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Synthesis And Characterization Of Boronic Acid Chalcones As Potential Cancer Chemoprevention Drug Candidates

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Synthesis and Characterization of Boronic Acid Chalcones as Potential Cancer Chemoprevention Drug Candidates

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Biographical Sketch

Davia Lauren McKoy was born on October 13, 1987 in Newark, DE. She graduated from St. Mark's High School in Wilmington, DE in 2005 and received her Bachelor's of Science degree in Chemistry from North Carolina A&T State University, Greensboro, NC in 2010. She joined the Master's program in Chemistry at North Carolina A&T State University in the Fall of 2010. Her research was on the Synthesis and Characterization of Boronic Acid Chalcones as Potential Cancer Chemoprevention Drug Candidates.

Dedication

This thesis is dedicated to my mother, Yvonne McKoy, for her love, support, sacrifice and constant reminder to work hard and always smile, to my little sister, Denée McKoy who has the best smile and the brightest future ahead of her, and to the blessed memory of Nemo, which has brought me a new perspective of life and I love more than ever.

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Nomanclature

°C	degree Celsius
^{1}H	proton
^{13}C	carbon 13
α	alpha
ATP	adenosine triphosphate
β	beta
C	Carbon
CD_3OD	deuterated methanol or Methanol-d4
$CDCl_3$	deuterated chloroform or Chloroform-*d*
DMF	dimethylformamide
DNA	deoxyribonucleic acid
EtOH	ethanol
g	gram
Hz	Hertz
µg	microgram
MDM2	Mouse Double Minute 2 homolog
MEK	methyl ethyl ketone
MHz	megahertz
mL	milliliter
mmol	millimole
m.p.	melting point
NMR	Nuclear Magnetic Resonance

p53	protein 53 or tumor protein 53
Pd	Palladium
pKa	acid dissociation constant
ppm	parts per million
RNA	ribonucleic acid
S. No.	synthetic number

Abstract

Carcinogenesis is the transformation of a normal cell into a cancerous cell. Cancer chemoprevention is the use of natural and synthetic compounds to stop carcinogenesis. These compounds have been labeled chemopreventives and they take advantage of the human body's natural defenses to stop carcinogenesis. Chalcones have demonstrated antibacterial, antifungal, antitumor, and anti-inflammatory properties. In this project, chalcones and their derivatives are synthesized with the goal to be used as possible chemopreventives. We believe that when tested on cancer cell lines, the boronic acid derivative will show greater chemopreventive activity because of the boronic acid's increased bioavailability. We have synthesized and characterized a series of methoxy and boronic acid chalcones via adol condensation. Our synthetic methodology included the conversion of hydroxybenzaldehydes into alkoxybenzaldehydes via Williamson Ether Synthesis, followed by a Clasien-Schmidt condensation between the alkoxybenzaldehydes and an acetophenone. The synthesized chalcones were characterized ^{1}H, ^{13}C, and 2D NMR spectroscopy and were shown to exhibit yields ranging from 58% to 91%.

CHAPTER 1

Introduction

Cancer can best be described as the disease of mayhem. This disease goes against the natural order in which normal cells operate. Cancer typically attacks the organs in the human body, by causing the uncontrollable growth of transformed cells. During this process, the human genome acquires mutant alleles of proto-oncogenes, tumor suppressors and other genes that can regulate cell proliferation. This accumulation of a transformed cell form a tumor which can be either be benign (localized/noninvasive) or malignant (metastatic/invasive). In the majority of cases it is the malignant tumors that are responsible for the largest part of deaths from cancer. This disease is a complicated, multi step process that takes years to develop in humans, and can involve a number of genes. Combinations of mutated-genes bring about the process of carcinogenesis and studies have shown that a single gene mutation is not enough to start the process of cancer. Carcinogenesis, the transformation of a normal cell to a cancer cell, can be influenced by a person's genetic makeup or by environmental factors.

Cancer has become a growing health epidemic plaguing the United States. It is estimated that there is about 1.5 million new cancer cases in the United States and approximately five hundred thousand deaths from cancer (Yadav, Prasad, Sung, & Aggarwal, 2011). Although cancer is a worldwide problem, the number of cancer incidence rates, the rates with which the disease is diagnosed, varies from country to country as well as regions to regions. According to the International Agency for Research on Cancer, African Americans, in the United States of America have the highest incidence rate of prostate cancer compared to any race in the world. Regionally cancer varies dramatically (Weinberg, 2007). For instance, African Americans in Louisiana have a higher incidence of lung cancer while Korean Americans in Los Angeles

experience a higher incidence of pancreas cancer. In any case, cancer is an occurring issue across the world.

1.1 Formation of Cancer

All cancers have a genetic basis. The accumulation of mutations in DNA is what brings about the formation of cancer. The blue print of DNA is genes, whose main responsibility is to keep cells in balanced. There are two known categories of genes that are associated with cancer, proto-oncogenes and tumor suppressor genes. The elimination or transformation of these two genes can result in the formation of cancer. Proto-oncogenes code for proteins that help with cell growth and differentiation. As a result of DNA damage, these normal cellular genes become inactivated and transform themselves into oncogenes. Oncogenes promote cell growth and are expressed in high level in tumor cells. Tumor suppressor genes are genes that protect the cells from advancing down the path towards cancer. Inactivation of these genes causes cell proliferation (cell growth). The formation of cancer has been found to be the cause of oncogenes rather than the tumor suppressor genes. This is because in order for the oncogene to be activated it only takes one mutation, whereas tumor suppressor genes require multiple hits to become activated (Weinberg, 2007).

The risk of developing cancer can be attributed to random mutations, inherited mutations, viral infections and or environmental factors (Weinberg, 2007). Inherited mutations are pre-dispositions that cause an abnormal gene that is passed from generation to generation. A common misconception about inherited mutations is that a person will have cancer. In actuality, persons with inherited mutations only inherit an abnormal gene that has the potential to bring about cancer. There is still a possibility of that person never developing cancer.

The known or suspected causes of human cancers can vary from region to region and is based on a person environment or life style choices. Environmental factors are the leading causes in the formation of cancer. A person is exposed to many carcinogens on a daily basis. Studies have determined that only 5-10 % of cancer is caused by inheritance of mutated genes while 90-95% of cancer has been linked to lifestyles and environmental factors (Yadav et al., 2011). Infectious agents can lead to the transformation of a host cell, but is a preventable cause of cancer (Carrillo-Infante, Abbadessa, Bagella, & Giordano, 2007). To combat a person's constant exposure to carcinogens developing a therapeutic that can prevent carcinogenesis would be highly beneficial.

1.2 Cancer Cell Characteristics

Every cell goes through the cell cycle. The cell cycle for eukaryotes is divided into two major periods: interphase, the process in which the cell grows, and mitosis, the phase where cell division occurs. The duration of the cell cycle of a cancerous cell is sometimes faster or prolonged than that of a normal cell (Diaz-Moralli, Tarrado-Castellarnau, Miranda, & Cascante, 2013). Within the cell cycle, check points are used to monitor and regulate the progression of a cell. Check points are designed to ensure that damaged or incomplete DNA is not passed to a daughter cell. The cell cycle utilizes certain enzymes, such as tumor suppressors, to inhibit the cell cycle if a cell becomes cancerous.

