel using 5% ether in hexanes. Removal of the solvent under vacuum afforded 2,2,7-trimethyl-4-chromanone (**27c**, 57 mg, 0.30 mmol, 95%). The spectral data matched those reported for **27c** below.

General procedure for the preparation of 4-chromanones from the corresponding phenol and the carboxylic acids. To a solution of the specific phenol (**28**, 1.0 mmol) and **29** or **30** (1.0 mmol) in 8 mL of toluene was added bismuth(III) trifluoromethansesulfonate (41 mg, 0.06 mmol, 20 mol%). The reaction was heated under reflux for 12-24 h and then cooled. Removal of the solvent under vacuum and purification by PTLC eluted with 5% ether in hexane (8-10% ether in hexanes for the methoxy-substituted products) showed several bands. The major band (bright fluorescent

blue) was isolated and extracted with ether to give the corresponding 4-chromanone **27**or **31**. The other bands consisted of varying amounts of the aryl ester of the carboxylic acid and unreacted substituted phenol. The following compounds were prepared by this method.

2,2,6-Trimethyl-4-chromanone (27b): Yield: 140 mg (0.74 mmol, 74%) as a colorless oil (lit[74] reports a m.p. of 67 ºC); IR: 1692, 1619 cm^{-1}; ^{1}H NMR: ($CDCl_3$): δ 7.65 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 2.69 (s, 2H), 2.34 (s, 3H), 1.45 (s, 6H); ^{13}C NMR: ($CDCl_3$): δ 192.8, 158.0, 137.2, 130.0, 126.1, 119.8, 118.1, 79.0, 48.9, 26.6, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; Found: 191.1077.

2,2,7-Trimethyl-4-chromanone (27c): Yield: 129 mg (0.68 mmol, 68%) as a white solid, m.p. 69-70 ºC (lit[75] m.p. 70 ºC); IR: 1686, 1617 cm^{-1}; ^{1}H NMR: ($CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 2.69 (s, 2H), 2.30 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: ($CDCl_3$): δ 192.2, 160.0, 149.6, 126.4, 122.0, 118.3, 118.0, 79.1, 48.8, 26.7, 21.9; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; Found: 191.1074.

2,2,5,7-Tetramethyl-4-chromanone (27d): Yield: 140 mg (0.69 mmol, 69%) as a white solid, m.p. 61-63 ºC; IR: 1682, 1614 cm^{-1}; ^{1}H NMR: ($CDCl_3$): δ 6.60 (s, 1H), 6.57 (s, 1H), 2.67 (s, 2H), 2.59 (s, 3H), 2.28 (s, 3H), 1.43 (s, 6H); ^{13}C NMR: ($CDCl_3$): δ 194.1, 161.5, 146.3, 141.8, 125.6, 116.9, 116.8, 78.4, 50.8, 27.0, 23.1, 22.1; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; Found: 205.1223.

2,2,5-Trimethyl-8-isopropyl-4-chromanone (27e): Yield: 102 mg (0.44 mmol, 44%; 54% brsm—based on recovered phenol) as a white solid, m.p. 73-75 ºC; IR: 1684, 1578 cm^{-1}; ^{1}H NMR: ($CDCl_3$): δ 7.23 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 3.25 (septet, *J* = 6.9 Hz, 1H), 2.70 (s, 2H), 2.59 (s, 3H), 1.45 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: ($CDCl_3$): δ 194.6, 158.1, 138.5, 135.3, 131.3, 123.4, 118.6, 77.8, 50.3, 26.9, 26.6, 22.7, 22.4; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{20}O_2 + H]^+$: 233.1542; Found: 233.1541. A faster moving band contained 2-isopropyl-5-

methylphenyl 3-methyl-2-butenoate [(X= 2-*i*-Pr-5-Me), 51 mg, 0.22 mmol, 22%; 27% brsm] as a colorless oil. The spectral data matched those reported above.

7-Fluoro-2,2-dimethyl-4-chromanone (27f): Yield: 126 mg (0.65 mmol, 65%) as a colorless oil; IR: 1694, 1616 cm^{-1}; ^{1}H NMR: δ 7.78 (dd, *J* = 8.8, 6.8 Hz, 1H), 6.69 (td, *J* = 8.5, 2.4 Hz, 1H), 6.62 (dd, *J* = 10.1, 2.4 Hz, 1H), 2.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.1, 167.8 (d, *J* = 238.4 Hz), 161.7 (d, *J* = 13.6 Hz), 129.0 (d, *J* = 11.4 Hz), 117.8 (d, *J* = 2.5 Hz), 109.7 (d, *J* = 22.7 Hz), 105.7 (d, *J* = 24.3 Hz), 80.1, 48.6, 26.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}FO_2 + H]^+$: 195.0821; found: 195.0815.

7-Methoxy-2,2-dimethyl-4-chromanone (27g): Yield: 93 mg (0.45 mmol, 45%) as a colorless solid, m.p. 79-81 ºC (lit[154] m.p. 81-82 ºC); IR: 2838, 1681, 1609 cm^{-1}; ^{1}H NMR: δ 7.79 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 2.67 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.1, 166.2, 162.0, 128.3, 114.1, 109.3, 101.1, 79.6, 55.4, 48.6, 26.7; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; found: 207.1012.

2,2,5,8-Tetramethyl-4-chromanone (27h): Yield: 51 mg (0.25 mmol, 25%; 42% brsm) as a colorless oil; IR: 1688, 1586 cm^{-1}; ^{1}H NMR: δ 7.16 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 2.69 (s, 2H), 2.58 (s, 3H), 2.17 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: δ 193.5, 159.0, 138.7, 135.5, 125.0, 123.0, 118.4, 77.9, 50.3, 26.7, 22.6, 16.0; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1225. A faster moving band contained 2,5-dimethylphenyl 3-methyl-2-butenoate [(X = 2,5-diMe), 45 mg, 0.22 mmol, 22%; 37% brsm] as a colorless oil. IR: 1734, 1649 cm^{-1}; ^{1}H NMR: δ 7.10 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 5.94 (apparent t, *J* = 0.7 Hz, 1H), 2.31 (s, 3H), 2.23 (d, *J* = 0.7 Hz, 3H), 2.13 (s, 3H), 1.99 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR: δ 164.8, 159.6, 149.1, 136.7, 130.7, 127.0, 126.5, 122.6, 115.1, 27.6, 20.9, 20.5, 15.8; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1221.