Cancer cells exhibit behaviors found in a normal cell during development, differentiation and homeostasis, but do not show normal regulatory control over these functions. There are certain distinct properties of cancer cells that differentiate themselves from normal cells. Most normal cells have a limited potential to divide, where as cancer cells show no limitations towards divisions. Cancer cells do not undergo contact inhibition. They are invasive by creating new

network of blood sources (angiogenesis) and most importantly they do not undergo apoptosis naturally. Cancer cells are also known to metabolize glucose through glycolsis without the formation of ATP and have a high pH levels within the cell. Given that cancer requires an acidic and low oxygen environment to flourish, cancer patients have a very high blood pH of 6.5- 7.0 or lower. Another factor that is common in all cancers is inflammation. Inflammation is a biological response to harmful stimuli, and is classified into two stages; acute and chronic. Chronic inflammation is known to be associated with most chronic illnesses, including diabetes, obesity and cancer. Studies have shown that chronic inflammation is mandatory for the induction of an immunosuppressive environment, due to the high concentrations of oxygen (Mikirova, Casciari, Rogers, & Taylor, 2012).

1.3 Cancer Treatments

Treatments for cancer are prescribed based on a variety of factors that are specific to the patients' individual circumstances ("Overview: Cancer Treatments - Cancer," 2012). These factors include the cancer stage, patients' age, medical history and overall health. Each form of cancer is different and requires different treatment approaches. However, the most common approaches are radiation and chemotherapy. Both forms of therapy have the potential of damaging both cancer cells and healthy cells. There are also newer forms of treatments emerging on the frontier of cancer treatments and are in clinical trials.

Both surgical oncology and radiation therapy is used to treat localized cancer in the body. Both forms are focused on the management of cancer. Surgery physically removes a tumor or is sometimes used as a prevention measure. Radiation therapy is a method of treating cancer using high-energy waves with the goal to kill cancer cells or limit their ability to grow and divide.

Chemotherapy utilizes combinations of drugs that are either administered orally or intravenously. Chemotherapy drugs target cells in the body that divide and grow at a rapid rate ("Overview: Cancer Treatments - Cancer," 2012). This form of treatment is commonly prescribed to patients' whose cancer is not localized. Chemotherapy can be used to reduce symptoms as well as the pain associated with cancer. The duration of treatment is dependent on the type of cancer, the area and a person's individual response from their body to the drugs.

Chemotherapy drugs can be divided into several groups based on the following factors of how they work, their chemical structures, and their relationship to another drug ("What are the different types of chemotherapy drugs?," 2012). Alkylating agents work in all phases of the cell cycle. Temodar® is an alkylating agents used to damage DNA and prevent cancer cells from reproducing. Antimetabolites interfere with DNA and RNA growth during the S phase. Some examples of antimetabolites are 5-fluorouracil, 6-mercaptopurine, Xeloda®, Hydroxyurea, and Methotrexate. Mitotic inhibitors are plant alkaloids and other compounds derived from natural products. Taxol® is an example of a mitotic inhibitor that stops mitosis or inhibit enzymes from making proteins needed for cell reproduction.

Doctors also rely on clinical drugs and studies as an option to treat cancer patients. Clinical trials are studies that utilize volunteers to take part in test of new drugs or procedures. Amongst these new classes of drugs and procedures are electrochemotherapy and chemopreventives. Electrochemotherapy combines injection of a chemotherapeutic drug followed by the application of high-voltage electric pulses to the tumor site (Heller, Gilbert, & Jaroszeski, 1999). Chemopreventive agents interfere with a disease process by halting carcinogenesis.

CHAPTER 2

Literature Review

2.1 Flavonoids

Phytohemicals are chemical compounds made by plants to help protect cells against oxidative damage. Flavonoids are a group of compounds found in plants and serve as defense mechanisms against herbivores and provide the intense pigments in flowers, fruits and leaves (Dyrager, 2012).This group of compounds is made up of a structural class known as polyphenols. Polyphenols are unique for the reason that they can be found within nature, but can be synthesized. Flavonoids are recognized for their antioxidant properties, and are referred to as "natures' biological response" because of their ability to modify the body's reaction to allergens and viruses.

Dietary agents from fruits, vegetables, and spices are beginning to draw attention from both the public and medical community because of their ability to suppress a variety of diseases (Yadav et al., 2011). There is a variety of flavonoids and each kind is divided into classes based off their molecular structures. The most common flavonoids found in the human diet are flavones, flavonols, isoflavones, and neoflavones (Figure 1). Flavonoids are made up of three heterocyclic rings, A, B & C. The common component within all the flavonoids is the ketone functional group located in the C ring. This is believed to give the compound its activity as well as its dynamic color, yellow. Given that flavonoids are distributed in the human diet they are believed to be non-toxic compounds (Dyrager, 2012). Because they naturally occur and are easily synthesized, they are appealing drug candidates, and can be classified as a chemopreventive.

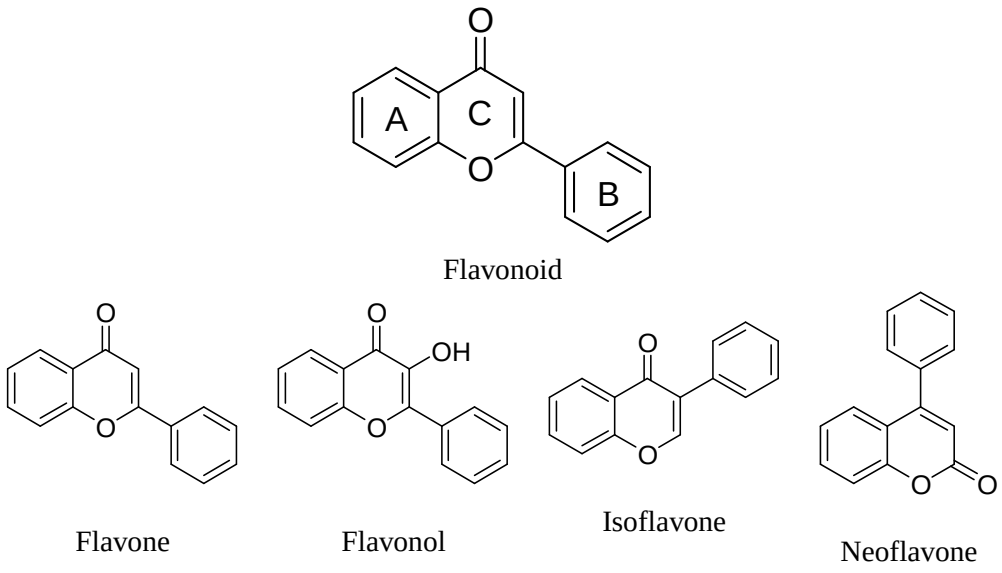


Figure 1. Common flavonoids.

2.2 Chalcones

Chalcones (Figure 2) are the major intermediates in the biosynthesis of flavonoids. These compounds and their derivatives can either be isolated from natural products or synthesized using classic synthetic chemistry. Chalcones are being considered as anticancer agents because they demonstrate variety of properties such as, antibacterial, antitumor and anti-inflammatory. Chemically, they consist of two aromatic rings joined by a three carbon α, β- unsaturated carbonyl system.