2,2,6,7-Tetramethyl-4-chromanone (27i): Yield: 178 mg (0.87 mmol, 87%) as a white solid, m.p. 69-71 ºC; IR: 1688, 1621 cm^{-1}; ^{1}H NMR: δ 7.59 (s, 1H), 6.72 (s, 1H), 2.67 (s, 2H), 2.25 (s, 3H),

2.20 (s, 3H), 1.43 (s, 6H); ^{13}C NMR: δ 192.9, 158.7, 147.0, 129.7, 126.9, 119.3, 118.4, 79.4, 49.3, 27.1, 20.9, 19.2; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1228.

2,2,6,8-Tetramethyl-4-chromanone (27j): Yield: 155 mg (0.76 mmol, 76%) as a white solid, m.p. 63-65 ºC; IR: 1689, 1614 cm^{-1}; ^{1}H NMR: δ 7.51 (s, 1H), 7.16 (s, 1H), 2.69 (s, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: δ 193.3, 156.3, 138.1, 129.2, 127.3, 123.6, 119.4, 78.6, 49.8, 26.7, 20.3, 15.7; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1221.

2,2,7,8-Tetramethyl-4-chromanone (27k): Yield: 177 mg (0.87 mmol, 87%) as a white solid, m.p. 52-54 ºC; IR: 1688, 1604 cm^{-1}; ^{1}H NMR: δ 7.62 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 2.67 (s, 2H), 2.29 (s, 3H), 2.14 (s, 3H), 1.45 (s, 6H); ^{13}C NMR: δ 193.5, 158.3, 146.0, 125.9, 123.7, 122.7, 118.5, 49.1, 27.3, 21.2, 11.9; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1233.

3,3-Dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (27l): Yield: 174 mg (0.77 mmol, 77%) as a light yellow solid, m.p. 78-80 ºC; IR: 1672, 1618 cm^{-1}; ^{1}H NMR: δ 9.44 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 2.82 (s, 2H), 1.51 (s, 6H); ^{13}C NMR: δ 193.6, 162.0, 137.3, 131.3, 129.5, 128.8, 128.3, 125.5, 124.5, 119.4, 111.4, 79.4, 50.1, 26.3; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{14}O_2 + H]^+$: 227.1072; found: 227.1068.

2,2-Dimethyl-2,3,6,7,8,9-hexahydro-4*H*-benzo[*g*]chromen-4-one (27m): Yield: 193 mg (0.84 mmol, 84%) as a white solid, m.p. 75-76 ºC; IR: 1687, 1618 cm^{-1}; ^{1}H NMR: δ 7.56 (s, 1H), 6.63 (s, 1H), 2.76 (m, 4H), 2.67 (s, 2H), 1.77 (m, 4H), 1.43 (s, 6H); ^{13}C NMR: δ 192.6, 157.6, 147.1, 129.9, 126.3, 118.2, 117.7, 78.8, 49.0, 30.7, 28.4, 26.7, 23.2, 22.7; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{18}O_2 + H]^+$: 231.1385; found: 231.1377.

7-Chloro-2,2-dimethyl-4-chromanone (27n): Yield: 84 mg (0.40 mmol, 40%; 48% brsm) as a white solid, m.p. 69-70 ºC; IR: 1694, 1599 cm^{-1}; ^{1}H NMR: δ 7.79 (d, *J* = 9.0 Hz, 1H), 6.95 (m, 2H), 2.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.5, 160.4, 141.9, 127.8, 121.5, 118.7, 118.5, 80.0, 48.7, 26.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}ClO_2 + H]^+$: 211.0526; found: 211.0529. A faster moving

band contained 3-chlorophenyl 3-methyl-2-butenoate [**1m** (X = 3-Cl), 55 mg, 0.26 mmol, 26%; 31% brsm] as a colorless oil. IR: 1742, 1649 cm^{-1}; ^{1}H NMR: δ 7.30 (t, *J* = 8.1 Hz, 1H), 7.20 (dm, *J* = 9.0 Hz, 1H), 7.15 (t, *J* = 2.4 Hz, 1H), 7.01 (dm, *J* = 8.1 Hz, 1H), 5.89 (s, 1H), 2.24 (s, 3H), 2.00 (s, 3H); ^{13}C NMR: δ 164.4, 160.9, 151.2, 134.6, 130.1, 125.8, 122.5, 120.2, 114.8, 27.7, 20.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}ClO_2 + H]^+$: 211.0526; found: 211.0520.

6-Methoxy-2,2-dimethyl-4-chromanone (27o): Yield: 165 mg (0.80 mmol, 80%) as a light yellow solid, m.p. 69-71 ºC; IR: 2834, 1686, 1619 cm^{-1}; ^{1}H NMR: δ 7.29 (s, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 2.70 (s, 2H), 1.44 (s, 6H); ^{13}C NMR: δ 193.1, 155.1, 154.0, 125.8, 120.4, 120.1, 107.4, 79.5, 56.2, 49.3, 27.0; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; found: 207.1015.

(±)-2,6-Dimethyl-4-chromanone (31b): Yield: 114 mg (0.65 mmol, 65%) as a yellow oil; IR: 1691, 1618 cm^{-1}; ^{1}H NMR: δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.55 (m, 1H), 2.67 (AB pattern, *J* = 16.9 Hz, 1H), 2.65 (s, 1H), 2.30 (s, 3H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.8, 159.8, 137.1, 130.6, 126.5, 120.4, 117.7, 74.2, 44.7, 21.0, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; found: 177.0913.

(±)-2,7-Dimethyl-4-chromanone (31c): Yield: 91 mg (0.52 mmol, 52%) as a light yellow oil; IR: 1689, 1615 cm^{-1}; ^{1}H NMR: δ 7.77 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 4.56 (m, 1H), 2.66 (AB pattern, *J* = 16.5 Hz, 1H), 2.64 (s, 1H), 2.35 (s, 3H), 1.50 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.3, 161.7, 147.5, 126.8, 122.6, 118.6, 117.9, 74.3, 44.6, 21.9, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; found: 177.0921.