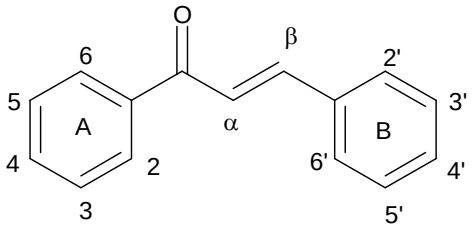
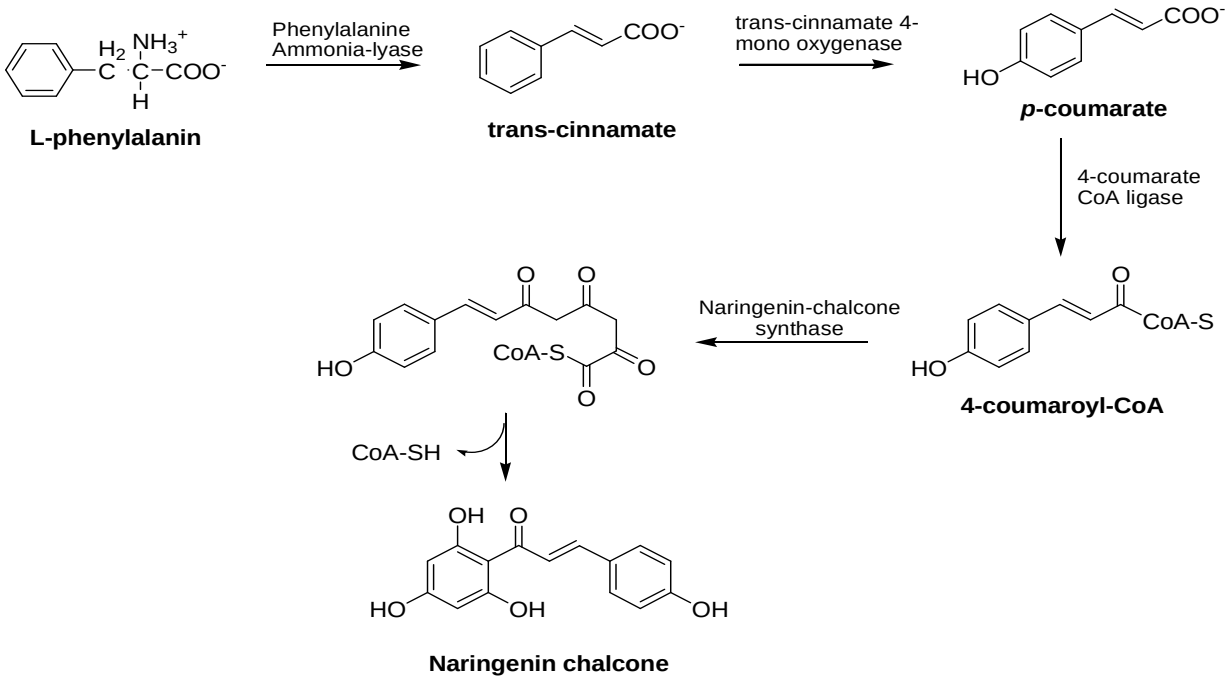


Figure 2. General structure and numbering of a chalcone.

2.2.1 Synthesis of chalcones. Chalcones can be derived both naturally and synthetically.

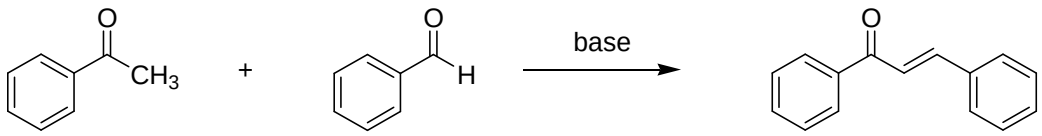
2.2.1.1 Natural biosynthesis of chalcones. Chalcones participate in the biosynthetic pathways of flavonoids. Naturally, they are produced as a plant's secondary metabolism mechanism to aid in the growth and development of a plant. Secondary metabolisms play a key role in keeping all of the plants' system working properly by severing as defense mechanisms. In a stepwise addition of L-phenylalanine, an amino acid, as the starting compound for the flavonoid skeleton is formed (Scheme 1). In this reaction ammonia is removed to form a trans-cinnamate that is converted to a *p*-coumarate. The *p*-coumarate then undergoes ligation with CoA-SH to form 4-coumaroyl-CoA (Yadav et al., 2011). From there 4-coumaroyl-CoA can go through a naringenin-chalcone synthase and form a naringenin-chalcone. This chalcone can be extracted from an apple tree leaf.



Scheme 1. Natural synthesis of chalcones.

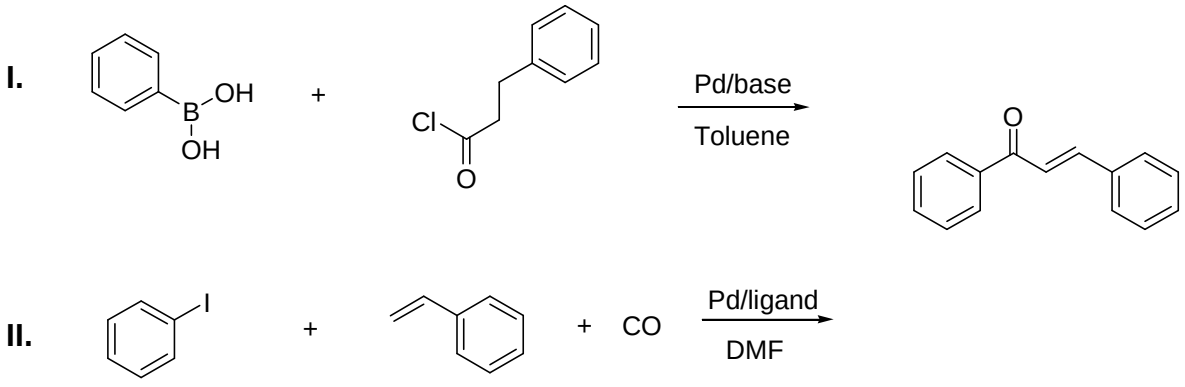
2.2.1.2 Synthetic biosynthesis of chalcones. Synthetic chalcones are less complicated to form than a naturally occurring chalcone. The key to forming a chalcone is the formation of the enone functional group. An aldol condensation is an organic reaction involving an enol reacting

with a carbonyl compound to form a β-hydroxyketone, followed by a dehydration to give a conjugated enone. The more common way to form a chalcone is the Clasien-Schmidt condensation. This reaction is an aldol condensation between a benzaldehyde and an acetophenone in the presents of a base in a polar solvent (Scheme 2).



Scheme 2. Claisen-Schmidt condensation of a chalcone.

Recently different reactions have been used to form chalcones (Scheme 3). Scheme 3, reaction I is the Suzuki coupling between cinnamoyl chloride and phenylboronic acid has been reported but formed chalcones in yields ranging from 68%- 93% (Eddarir, Cotelle, Bakkour, & Rolando, 2003). Another approach was the Heck coupling (Scheme 3, reaction II) with an aryl halide with styrenes in the presence of carbon monoxide with yields ranging from 24%-65% (Reichwald, Shimony, Sacerdoti-Sierra, Jaffe, & Kunick, 2008). Between both these reactions the more promising yields came from the Suzuki coupling.



Scheme 3. Suzuki cross-coupling and Heck reaction formation of a chalcone.

2.2.2 Application of chalcones.

2.2.2.1 Antibacterial. Chalcones have a broad spectrum of antibacterial activities, and their diverse applications have become popular in the medical field. The equilibrium between the open chalcone structures allows a variety of substitution on their rings which results in different effects (Ávila, Smânia, Monache, & Smânia Júnior, 2008). Licochalcone is a chalcone obtained from the *glycyrrhiza glabra,* a root in which licorice flavor comes from, has shown the ability disrupt the cell membrane (Sivakumar et al., 2012). This is useful in the medical field where they use chalcones to coat medical devices to prevent the colonization of bacteria.

2.2.2.2 Anti-inflammatory. Inflammation associated with cancer has been linked to the excess production of nitric oxide, a free radical produced by the body. This nitric oxide has the potential to destroy normal tissue during acute and chronic inflammation (Honda et al., 2000). This is can also be correlated to the process of carcinogenesis (Honda et al., 2000). Broussochalcone is a natural chalcone isolated from the *Moraceae,* a plant from the fig family. This chalcone exerted potent antioxidant activity and inhibited the inducible nitric oxide synthase (iNOS) expression in macrophages (Won et al., 2005). This inhibition of nitric oxide production demonstrates how chalcones are potential anti-inflammatory and cancer chemopreventive drugs.