(±)-2,5,7-Trimethyl-4-chromanone (31d): Yield: 159 mg (0.84 mmol, 84%) as a white solid, m.p. 53-54 ºC; IR: 1681, 1613 cm^{-1}; ^{1}H NMR: δ 6.64 (s, 1H), 6.60 (s, 1H), 4.51 (m, 1H), 2.65-2.58 (obscured pattern, 2H), 2.60 (s, 3H), 2.29 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 193.6, 162.8, 145.8, 141.8, 125.8, 117.1, 115.9, 73.5, 46.1, 22.7, 21.7, 20.9; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1070.

(±)-2,5-Dimethyl-8-isopropyl-4-chromanone (31e): Yield: 72 mg (0.33 mmol, 33%; 40% brsm) as a white solid, m.p. 64-65 ºC; IR: 1685, 1579 cm^{-1}; ^{1}H NMR: δ 7.24 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 4.52 (m 1H), 3.28 (septet, *J* = 6.9 Hz, 1H), 2.68 (AB pattern, *J* = 16.8 Hz, 1H), 2.65 (s, 1H), 2.60 (s, 3H), 1.51 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ 195.1, 160.5, 139.5, 135.5, 131.7, 124.5, 119.8, 73.8, 46.6, 27.2, 23.2, 23.0, 22.9, 21.4; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{18}O_2 + H]^+$: 219.1385; found: 219.1388. A faster moving band contained 2-isopropyl-5-methylphenyl (*E*)-2-butenoate [(X = 2-*i*-Pr-5-Me), 72 mg, 0.33 mmol, 33%; 40% brsm] as a light yellow oil; IR: 1739, 1659 cm^{-1}; ^{1}H NMR: δ 7.24-7.14 (complex, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.83 (s, 1H), 6.07 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.98 (septet, *J* = 6.9 Hz, 1H), 2.32 (s, 3H), 1.97 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ 165.1, 147.9, 146.7, 137.1, 136.5, 127.0, 126.4, 122.8, 122.1, 27.1, 23.0, 20.8, 18.2; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{18}O_2 + H]^+$: 219.1385; found: 219.1378.

(±)-7-Fluoro-2-methyl-4-chromanone (31f): Yield: 128 mg (0.71 mmol, 71%) as a light yellow oil; IR: 1695, 1612 cm^{-1}; ^{1}H NMR: δ 7.89 (dd, *J* = 8.8, 6.6 Hz, 1H), 6.72 (td, *J* = 8.4, 2.4 Hz, 1H), 6.65 (dd, *J* = 10.1, 2.4 Hz, 1H), 4.61 (m, 1H), 2.68 (s, 1H), 2.66 (AB, *J* = 16.4 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 191.1, 167.4 (d, *J* = 256.0 Hz), 163.3 (d, *J* = 13.7 Hz), 129.4 (d, *J* = 11.4 Hz), 117.7 (d, *J* = 2.6 Hz), 109.6 (d, *J* = 22.7 Hz), 104.6 (d, *J* = 24.3 Hz), 74.9, 44.1, 20.8; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9FO_2 + H]^+$: 181.0664; found: 181.0661.

(±)-7-Methoxy-2-methyl-4-chromanone (31g): Yield: 105 mg (0.55 mmol, 55%) as a yellow solid, m.p. 67-69 ºC; IR: 2839, 1682, 1607 cm^{-1}; ^{1}H NMR: δ 7.52 (d, *J* = 8.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.59 (m, 1H), 3.83 (s, 3H), 2.64 (AB, *J* = 16.8 Hz, 1H), 2.62 (s, 1H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 191.1, 166.0, 163.6, 128.7, 114.8, 109.8, 100.7, 74.7, 55.6, 44.3, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_3 + H]^+$: 193.0865; found: 193.0859.

(±)-2,5,8-Trimethyl-4-chromanone (31h): Yield: 80 mg (0.42 mmol, 42%; 47% brsm) as a light yellow oil; IR: 1685, 1583 cm^{-1}; ^{1}H NMR: δ 7.17 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 4.53

(m, 1H), 2.67 (AB pattern, *J* = 16.6 Hz, 1H), 2.64 (s, 1H), 2.59 (s, 3H), 2.19 (s, 3H), 1.50 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: 194.9, 161.3, 139.6, 135.9, 125.1, 124.0, 118.8, 73.8, 46.5, 23.2, 21.4, 16.3; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1066. A faster moving band contained 2,5-dimethylphenyl (*E*)-2-butenoate [(X = 2,5-diMe), 67 mg, 0.35 mmol, 35%; 39% brsm] as a colorless oil; IR: 1739, 1656 cm^{-1}; ^{1}H NMR: 7.16 (dq, *J* = 15.5, 6.9 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 6.07 (dq, *J* = 15.5, 1.7 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 1.96 (dd, *J* = 6.9, 1.7 Hz, 3H); ^{13}C NMR: δ 164.7, 149.2, 146.7, 136.8, 130.8, 127.0, 126.7, 122.5, 122.0, 20.9, 18.2, 15.8; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1062.

(±)-2,6,7-Trimethyl-4-chromanone (31i): Yield: 136 mg (0.72 mmol, 72%) as a tan solid, m.p. 73-75 ºC; IR: 1681, 1621 cm^{-1}; ^{1}H NMR: δ 7.61 (s, 1H), 6.76 (s, 1H), 4.55 (m, 1H), 2.64 (AB pattern, *J* = 16.9 Hz, 1H), 2.62 (s, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.49 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.5, 160.0 146.5, 129.8, 126.9, 118.6, 118.3, 74.2, 44.6, 21.0, 20.5, 18.8; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1075.