2.2.2.3 Antitumor. Invasion is the trademark of malignant tumors and usually leads to the major cause of death in cancer patients (Mukherjee et al., 2001). If a cell is allowed to replicate itself, its end result is the formation of a tumor. Chalcones contain an enone in its structure which have been shown to reduce tubulin assembly (Johnson et al., 2007). Tubulins are composed of microtubules which is a key component of the cytoskeleton of protein. Chalcones bind to the tublin and prevent it from polymerizing into microtubules (Bandgar, Gawande, Bodade, Totre, & Khobragade, 2010). When the cytoskeleton of a cell is destroyed it results in cell death. The

obstruction of the microtubule system for the eukaryotic cells can be considered an important target for the development of antitumor agents (Kong et al., 2010).

2.2.3 Chalcones as a chemopreventive. Carcinogenesis is a complex and a multistage process in which a normal cell is transformed into a cancer cell. The human body is naturally equipped with mechanisms to stop a transformed cell from continuing in the cell cycle by utilizing the check points within the cycle and tumor suppressor genes. Chemopreventives are synthetic drugs, whose structures are similar to compounds found in nature, and improve or facilitate those processes the body uses to interrupt carcinogenesis. The goal as a chemopreventive is to protect cells from carcinogens.

There are nine classes of chemopreventive drugs, (*i*) oxidizable diphenols and quinines, (*ii*) Michael reations acceptors (olefins or acetylenes conjugated to electron withdrawing groups), (*iii*) isothiocyanates, (*iv*) hydroperoxides, (*v*) trivalent arsenic derivatives, (*vi*) divalent heavy metal cations (Hg^{2+} and Cd^{2+}), (*vii*) vicinal dithiols, (*vii*) 1,2-dithiole-3-thiones, and (*ix*) carotenoids and other conjugated polymers. These compounds induce phase II enzymes that detoxify electrophiles and serve as an indirect antioxidant. Phase 2 drug-metabolizing enzymes, glutathione *S*-transferases (GST) have the ability to conjugate Glutathione (GSH) and thereby detoxify cellular environments (A. T. Dinkova-Kostova, Massiah, Bozak, Hicks, & Talalay, 2001). Glutathion is tripeptides produced naturally in humans, and with respect to cancer GSH metabolism is ablet to play both protective and pathogenic roles (Balendiran, Dabur, & Fraser, 2004). Michael acceptors, cinnamates, chalcones, coumarins and curcuminods, have some type of relationship between their conjugated benzylidene ketone structure that raises GSH levels in cells (A. T. Dinkova-Kostova et al., 2001).

Chalcones have been linked to inducing phase II enzymes (Albena T. Dinkova-Kostova, Abeygunawardana, & Talalay, 1998). These enzymes provide protection against toxic chemical species. Studies have shown that an elevation of phase II enzymes show a relationship with protecting a cell against chemical-induced carcinogenesis (Bandgar et al., 2010). An approach for protecting a cell is decreasing the metabolic enzymes response for generating reactive species, while increasing phase II enzymes that can deactivate radicals (Bandgar et al., 2010). For these reasons, cancer chemopreventives have become an attractive topic for the pharmaceutical industry.

Other studies have also shown that chalcones have been effective in activating p53, a tumor suppressor gene, resulting in apoptosis (Achanta, Modzelewska, Feng, Khan, & Huang, 2006). Many tumors are formed when tumor suppressor p53 becomes inactive, either by mutation or by binding to oncoproteins. Oncoprotein MDM2 inhibits tumor suppressor protein p53, by binding to its transactivation domain. When MDM2 is over expressed it disables a genome checkpoint and allows the cell cycle to generate defective cells. Chalcones inhibit MDM2 in which releases p53 (Stoll et al., 2001).

2.3 Boron

2.3.1 Origins. Boron is a non-metallic element, which can be found abundantly in nature only when paired with sodium or carbon. Boron is required for normal growth and health of the body, making it essential for life. American adults consume more boron than any other essential trace elements such as copper or magnesium (Hunt, 2012). Small amount of boron compounds play a strengthening role in cell walls of plants. This element is present in nuts, fresh fruits, green vegetables as well as a main ingredient in multivitamins. Boron is also used in cosmetic products as a preservative and pH adjuster ("Part 3 Trace Elements 3 164 General information Chemistry

Boron is a," 2010). Boron containing compounds have found a common use in synthetic organic chemistry in addition to applications in the biomedical field as a treatment for HIV, obesity, diabetes and cancer (Cambre & Sumerlin, 2011).

2.3.2 Biological functions. Traces of boron can be located throughout the human body, the main source being the consumption of plants in our diet. Boron is present in human plasma (0.017-0.191 μg/mL) and in the liver (1.1-5.4 μg/g) (Hunt, 2012). In the human body, boron is used to support biological functions such as inducing calcium and insulin metabolism as well as bone growth. It is believed that boron improves the human body natural ability to absorb calcium and magnesium. Diets depleted in boron have been shown to affect both the immune and nervous systems (Cui et al., 2004). Many disease conditions, such as arthritis, osteoporosis, and menopausal symptoms, are managed by boron. Boron is also known to alter human steroid hormone levels, mainly testosterone and estrogen (Cui et al., 2004). Evidence from animal experiments suggests that boron is essential during the rapid cell replication during the fertilization cycles.

2.4 Boronic Acid

Boronic Acid is a Lewis acid belonging to the larger class of organoboranes (Figure 3). This compound is stable and is easily handle which makes them an attractive class of synthetic intermediates (*Boronic Acids*, 2005). Chemically, they consist of trivalent boron atom bonded to one alkyl/aryl substituent and two hydroxyl groups, R-B$(OH)_2$. Their empty *p*-orbital on Boron allows the interconversion from sp^2 to sp^3 hybridization in the presences of a Lewis Base. These compounds are unique and versatile which allows them to be used for the formation of C-C bonds, asymmetric synthesis, molecular sensing, therapeutic agents and enzyme inhibitors (Cambre & Sumerlin, 2011). Boronic acid is low in toxicity and degradation into

environmentally friendly boric acid allows it to be considered a “green” compound. There are a variety of Boronic acids but arylboronic acids remain the most acknowledged class of boronic acids.

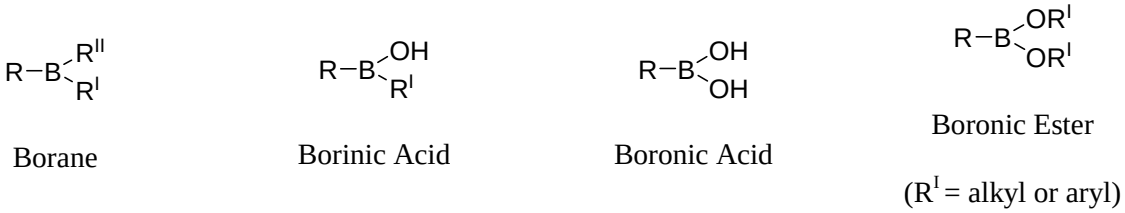
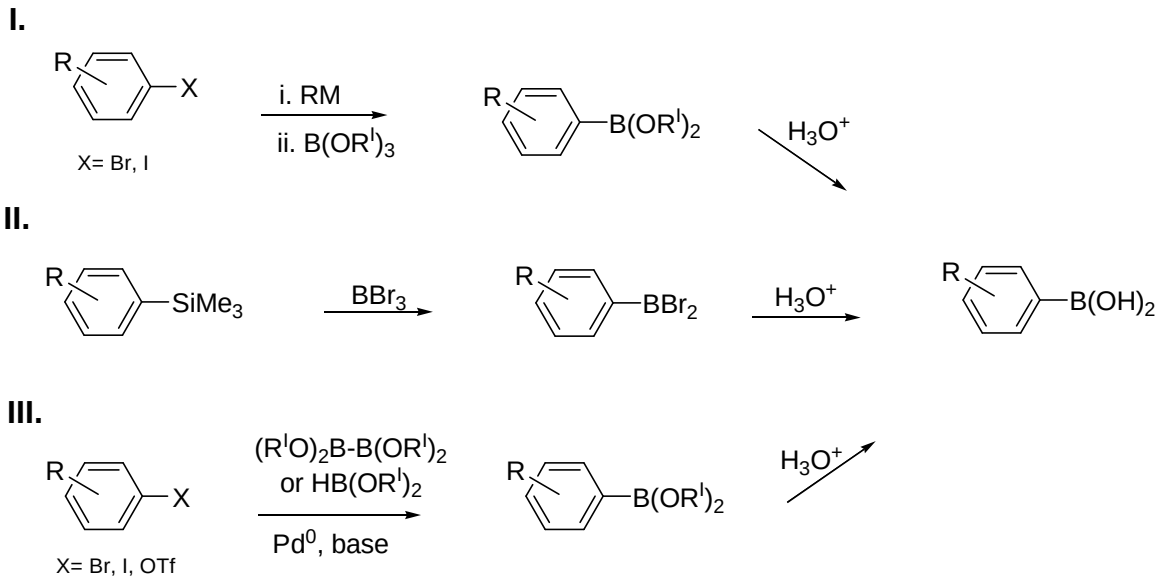


Figure 3. Oxygenated organoboron compounds.

2.4.1 Synthesis of boronic acid. Boronic acids are widely used in organic chemistry as building blocks or intermediates. These compounds are not naturally occurring but are commercially available. They can also be synthesized through several different methods. The most familiar way is through organometallic compounds based on lithium or magnesium grignard with a borate ester (Scheme 4, Reaction I). Another method is a transmetallation reaction involving a trialkylsiyl derivative with a boron halide (Scheme 4, Reaction II). Boronic acids are also popular cross-coupling intermediates in natural products synthesized in medicinal chemistry. An example is the Suzuki-Miyaura cross-coupling reaction for synthesis of dienes and other unsaturated units present in many natural products (Scheme 4, Reaction III). Presently, this method is used in the pharmaceutical industry for the synthesis of PS-341, a new cancer therapy in Phase I clinical evaluation for advanced cancer patients as an enzyme inhibitor (Yang, Gao, & Wang, 2003).

2.4.2 Boronic acid as a chemopreventive. Boronic acid derivatives are of interest in drug development because of their diverse characteristics towards cancers. These compounds are known to have a role in the controlling of normal inflammatory response, as it relates to the

production of various cell signaling (Hunt, 2012). The "potential mode of action" is through the synthesis or activation of metabolites that regulate growth (Cui et al., 2004).



Scheme 4. Common methods for the synthesis of arylboronic acids.

Boronic acid was also identified as a potential inhibitor of human cancer in cell proliferation and angiogenesis (Kong et al., 2010). Other characteristic boronic acids have is their ability to affect the cell pH level (Cambre & Sumerlin, 2011). When added on a phenyl ring, it allows the pKa to be tuned so that boronic acid containing polymers can be employed in a physiologically relevant pH range (Cambre & Sumerlin, 2011). It is the presence of the hydroxyl groups that gives a compound its hydrophilicity (A. T. Dinkova-Kostova et al., 2001). Cancer cells have a pH between 6.0-7.0, being very acidic, while Boronic acid derivatives have a moderate pH of 9.0-10.0 and while maintaining air stability (Kong et al., 2010). Antibiotics containing Boron inhibit DNA, RNA & protein synthesis and or disrupt membrane permeability. There are several potential Boronic acid binding sites involved in prostate cancer (Cui et al., 2004). The drug Bortezomib® is a compound containing a Boronic acid group which is used in chemotherapy. This drug was the first proteasome inhibitor, a drug that blocks the breakdown of

proteins, approved by the U.S. Food & Drug Administration in May of 2003 to treat myeloma, with no toxicity issues.

CHAPTER 3

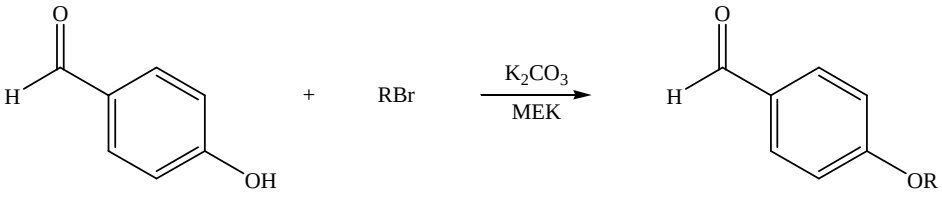
Experimental

3.1 General Procedure

All chemicals were reagent grade from Acros Organics Incorporated and used as purchased. The moisture sensitive reactions were performed under an inert atmosphere of dry nitrogen with dried solvents. 4-hydroxybenzaldehyde was converted into 4-alkoxybenzaldehyde via Williamson Ether synthesis. The Claisen-Schmidt condensation was then utilized to convert 4-alkozybenzaldehyde into both the methoxychalcones as well as the boronic acid chalcones. Each compound prepared was then characterized by ^{1}H and ^{13}C NMR spectra were recorded on a VANCE II at 400 and 100 MHz. The coupling constant (*J*) are reported in Hz. Melting point ranges were ran on MEL TEMP and recorded in degree Celsius .

3.2 Synthesis of 4-alkoxybenzaldehydes (1a-8a)

4-Hydroxybexnzaldehyde (50 mmol, 6.106 g) and potassium carbonate, K_2CO_3 (50 mmol, 6.91 g) were added to 2-butanone (75 mL) in a 250 mL round bottom flask. The reaction mixture was heated to 60-65 °C for 30 minutes, followed by the addition of 1-bromoalkane (C_3H_7Br to $C_{12}H_{25}Br$, 50 mmol) was added drop wise and the reaction mixture was heated to reflux for 18 hours. The solvent was evaporated under reduced pressure on a rotary evaporator, then separated with diethyl ether (125 mL). Unreacted starting materials were washed with distilled water and 10% sodium hydroxide, NaOH. Ether layer was dried over magnesium sulfate, $MgSO_4$, then evaporated and distilled to give 4-alkoxybenzaldehydes **1a-8a**. All resulting compounds were either pale yellow or yellow liquids, but some resulted in solids.



Scheme 5. Williamson Ether synthesis of 4-alkoxybenzaldehyde.

3.2.1 4-(pentyloxy)benzaldehyde (1a). 4-hydroxybenzaldehyde (6.121 g, 50 mmol) and 1-bromopentane (7.592 g, 50 mmol) were reacted according to the general procedure. A pale yellow liquid was obtained with a yield of 69% (6.627 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.86 (d, *J* = 3.1 Hz, 1H), 8.13 – 7.50 (m, 2H), 7.14 – 6.61 (m, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 1.81 (q, *J* = 7.5, 6.5 Hz, 2H), 1.69 – 1.16 (m, 4H), 1.13 – 0.64 (m, 3H).

3.2.2 4-(hexyloxy)benzaldehyde (2a). 4-hydroxybenzaldehyde (6.127 g, 50 mmol) and 1-bromohexane (8.294 g, 50 mmol) were reacted according to the general procedure. A yellow liquid was collected with a yield of 68% (6.976 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 3.6 Hz, 1H), 8.17 – 7.57 (m, 2H), 7.19 – 6.61 (m, 2H), 4.03 (q, *J* = 6.5, 5.4 Hz, 2H), 1.79 (dd, *J* = 13.5, 7.0 Hz, 2H), 1.39 (d, *J* = 45.2 Hz, 9H), 1.16 – 0.71 (m, 4H).