(±)-2,6,8-Trimethyl-4-chromanone (31j): Yield: 68 mg (0.36 mmol, 36%; 44% brsm) as a light yellow solid, m.p. 48-51 ºC; IR: 1692,1616 cm^{-1}; ^{1}H NMR: δ 7.53 (s, 1H), 7.16 (s, 1H), 4.54 (m, 1H), 2.65 (apparent s, 1H), 2.63 (s, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.52 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 193.2, 158.1, 138.0, 129.8, 126.8, 124.0, 120.1, 74.0, 44.6, 21.0, 20.4, 15.6; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1064. A faster moving band contained 2,4-dimethylphenyl (*E*)-2-butenoate [(X = 2,4-diMe), 57 mg, 0.30 mmol, 30%; 37% brsm] as a light yellow oil; IR: 1740, 1657 cm^{-1}; ^{1}H NMR: δ 7.19 (dq, *J* = 16.9, 6.9 Hz, 1H), 7.03 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.07 (dd, *J* = 16.9, 1.8 Hz, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 1.96 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR: δ 164.8, 147.1, 146.6, 135.4, 131.7, 129.8, 127.4, 122.0, 121.6, 20.8, 18.2, 16.1; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1066.

(±)-2,7,8-Trimethyl-4-chromanone (31k): Yield: 152 mg (0.80 mmol, 80%) as a yellow oil; IR: 1688, 1604 cm^{-1}; ^{1}H NMR: δ 7.66 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.55 (m, 1H), 2.65

(s, 1H), 2.63 (AB, *J* = 16.5 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 1.53 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.8, 159.5, 145.3, 124.9, 123.5, 122.6, 118.5, 73.9, 44.2, 20.9, 20.5, 11.2; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1067.

(±)-3-Methyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (31l): Yield: 159 mg (0.75 mmol, 75%) as a white solid, m.p. 66-68 ºC; IR: 1667, 1618 cm^{-1}; ^{1}H NMR: δ 9.45 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 4.71 (m, 1H), 2.87-2.69 (complex, 2H), 1.57 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR: δ 193.4, 163.6, 137.2, 131.1, 129.4, 128.9, 128.1, 125.6, 124.6, 118.7, 112.2, 74.2, 45.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{12}O_2 + H]^+$: 213.0916; found: 213.0909.

(±)-2-Methyl-2,3,6,7,8,9-hexahydro-4*H*-benzo[*g*]chromen-4-one (31m): Yield: 112 mg (0.52 mmol, 52%) as a light yellow solid, m.p. 60-61 ºC; IR: 1686, 1618 cm^{-1}; ^{1}H NMR: δ 7.58 (s, 1H), 6.67 (s, 1H), 4.51 (m, 1H), 2.72 (dm, *J* = 15.8 Hz, 4H), 2.64 (AB, *J* = 15.8 Hz, 1H), 2.62 (s, 1H), 1.77 (m, 4H), 1.48 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.6, 159.3, 146.9, 130.5, 126.7, 118.8, 117.2, 74.1, 44.7, 30.1, 28.5, 23.1, 22.7, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{16}O_2 + H]^+$: 217.1229; found: 217.1232.

(±)-7-Chloro-2-methyl-4-chromanone (31n): Yield: 52 mg (0.26 mmol, 36%; 46% brsm) as a white solid, m.p. 53-55 ºC; IR: 1690, 1598 cm^{-1}; ^{1}H NMR: δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.00 (s, 1 H), 6.99 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.61 (m, 1H), 2.69 (s, 1H), 2.67 (AB pattern, *J* = 16.8 Hz, 1H), 1.52 (d, *J* = 6.3 Hz, 3H),; ^{13}C NMR: δ 191.2, 161.8, 141.6, 128.0, 121.9, 119.2, 117.9, 74.7, 44.2, 20.7; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9ClO_2 + H]^+$: 197.0369; found: 197.0376. A faster moving band contained 3-chlorophenyl (*E*)-2-butenoate [(X = 3-Cl), 43 mg, 0.22 mmol, 22%; 28% brsm] as a light yellow oil; IR: 1736, 1655 cm^{-1}; ^{1}H NMR: δ 7.30 (t, *J* = 8.1 Hz, 1H), 7.24-7.14 (complex, 3H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 1.98 (dd, *J* = 6.9, 1.7 Hz, 3H); ^{13}C NMR: δ 164.2, 151.1, 147.4, 134.4, 129.9, 125.8, 122.2, 121.5, 119.9, 18.1; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9ClO_2 + H]^+$: 197.0369; found: 197.0362.

(±)-6-Methoxy-2-methyl-4-chromanone (31o): Yield: 99 mg (0.52 mmol, 52%) as an orange solid, mp 58-61 ºC; IR: 2834, 1689, 1621 cm^{-1}; ^{1}H NMR: δ 7.31 (d, *J* = 3.2 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.55 (m, 1H), 3.80 (s, 3H), 2.67 (apparent br s, 1H), 2.65 (s, 1H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 193.1, 156.9, 154.4, 125.7, 121.7, 119.6, 107.7, 74.8, 56.3, 45.0, 21.4; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_3 + H]^+$: 193.0865; found: 193.0866.

REFERENCES

(1) Tacconelli, E.; Carrara, E.; Savoldi, A.; Harbarth, S.; Mendelson, M.; Monnet, D. L.; Pulcini, C.; Kahlmeter, G.; Kluytmans, J.; Carmeli, Y.; et al. Discovery, Research, and Development of New Antibiotics: The WHO Priority List of Antibiotic-Resistant Bacteria and Tuberculosis. *The Lancet Infectious Diseases* **2018**, *18* (3), 318–327. https://doi.org/10.1016/S1473-3099(17)30753-3.

(2) Singh, S. B.; Young, K.; Silver, L. L. What Is an "Ideal" Antibiotic? Discovery Challenges and Path Forward. *Biochemical Pharmacology* **2017**, *133*, 63–73. https://doi.org/10.1016/j.bcp.2017.01.003.

(3) Rivera, M. Bacterioferritin: Structure, Dynamics, and Protein–Protein Interactions at Play in Iron Storage and Mobilization. *Accounts of Chemical Research* **2017**, *50* (2), 331–340. https://doi.org/10.1021/acs.accounts.6b00514.

(4) Eshelman, K.; Yao, H.; Punchi Hewage, A. N. D.; Deay, J. J.; Chandler, J. R.; Rivera, M. Inhibiting the BfrB:Bfd Interaction in Pseudomonas Aeruginosa Causes Irreversible Iron Accumulation in Bacterioferritin and Iron Deficiency in the Bacterial Cytosol. *Metallomics* **2017**, *9* (6), 646–659. https://doi.org/10.1039/C7MT00042A.