3.2.3 4-(heptyloxy)benzaldehyde (3a). 4-hydroxybenzaldehyde (6.111 g, 50 mmol) and 1-bromoheptane (8.968 g, 50 mmol) were reacted according to the general procedure. A yellow liquid/solid matter was obtained with a yield of 61% (6.791 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 10.16 – 9.67 (m, 1H), 8.15 – 7.72 (m, 2H), 7.44 – 6.85 (m, 2H), 4.02 (dd, *J* = 7.5, 5.8 Hz, 2H), 1.80 (dq, *J* = 14.1, 6.9, 6.4 Hz, 2H), 1.56 – 1.06 (m, 11H), 1.06 – 0.75 (m, 3H).

3.2.4 4-(octyloxy)benzaldehyde (4a). 4-hydroxybenzaldehyde (6.104 g, 50 mmol) and 1-bromooctane (9.716g, 50 mmol) were reacted according to the general procedure. An orange liquid was observed with a yield of 30% (3.492 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.87 (s,

1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.28 – 6.52 (m, 2H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.39 (t, *J* = 6.6 Hz, 0H), 1.81 (h, *J* = 6.6 Hz, 2H), 1.69 – 1.08 (m, 15H), 1.08 – 0.57 (m, 5H).

3.2.5 4-(nonyloxy)benzaldehyde (5a). 4-hydroxybenzaldehyde (6.913 g, 50 mmol) and 1-bromononane (10.377 g, 50 mmol) were reacted according to the general procedure. A yellow solid was gathered with a yield of 28% (3.528 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 1.78 (q, *J* = 6.9 Hz, 2H), 1.58 – 1.13 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 2H).

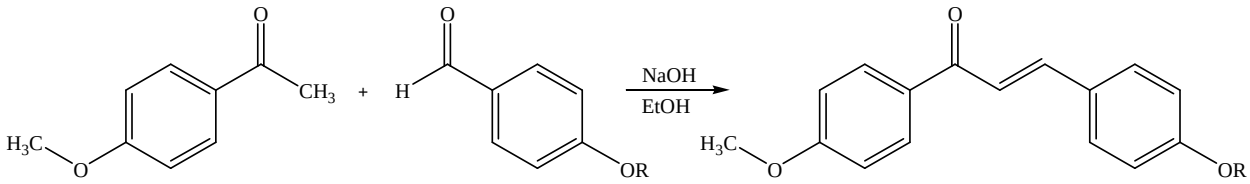
3.2.6 4-(decyloxy)benzaldehyde (6a). 4-hydroxybenzaldehyde (6.177 g, 50 mmol) and 1-bromodecane (11.079 g, 50 mmol) were reacted according to the general procedure. A yellow solid/liquid matter was observed with a yield of 51% (6.707 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.86 (d, *J* = 1.8 Hz, 1H), 8.06 – 7.66 (m, 1H), 7.17 – 6.58 (m, 2H), 4.28 – 3.57 (m, 2H), 1.80 (t, *J* = 7.1 Hz, 1H), 1.56 – 1.08 (m, 8H), 1.02 – 0.64 (m, 2H).

3.2.7 4-(undecyloxy)benzaldehyde (7a). 4- hydroxybenzaldehyde (6.176 g, 50 mmol) and 1-bromoundecane (11.776 g, 50 mmol) were reacted according to the general procedure. A yellow solid with a yield of 52% (7.250 g) was collected. ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 3.1 Hz, 1H), 8.06 – 7.59 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 4.46 – 3.72 (m, 2H), 2.16 – 1.73 (m, 1H), 1.73 – 1.04 (m, 11H), 1.08 – 0.41 (m, 3H).

3.2.8 4-(dodecyloxy)benzaldehyde (8a). 4-hydroxybenzaldehyde (6.109 g, 50 mmol) and 1-bromododecane (12.482 g, 50 mmol) were reacted according to the general procedure. A pale yellow solid was collected with a yield of 67% (9.781 g). ^{1}H NMR (301 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 3.1 Hz, 1H), 8.06 – 7.59 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 4.46 – 3.72 (m, 2H), 1.80 (p, *J* = 6.7 Hz, 1H), 1.73 – 1.04 (m, 11H), 1.08 – 0.41 (m, 3H).

3.3 Synthesis of 4-alkoxymethoxychalcones (1b-8b)

In a 100 mL round bottom 4-methoxyacetophenone (equal molar equivalence) was dissolved in ethanol (20 mL). 10% NaOH (5 equivalence) was added and the reaction mixture was stirred for 30 minutes at room temperature. Then 4-alkoxybenzaldehyde **1a-8a** (1.000 g) was added to the reaction mixture that was further stirred for 18 hours until pale yellow precipitates appeared. Crushed ice (35 mL) was added to the solid mass and the reaction was neutralized with dilute HCl. The products **1b-8b** was obtained as yellow solids, which were filtered and recrystallized from ethanol.



Scheme 6. Claisen-Schmidt condensation of 4-alkoxymethoxychalcone.

3.3.1 (E)-1-(4-methoxyphenyl)-3-(4-(pentyloxy)phenyl)prop-2-en-1-one (1b). 4-methoxyacetophenone (1.009 g, 5.2 mmol) and 4-(pentyloxy)benzaldehyde (0.788 g, 5.2 mmol) were reacted according to the general procedure. Yellow solids were obtained with a yield of 68% (1.146 g). m.p. 94-99 °C; ^{1}H NMR (301 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 15.5 Hz, 0H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 18.6 Hz, 1H), 6.96 (dd, *J* = 17.4, 8.2 Hz, 2H), 4.44 – 3.46 (m, 3H), 2.51 (d, *J* = 5.6 Hz, 0H), 1.81 (s, 2H), 1.46 (d, *J* = 14.8 Hz, 3H), 0.96 (q, *J* = 7.0, 6.1 Hz, 3H).

3.3.2 (E)-1-(4-(hexyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (2b). 4-methoxyacetophenone (1.002 g, 4.85 mmol) and 4-(hexyloxy)benzaldehyde (0.731 g, 4.85 mmol) were reacted according to the general procedure. Pale yellow solids were collected with a yield of 81% (1.334 g). m.p. 93-99 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 7.99 (m, 2H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.50 – 7.46 (m, 1H), 7.42 (d, *J* = 15.6 Hz,

1H), 7.00 – 6.96 (m, 2H), 6.94 – 6.89 (m, 2H), 3.99 (q, *J* = 6.5 Hz, 3H), 3.93 – 3.82 (m, 3H), 1.88 – 1.69 (m, 3H), 1.46 (tdd, *J* = 9.5, 5.0, 2.9 Hz, 3H), 1.41 – 1.27 (m, 5H), 0.97 (d, *J* = 6.6 Hz, 2H), 0.91 (ddt, *J* = 7.3, 5.1, 2.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.33, 188.75, 163.21, 161.13, 143.90, 142.26, 131.39, 130.66, 130.07, 129.92, 127.55, 126.97, 124.30, 119.35, 114.87, 113.74, 68.16, 55.46, 49.84, 31.54, 29.12, 25.67, 25.66, 25.35, 22.72, 22.58, 14.01.

3.3.3 (E)- 3-(4-(heptyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (3b). 4-methoxyacetophenone (0.686 g, 4.54 mmol) and 4-(heptyloxy)benzaldehyde (1.011 g, 4.54 mmol) were reacted according to the general procedure. Pale yellow solids were gathered with a yield of 70% (1.116 g). m.p. 85-94 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 7.99 (m, 2H), 7.81 – 7.73 (m, 1H), 7.60 – 7.53 (m, 2H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.94 – 6.88 (m, 2H), 4.07 – 3.93 (m, 3H), 3.87 (s, 3H), 1.91 – 1.70 (m, 4H), 1.44 (dddd, *J* = 9.2, 5.9, 4.5, 2.9 Hz, 3H), 1.39 – 1.22 (m, 9H), 0.92 – 0.81 (m, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 188.52, 163.02, 160.94, 143.71, 131.18, 129.88, 129.73, 127.33, 119.13, 114.66, 113.55, 67.96, 55.25, 49.64, 31.56, 28.97, 28.84, 25.77, 25.15, 22.53, 22.40, 13.89.

3.3.4 (E)-1-(4-methoxyphenyl)-3-(4-(octyloxy)phenyl)prop-2-en-1-one (4b). 4-methoxyacetophenone (0.672 g, 4.27 mmol) and 4-(octyloxy)benzaldehyde (1.006 g, 4.27 mmol) were reacted according to the general procedure. Beige solids; yield 58% (0.914 g); m.p. 94-96 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 7.99 (m, 1H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.47 – 7.37 (m, 1H), 7.02 – 6.94 (m, 1H), 6.94 – 6.88 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 1H), 3.88 (s, 2H), 1.89 – 1.69 (m, 1H), 1.53 – 1.40 (m, 1H), 1.40 – 1.19 (m, 5H), 0.94 – 0.80 (m, 2H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 188.59, 163.05, 160.96, 143.74, 142.11, 131.22, 130.50, 129.91, 129.76, 127.38, 126.80, 124.13, 119.18, 114.69, 113.58, 68.01, 55.29, 49.67, 31.63, 29.16, 28.99, 25.83, 22.56, 13.93.

3.3.5 (E)-1-(4-methoxyphenyl)-3-(4-(nonyloxy)phenyl)prop-2-en-1-one (5b). 4-methoxyacetophone (0.607 g, 4.03 mmol) and 4-(nonyloxy)benzaldehyde (1.000 g, 4.03 mmol) were reacted according to the general procedure. Beige solid were collected with a yield of 68% (1.048 g). m.p. 105-106°C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.01 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.70 – 7.65 (m, 1H), 7.60 (d, *J* = 9.6 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.01 – 6.87 (m, 2H), 6.68 (d, *J* = 16.1 Hz, 1H), 3.99 (dt, *J* = 8.2, 6.4 Hz, 2H), 1.82 – 1.68 (m, 2H), 1.50 – 1.37 (m, 3H), 1.39 – 1.22 (m, 11H), 0.91 – 0.84 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 188.59, 163.04, 160.96, 143.75, 131.20, 130.50, 129.92, 127.35, 119.14, 114.68, 113.58, 68.00, 55.30, 31.70, 29.35, 29.21, 29.09, 28.99, 25.83, 22.50, 13.95.

3.3.6 (E)- 3-(4-(decyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (6b). 4-methoxyacetophenone (0.575 g, 3.81 mmol) and 4-(decyloxy)benzaldehyde (1.060 g, 3.81 mmol) were reacted according to the general procedure. Beige solid were collected with a yield of 91% (1.361 g). m.p. 82-97 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 15.6 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.50 – 7.46 (m, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.94 – 6.89 (m, 2H), 3.98 (q, *J* = 6.5 Hz, 3H), 3.88 (s, 3H), 2.50 (d, *J* = 7.0 Hz, 1H), 1.88 – 1.71 (m, 3H), 1.52 – 1.18 (m, 18H), 0.93 – 0.80 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.60, 163.04, 160.96, 143.76, 142.13, 131.20, 130.50, 129.92, 129.76, 127.36, 126.78, 124.11, 119.15, 114.69, 113.58, 68.00, 55.30, 49.67, 31.72, 29.20, 29.14, 28.99, 25.82, 25.19, 22.51, 13.95.

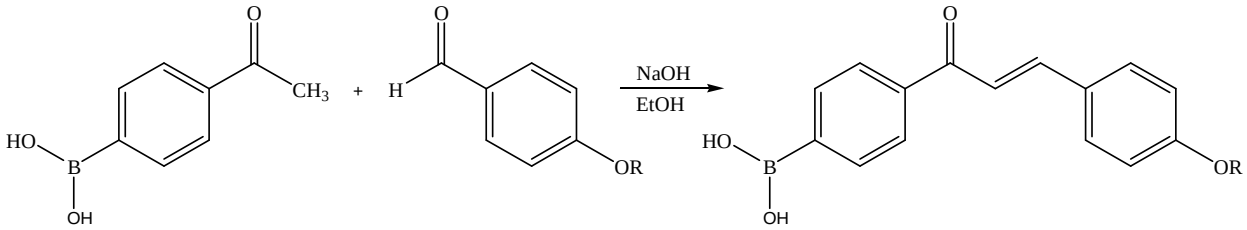
3.3.7 (E)-1-(4-methoxyphenyl)-3-(4-(undecyloxy)phenyl)prop-2-en-1-one (7b). 4-methoxyacetophenone (0.549 g, 3.62 mmol) and 4-(undecyloxy)benzaldehyde (1.006 g, 3.62 mmol) were reacted according to the general procedure. White solid with a yield 76% (1.121 g) were collected. m.p. 95-102 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 7.99 (m, 1H), 7.77 (d, *J* = 15.6 Hz, 0H), 7.63 – 7.54 (m, 1H), 7.42 (d, *J* = 15.6 Hz, 0H), 7.02 – 6.95 (m, 1H), 6.94 –

6.89 (m, 1H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.88 (s, 1H), 2.50 (d, *J* = 7.0 Hz, 1H), 1.87 – 1.68 (m, 1H), 1.53 – 1.09 (m, 10H), 0.92 – 0.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.76, 163.21, 161.13, 143.91, 142.28, 131.38, 130.67, 130.08, 129.92, 127.54, 126.96, 124.29, 119.34, 114.87, 113.75, 68.17, 55.46, 49.84, 31.90, 29.60, 29.32, 29.15, 25.99, 25.36, 22.68, 14.11.

3.3.8 (E)-3-(4-(dodecyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (8b). 4-methoxyacetophenone (0.523 g, 3.44 mmol) and 4-(dodecyloxy)benzaldehyde (1.007 g, 3.44 mmol) were reacted according to the general procedure. White solids were collected with a yield of 70% (1.017 g). m.p. 94-102 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 8.00 (m, 1H), 7.77 (d, *J* = 15.6 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.00 – 6.94 (m, 1H), 6.94 – 6.88 (m, 1H), 4.07 – 3.92 (m, 2H), 3.88 (s, 2H), 1.85 – 1.66 (m, 2H), 1.52 – 1.40 (m, 2H), 1.40 – 1.21 (m, 14H), 0.92 – 0.79 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.58, 188.54, 163.03, 160.95, 143.72, 142.08, 131.21, 130.48, 129.89, 129.74, 127.36, 124.11, 119.15, 114.68, 113.57, 67.99, 55.27, 49.66, 31.73, 29.47, 29.41, 29.19, 28.98, 28.86, 25.82, 25.17, 22.55, 13.94.

3.4 Synthesis of 4-alkoxyboronic acid chalcones (1c-8c)

In a 100 mL round bottom 4-acetylphenylboronic acid (equal molar equivalence) was dissolved in ethanol (20 mL). 10% NaOH (5 equivalence) was added and the reaction mixture was stirred for 30 minutes at room temperature. Then 4-alkoxybenzaldehyde **1a-8a** (1.000 g) was added to the reaction mixture that was further stirred for 18 hours until pale yellow precipitates appeared. Crushed ice (35 mL) was added to the solid mass and the reaction was neutralized with dilute HCl. The products **1c-8c** was obtained as yellow solids, which were filtered and recrystallized from ethanol.