(5) Wijerathne, H.; Yao, H.; Wang, Y.; Lovell, S.; Battaile, K. P.; Rivera, M. Bfd, a New Class of [2Fe-2S] Protein That Functions in Bacterial Iron Homeostasis, Requires a Structural Anion Binding Site. *Biochemistry* **2018**, *57* (38), 5533–5543. https://doi.org/10.1021/acs.biochem.8b00823.

(6) Zughaier, S. M.; Cornelis, P. Editorial: Role of Iron in Bacterial Pathogenesis. *Frontiers in Cellular and Infection Microbiology* **2018**, *8*. https://doi.org/10.3389/fcimb.2018.00344.

(7) *Metallomics and the Cell*; Banci, L., Ed.; Metal ions in life sciences; Springer: Dordrecht,

(8) Köster, W. ABC Transporter-Mediated Uptake of Iron, Siderophores, Heme and Vitamin B12. *Research in Microbiology* **2001**, *152* (3–4), 291–301. https://doi.org/10.1016/S0923-2508(01)01200-1.

(9) Frawley, E. R.; Fang, F. C. The Ins *and Outs* of Bacterial Iron Metabolism: Bacterial Iron Effux Transporters. *Molecular Microbiology* **2014**, *93* (4), 609–616. https://doi.org/10.1111/mmi.12709.

(10) Patschinski, P.; Zhang, C.; Zipse, H. The Lewis Base-Catalyzed Silylation of Alcohols—A Mechanistic Analysis. *The Journal of Organic Chemistry* **2014**, *79* (17), 8348–8357. https://doi.org/10.1021/jo5016568.

(11) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2006. https://doi.org/10.1002/0470053488.

(12) Kim, S.; Chang, H. 1,8-Diazabicyclo[5.4.0]Undec-7-Ene. An Effective and Selective Catalyst for the *t* -Butyldimethylsilylation of Alcohols. *Bulletin of the Chemical Society of Japan* **1985**, *58* (12), 3669–3670. https://doi.org/10.1246/bcsj.58.3669.

(13) Lombardo, L. Diisopropylethylamine: An Effective Catalyst for the Introduction of the t-Butyldimethylsilyl Group. *Tetrahedron Letters* **1984**, *25* (2), 227–228. https://doi.org/10.1016/S0040-4039(00)99846-0.

(14) Akiba, K.; Iseki, Y.; Wada, M. A Convenient Method for the Regioselective Synthesis of 4-Alkyl(Aryl)Pyridines Using Pyridinium Salts. *Bulletin of the Chemical Society of Japan* **1984**, *57* (7), 1994–1999. https://doi.org/10.1246/bcsj.57.1994.

(15) *Category 1, Organometallics: Compounds of Groups 15 (As, Sb, Bi) and Silicon Compounds*, 1st ed.; Fleming, Ley, Eds.; Georg Thieme Verlag: Stuttgart, 2002. https://doi.org/10.1055/b-003-121793.

(16) Ando, K. A Mechanistic Study of the Horner−Wadsworth−Emmons Reaction: Computational Investigation on the Reaction Pass and the Stereochemistry in the Reaction of Lithium Enolate Derived from Trimethyl Phosphonoacetate with Acetaldehyde. *The Journal of Organic Chemistry* **1999**, *64* (18), 6815–6821. https://doi.org/10.1021/jo9909150.

(17) Kumar, P. Synthesis of substituted 1-tetralones. *Organic Preparations and Procedures International* **1997**, *29* (4), 477–480. https://doi.org/10.1080/00304949709355222.

(18) Hao, X.-Q.; Wang, Y.-N.; Liu, J.-R.; Wang, K.-L.; Gong, J.-F.; Song, M.-P. Unsymmetrical, Oxazolinyl-Containing Achiral and Chiral NCN Pincer Ligand Precursors and Their Complexes with Palladium(II). *Journal of Organometallic Chemistry* **2010**, *695* (1), 82–89. https://doi.org/10.1016/j.jorganchem.2009.09.031.

(19) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures [1]. *The Journal of Organic Chemistry* **1996**, *61* (11), 3849–3862. https://doi.org/10.1021/jo960057x.

(20) Yang, L.-X.; Hofer, K. G. Reductive Amination of Nitroimidazole Aldehyde with Diamines Using Sodium Triacetoxyborohydride. *Tetrahedron Letters* **1996**, *37* (34), 6081–6084. https://doi.org/10.1016/0040-4039(96)01297-X.

(21) Abdel-Magid, A. F.; Mehrman, S. J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Organic Process Research & Development* **2006**, *10* (5), 971–1031. https://doi.org/10.1021/op0601013.

(22) Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed Reduction of .Beta.-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *Journal of the American Chemical Society* **1988**, *110* (11), 3560–3578. https://doi.org/10.1021/ja00219a035.

(23) Pedrajas, E.; Sorribes, I.; Junge, K.; Beller, M.; Llusar, R. Selective Reductive Amination of Aldehydes from Nitro Compounds Catalyzed by Molybdenum Sulfide Clusters. *Green Chemistry* **2017**, *19* (16), 3764–3768. https://doi.org/10.1039/C7GC01603D.

(24) Xu, F.; Wang, Y.; Luo, D.; Yu, G.; Wu, Y.; Dai, A.; Zhao, Y.; Wu, J. Novel Trifluoromethyl Pyridine Derivatives Bearing a 1,3,4-Oxadiazole Moiety as Potential Insecticide. *ChemistrySelect* **2018**, *3* (10), 2795–2799. https://doi.org/10.1002/slct.201800123.

(25) Latacz, G.; Kieć-Kononowicz, K. Biotransformation of New Racemic (R,S)-5-Benzylhydantoin Derivatives by D-Hydantoinases from Adzuki Bean. *Biocatalysis and Biotransformation* **2014**, *32* (2), 117–124. https://doi.org/10.3109/10242422.2014.893578.

(26) Hayashi, S.; Hirao, A.; Imai, A.; Nakamura, H.; Murata, Y.; Ohashi, K.; Nakata, E. Novel Non-Peptide Nociceptin/Orphanin FQ Receptor Agonist, 1-[1-(1-Methylcyclooctyl)-4-Piperidinyl]-2-[(3*R*)-3-Piperidinyl]-1*H*-Benzimidazole: Design, Synthesis, and Structure−Activity Relationship of Oral Receptor Occupancy in the Brain for Orally Potent Antianxiety Drug. *Journal of Medicinal Chemistry* **2009**, *52* (3), 610–625. https://doi.org/10.1021/jm7012979.

(27) Watanuki, S.; Matsuura, K.; Tomura, Y.; Okada, M.; Okazaki, T.; Ohta, M.; Tsukamoto, S. Synthesis and Pharmacological Evaluation of 1-Alkyl-*N*-[(1R)-1-(4-Fluorophenyl)-2-Methylpropyl]Piperidine-4-Carboxamide Derivatives as Novel Antihypertensive Agents. *Chemical & Pharmaceutical Bulletin* **2011**, *59* (11), 1376–1385. https://doi.org/10.1248/cpb.59.1376.

(28) Dwyer, D. J.; Belenky, P. A.; Yang, J. H.; MacDonald, I. C.; Martell, J. D.; Takahashi, N.; Chan, C. T. Y.; Lobritz, M. A.; Braff, D.; Schwarz, E. G.; et al. Antibiotics Induce Redox-Related Physiological Alterations as Part of Their Lethality. *Proceedings of the National Academy of Sciences* **2014**, *111* (20), E2100–E2109. https://doi.org/10.1073/pnas.1401876111.

(29) Belenky, P.; Ye, J. D.; Porter, C. B. M.; Cohen, N. R.; Lobritz, M. A.; Ferrante, T.; Jain, S.; Korry, B. J.; Schwarz, E. G.; Walker, G. C.; et al. Bactericidal Antibiotics Induce Toxic Metabolic Perturbations That Lead to Cellular Damage. *Cell Reports* **2015**, *13* (5), 968–980. https://doi.org/10.1016/j.celrep.2015.09.059.

(30) Gnanasekaran, K. K.; Benbrook, D. M.; Nammalwar, B.; Thavathiru, E.; Bunce, R. A.; Berlin, K. D. Synthesis and Evaluation of Second Generation Flex-Het Scaffolds against the Human Ovarian Cancer A2780 Cell Line. *European Journal of Medicinal Chemistry* **2015**, *96*, 209–217. https://doi.org/10.1016/j.ejmech.2015.03.070.

(31) Bast Jr, R. C.; Hennessy, B.; Mills, G. B. The Biology of Ovarian Cancer: New Opportunities for Translation. *Nature Reviews Cancer* **2009**, *9*, 415.

(32) Álvarez, R.; Vaz, B.; Gronemeyer, H.; de Lera, Á. R. Functions, Therapeutic Applications, and Synthesis of Retinoids and Carotenoids. *Chemical Reviews* **2014**, *114* (1), 1–125. https://doi.org/10.1021/cr400126u.

(33) Benbrook, D. M.; Nammalwar, B.; Long, A.; Matsumoto, H.; Singh, A.; Bunce, R. A.; Berlin, K. D. SHetA2 Interference with Mortalin Binding to P66shc and P53 Identified Using Drug-Conjugated Magnetic Microspheres. *Investigational New Drugs* **2014**, *32* (3), 412–423. https://doi.org/10.1007/s10637-013-0041-x.

(34) Watts, F. M.; Pouland, T.; Bunce, R. A.; Berlin, K. D.; Benbrook, D. M.; Mashayekhi, M.; Bhandari, D.; Zhou, D. Activity of Oxygen-versus Sulfur-Containing Analogs of the Flex-Het Anticancer Agent SHetA2. *European Journal of Medicinal Chemistry* **2018**, *158*, 720–732. https://doi.org/10.1016/j.ejmech.2018.09.036.

(35) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L. S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. J. Conformationally Restricted Retinoids. *Journal of Medicinal Chemistry* **1984**, *27* (11), 1516–1531. https://doi.org/10.1021/jm00377a022.

(36) Sauer, J. C. Ketene Dimers from Acid Halides. *Journal of the American Chemical Society* **1947**, *69* (10), 2444–2448. https://doi.org/10.1021/ja01202a058.

(37) Munch, H.; Hansen, J. S.; Pittelkow, M.; Christensen, J. B.; Boas, U. A New Efficient Synthesis of Isothiocyanates from Amines Using Di-Tert-Butyl Dicarbonate. *Tetrahedron Letters* **2008**, *49* (19), 3117–3119. https://doi.org/10.1016/j.tetlet.2008.03.045.

(38) Narendar Reddy, T.; Jayathirtha Rao, V. Importance of Baylis-Hillman Adducts in Modern Drug Discovery. *Tetrahedron Letters* **2018**, *59* (30), 2859–2875. https://doi.org/10.1016/j.tetlet.2018.06.023.

(39) Yasareni Sumalatha, Tamma Ranga Reddy, Padi Pratap Reddy and Bollikonda Satyanarayana. A Simple, Efficient and Scalable Synthesis of Hypnotic Agent, Zolpidem. *ARKIVOC* **2009**, No. ii, 315–320.

(40) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. Synthesis of Imidazopyridines from the Morita–Baylis–Hillman Acetates of Nitroalkenes and Convenient Access to Alpidem and Zolpidem. *Organic Letters* **2012**, *14* (17), 4580–4583. https://doi.org/10.1021/ol3020418.

(41) Morita, K.; Suzuki, Z.; Hirose, H. A Tertiary Phosphine-Catalyzed Reaction of Acrylic Compounds with Aldehydes. *Bulletin of the Chemical Society of Japan* **1968**, *41* (11), 2815–2815. https://doi.org/10.1246/bcsj.41.2815.

(42) Methanolic Trimethylamine Mediated Baylis-Hillman Reaction. *Arkivoc* **2002**, *2002* (7), 136. https://doi.org/10.3998/ark.5550190.0003.715.

(43) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. The Asymmetric Baylis−Hillman Reaction. *Journal of the American Chemical Society* **1997**, *119* (18), 4317–4318. https://doi.org/10.1021/ja970079g.

(44) Srihari, E.; Kumar, G. S.; Kumar, C. N. S. S. P.; Seth, R. K.; Biswas, S.; Sridhar, B.; Jayathirtha Rao, V. Synthesis and Antimalarial Activity of Baylis-Hillman Adducts from Substituted 2-Chloroquinoline-3-Carboxaldehydes. *Heterocyclic Communications* **2011**, *17* (3–4). https://doi.org/10.1515/hc.2011.024.

(45) Makar, S.; Saha, T.; Singh, S. K. Naphthalene, a Versatile Platform in Medicinal Chemistry: Sky-High Perspective. *European Journal of Medicinal Chemistry* **2019**, *161*, 252–276. https://doi.org/10.1016/j.ejmech.2018.10.018.

(46) Feng, C.; Loh, T.-P. Palladium-Catalyzed Bisolefination of C−C Triple Bonds: A Facile Method for the Synthesis of Naphthalene Derivatives. *Journal of the American Chemical Society* **2010**, *132* (50), 17710–17712. https://doi.org/10.1021/ja108998d.

(47) Viswanathan, G. S.; Wang, M.; Li, C.-J. A Highly Regioselective Synthesis of Polysubstituted Naphthalene Derivatives through Gallium Trichloride Catalyzed Alkyne–Aldehyde Coupling. *Angewandte Chemie International Edition* **2002**, *41* (12), 2138. https://doi.org/10.1002/1521-3773(20020617)41:12<2138::AID-ANIE2138>3.0.CO;2-T.

(48) Kabalka, G. W.; Ju, Y.; Wu, Z. A New Titanium Tetrachloride Mediated Annulation of α-Aryl-Substituted Carbonyl Compounds with Alkynes: A Simple and Highly Efficient Method for the Regioselective Synthesis of Polysubstituted Naphthalene Derivatives. *The Journal of Organic Chemistry* **2003**, *68* (20), 7915–7917. https://doi.org/10.1021/jo034330o.

(49) Singh, B.; Chandra, A.; Singh, R. M. Base-Free Amination of BH Acetates of 2-Chloroquinolinyl-3-Carboxaldehydes: A Facile Route to the Synthesis of N-Substituted-1,2-Dihydrobenzo[b][1,8]Naphthyridines. *Tetrahedron* **2011**, *67* (13), 2441–2446. https://doi.org/10.1016/j.tet.2011.01.076.

(50) Gupta, T.; Singh, J. B.; Mishra, K.; Singh, R. M. Active Methylene Compounds (AMCs) Controlled Facile Synthesis of Acridine and Phenanthridine from Morita Baylis–Hillman Acetate. *RSC Advances* **2017**, *7* (86), 54581–54585. https://doi.org/10.1039/C7RA09447G.

(51) Liu, Z.; Patel, C.; Harvey, J. N.; Sunoj, R. B. Mechanism and Reactivity in the Morita–Baylis–Hillman Reaction: The Challenge of Accurate Computations. *Physical Chemistry Chemical Physics* **2017**, *19* (45), 30647–30657. https://doi.org/10.1039/C7CP06508F.

(52) Bruice, P. Y. *Organic Chemistry*, 6th ed.; Prentice Hall: Boston, 2011.

(53) Hamada, Y. Role of Pyridines in Medicinal Chemistry and Design of BACE1 Inhibitors Possessing a Pyridine Scaffold. In *Pyridine*; Pandey, P. P., Ed.; InTech, 2018. https://doi.org/10.5772/intechopen.74719.

(54) Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. Library Design, Synthesis, and Screening: Pyridine Dicarbonitriles as Potential Prion Disease Therapeutics. *Journal of Medicinal Chemistry* **2006**, *49* (2), 607–615. https://doi.org/10.1021/jm050610f.

(55) Beukers, M. W.; Chang, L. C. W.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Brussee, J.; I. Jzerman, A. P. New, Non-Adenosine, High-Potency Agonists for the Human Adenosine A_{2B} Receptor with an Improved Selectivity Profile Compared to the Reference Agonist *N* -Ethylcarboxamidoadenosine. *Journal of Medicinal Chemistry* **2004**, *47* (15), 3707–3709. https://doi.org/10.1021/jm049947s.

(56) Kumar, S. N.; Pavan Kumar, C. H. N. S. S.; Srihari, E.; Kancharla, S.; Srinivas, K.; Shrivastava, S.; Naidu, V. G. M.; Jayathirtha Rao, V. First Total Synthesis of Fuzanins C, D and Their Analogues as Anticancer Agents. *RSC Adv.* **2014**, *4* (16), 8365–8375. https://doi.org/10.1039/C3RA47263A.

(57) Wissner, A.; Hamann, P. R.; Nilakantan, R.; Greenberger, L. M.; Ye, F.; Rapuano, T. A.; Loganzo, F. Syntheses and EGFR Kinase Inhibitory Activity of 6-Substituted-4-Anilino [1,7] and [1,8] Naphthyridine-3-Carbonitriles. *Bioorganic & Medicinal Chemistry Letters* **2004**, *14* (6), 1411–1416. https://doi.org/10.1016/j.bmcl.2004.01.034.

(58) Zhang, F.; Duan, X.-F. Facile One-Pot Direct Arylation and Alkylation of Nitropyridine *N* -Oxides with Grignard Reagents. *Organic Letters* **2011**, *13* (22), 6102–6105. https://doi.org/10.1021/ol202597b.

(59) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. Direct, Catalytic, and Regioselective Synthesis of 2-Alkyl-, Aryl-, and Alkenyl-Substituted *N*-Heterocycles from *N*-Oxides. *Organic Letters* **2014**, *16* (3), 864–867. https://doi.org/10.1021/ol403631k.

(60) Wei, Y.; Yoshikai, N. Modular Pyridine Synthesis from Oximes and Enals through Synergistic Copper/Iminium Catalysis. *Journal of the American Chemical Society* **2013**, *135* (10), 3756–3759. https://doi.org/10.1021/ja312346s.

(61) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. Copper-Facilitated Suzuki Reactions: Application to 2-Heterocyclic Boronates. *Organic Letters* **2009**, *11* (2), 345–347. https://doi.org/10.1021/ol802556f.

(62) Wei, H.; Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H. Synthesis of Polysubstituted Pyridines via a One-Pot Metal-Free Strategy. *Organic Letters* **2015**, *17* (24), 5974–5977. https://doi.org/10.1021/acs.orglett.5b02903.

(63) Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. Chromones as a Privileged Scaffold in Drug Discovery: A Review. *European Journal of Medicinal Chemistry* **2014**, *78*, 340–374. https://doi.org/10.1016/j.ejmech.2014.03.047.

(64) Vinot, N.; Maitte, P. Synthèse de Dimethyl-2,2 Chromanne diones-3,4: Condensation Avec Les *Ortho*-Diaminopyridines. *Journal of Heterocyclic Chemistry* **1989**, *26* (4), 1013–1021. https://doi.org/10.1002/jhet.5570260422.

(65) Jovanovic, S. V.; Steenken, S.; Tosic, M.; Marjanovic, B.; Simic, M. G. Flavonoids as Antioxidants. *Journal of the American Chemical Society* **1994**, *116* (11), 4846–4851. https://doi.org/10.1021/ja00090a032.

(66) Zhou, T.; Shi, Q.; Lee, K. H. Anti-AIDS Agents 83. Efficient Microwave-Assisted One-Pot Preparation of Angular 2,2-Dimethyl-2H-Chromone Containing Compounds. *Tetrahedron Letters* **2010**, *51* (33), 4382–4386. https://doi.org/10.1016/j.tetlet.2010.06.058.

(67) Martens, S.; Mithöfer, A. Flavones and Flavone Synthases. *Phytochemistry* **2005**, *66* (20), 2399–2407. https://doi.org/10.1016/j.phytochem.2005.07.013.

(68) Ganguly, A. K.; Kaur, S.; Mahata, P. K.; Biswas, D.; Pramanik, B. N.; Chan, T. M. Synthesis and Properties of 3-Acyl-γ-Pyrones, a Novel Class of Flavones and Chromones. *Tetrahedron Letters* **2005**, *46* (23), 4119–4121. https://doi.org/10.1016/j.tetlet.2005.04.010.

(69) Varma, R. S.; Saini, R. K.; Kumar, D. An Expeditious Synthesis of Flavones on Montmorillonite K 10 Clay with Microwaves. *Journal of Chemical Research* **1998**, No. 6, 348–349. https://doi.org/10.1039/a709146j.

(70) Meraz, K.; Gnanasekaran, K. K.; Thing, R.; Bunce, R. A. Bismuth(III) Triflate Catalyzed Tandem Esterification–Fries–Oxa-Michael Route to 4-Chromanones. *Tetrahedron Letters* **2016**, *57* (46), 5057–5061. https://doi.org/10.1016/j.tetlet.2016.10.005.

(71) Nammalwar, B.; Bunce, R. A. Friedel–Crafts Cyclization of Tertiary Alcohols Using Bismuth(III) Triflate. *Tetrahedron Letters* **2013**, *54* (32), 4330–4332. https://doi.org/10.1016/j.tetlet.2013.06.026.

(72) Winn, M.; De, B.; Zydowsky, T. M.; Altenbach, R. J.; Basha, F. Z.; Boyd, S. A.; Brune, M. E.; Buckner, S. A.; Crowell, D. 2-(Alkylamino)Nicotinic Acid and Analogs. Potent Angiotensin II Antagonists. *Journal of Medicinal Chemistry* **1993**, *36* (18), 2676–2688. https://doi.org/10.1021/jm00070a012.

(73) Khunnawutmanotham, N.; Chimnoi, N.; Thitithanyanont, A.; Saparpakorn, P.; Choowongkomon, K.; Pungpo, P.; Hannongbua, S.; Techasakul, S. Dipyridodiazepinone Derivatives; Synthesis and Anti HIV-1 Activity. *Beilstein Journal of Organic Chemistry* **2009**, *5*. https://doi.org/10.3762/bjoc.5.36.

(74) Wissner, A.; Hamann, P. R.; Nilakantan, R.; Greenberger, L. M.; Ye, F.; Rapuano, T. A.; Loganzo, F. Syntheses and EGFR Kinase Inhibitory Activity of 6-Substituted-4-Anilino [1,7] and [1,8] Naphthyridine-3-Carbonitriles. *Bioorganic & Medicinal Chemistry Letters* **2004**, *14* (6), 1411–1416. https://doi.org/10.1016/j.bmcl.2004.01.034.

(75) Wilzbach, K. E.; Harkness, A. L.; Kaplan, L. Photochemical Rearrangement of Benzene-1,3,5-Tri Deutrium. *Journal of the American Chemical Society* **1968**, *90* (5), 1116–1118. https://doi.org/10.1021/ja01007a004.

(76) van De Sande, C.; Vandewalle, M. On The Occurrence of Fries Type Reactions in Polyphosphoric Acid. Synthesis of 2-Alkyl Substituted 4-Chromanones from Phenols and α, β-Unsaturated Carboxylic Acids. *Bulletin des Sociétés Chimiques Belges* **2010**, *82* (9–10), 705–710. https://doi.org/10.1002/bscb.19730820912.

(77) Vinot, N.; Maitte, P. Synthèse de Dimethyl-2,2 Chromanediones-3,4: Condensation Avec Les *Ortho* -Diaminopyridines. *Journal of Heterocyclic Chemistry* **1989**, *26* (4), 1013–1021. https://doi.org/10.1002/jhet.5570260422.

VITA

Kevin Meraz

Candidate for the Degree of

Doctor of Philosophy

Dissertation: SYNTHESIS OF SMALL MOLECULES AS POTENTIAL ANTIBIOTIC AND ANTICANCER CANDIDATES; SYNTHESIS OF BIOACTIVE HETEROCYCLIC SCAFFOLDS

Major Field: Organic Chemistry

Biographical:

Education:

Completed the requirements for the Doctor of Philosophy in Chemistry at Oklahoma State University, Stillwater, Oklahoma in May, 2019

Completed the requirements for the Bachelor of Science in Chemistry at Our Lady of the Lake University, San Antonio, Texas in 2015

Professional Memberships:
GAMMA SIGMA EPSILON, OMEGA DELTA PHI INC.
ROBERT E. MCNAIR FELLOW