Scheme 7. Claisen-Schmidt condensation of 4-alkoxyboronic acid chalcones.

3.4.1 4-((E)-3-(4-(pentyloxy)phenyl)acryloyl)phenylboronic acid (1c). 4-acetylphenylboronic acid (0.853 g, 5.20 mmol) and 4-(pentyloxy)benzaldehyde (1.016 g, 5.20 mmol) were reacted according to the general procedure.

3.4.2 4-((E)-3-(4-(hexyloxy)phenyl)acryloyl)phenylboronic acid (2c). 4-acetylphenylboronic acid (0.797 g, 4.85 mmol) and 4-(hexyloxy)benzaldehyde (1.005 g, 4.85 mmol) were reacted according to the general procedure. Yellow solids with a yield 64% (1.46 g) were collected. m.p. 184-195 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.04 – 7.96 (m, 1H), 7.90 (d, J = 7.7 Hz, 0H), 7.75 (d, J = 15.6 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.60 (d, J = 5.6 Hz, 0H), 7.57 – 7.52 (m, 1H), 6.99 – 6.89 (m, 1H), 6.69 (d, J = 16.1 Hz, 0H), 3.99 (q, J = 6.6 Hz, 1H), 1.76 (dtt, J = 7.9, 6.4, 5.2 Hz, 2H), 1.54 – 1.42 (m, 2H), 1.42 – 1.27 (m, 3H).

3.4.3 4- ((E)-3-(4-heptyloxy)phenyl)acryloyl)phenyloboronic acid (3c). 4-acetylphenylboronic acid (0.755g, 4.54 mmol) and 4-(heptyloxy)benzaldehyde (1.007 g, 4.54 mmol) were reacted according to the general procedure. Yellow solids with a yield of 88% (1.460 g) was collected. m.p. 121-186 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.8 Hz, 0H), 7.73 (d, J = 15.5 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.65 (s, 0H), 7.60 (d, J = 3.5 Hz, 0H), 7.59 – 7.54 (m, 1H), 4.06 (t, J = 6.4 Hz, 0H), 4.00 (dt, J = 7.7, 6.4 Hz, 2H), 3.89 (s, 0H), 2.25 – 2.03 (m, 1H), 1.77 (dddd, J = 12.7, 8.4, 6.5, 3.3 Hz, 3H), 1.56 – 1.41 (m, 2H), 1.41 – 1.21 (m, 6H), 1.03 – 0.75 (m, 6H).^{13}C NMR (101 MHz, CD_3OD) δ 201.77,

191.41, 161.42, 143.31, 133.20, 131.70, 130.10, 129.92, 127.43, 126.84, 126.52, 123.55, 119.38, 114.55, 31.57, 28.91, 28.79, 25.69, 22.27, 21.56, 13.02.

3.4.4 4-((E)-3-(4-(octyloxy)phenyl)acryloyl)phenylboronic acid (4c). 4-acetylphenylboronic acid (0.710 g, 4.27 mmol) and 4-(octyloxy)benzaldehyde (0.998 g, 4.27 mmol) were reacted according to the general procedure. Beige solid; yield 58% (0.938 g)

3.4.5 4-(E))-3-(4-(nonyloxy)phenyl)acryloyl)phenylboronic acid (5c). 4-acetylphenylboronic acid (0.667 g, 4.03 mmol) and 4-(nonyloxy)benzaldehyde (1.001 g, 4.03 mmol) were reacted according to the general procedure. Pale yellow solids were collected with a yield of 67% (1.069 g). m.p. 103-164 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.01 (d, J = 7.7 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.70 – 7.65 (m, 1H), 7.60 (d, J = 9.6 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.01 – 6.87 (m, 2H), 6.68 (d, J = 16.1 Hz, 1H), 3.99 (dt, J = 8.2, 6.4 Hz, 2H), 1.82 – 1.68 (m, 2H), 1.50 – 1.37 (m, 3H), 1.39 – 1.22 (m, 11H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 203.63, 163.49, 163.31, 146.99, 145.16, 133.21, 132.13, 131.77, 129.10, 128.89, 128.71, 125.41, 116.44, 116.39, 69.61, 31.12, 30.95, 30.85, 30.73, 27.57, 27.04, 24.17, 23.40, 14.88.

3.4.6 4-((E)-3-(4-decyloxy)phenyl)acryloyl)phenylboronic acid (6c). 4-acetylphenylboronic acid (0.629 g, 3.81 mmol) and 4-(decyloxy)benzaldehyde (1.019 g, 3.81 mmol) were reacted according to the general procedure. Yellow solids were collected with a yield of 84% (1.303 g). m.p. 109-163 °C.

3.4.7 4-((E)-3-(4-undecyloxy)phenyl)acryloyl)phenylboronic acid (7c). 4-acetylphenylboronic acid (0.599 g, 3.62 mmol) and 4-(undecyloxy)benzaldehyde (1.018 g, 3.62 mmol) were reacted according to the general procedure. Yellow solid were collected with a yield of 82% (1.247 g). m.p. 65-143 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (s, 1H), 7.84 (d, J =

8.8 Hz, 1H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.00 – 6.88 (m, 3H), 6.70 (d, *J* = 16.1 Hz, 1H), 4.06 (s, 0H), 4.02 – 3.92 (m, 3H), 2.55 (d, *J* = 7.0 Hz, 2H), 2.27 – 2.01 (m, 2H), 1.85 – 1.65 (m, 4H), 1.53 – 1.18 (m, 24H), 0.96 (d, *J* = 6.7 Hz, 4H), 0.92 – 0.82 (m, 4H).

3.4.8 4-((E)-3-(4-dodecyloxy)phenyl)acryloyl)phenylboronic acid (8c). 4-acetylphenylboronic acid (0.564 g, 3.44 mmol) and 4-(dodecyloxy)benzaldehyde (1.012 g, 3.44 mmol) were reacted according to the general procedure. Pale yellow solids were gathered with a yield of 75% (1.121 g).

CHAPTER 4

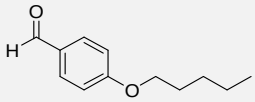
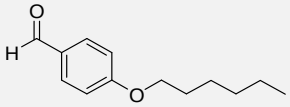
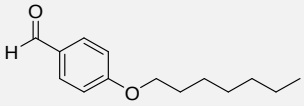
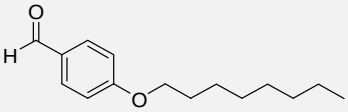
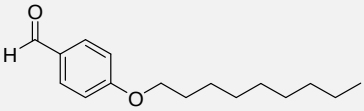
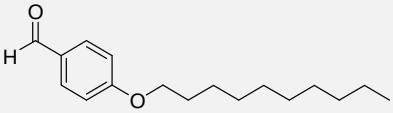
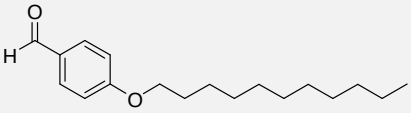
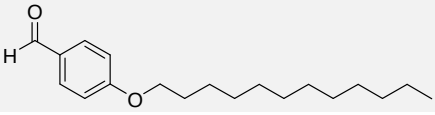
Results and Discussion

4.1 Results and Discussion of Ether Synthesis

4.1.1 Yields of 4-alkoxybenzaldehydes. Synthetic yields including cLogP values calculated from the 4-alkoxybenzaldehydes.

Table 1

Yields for 4-alkoxybenzaldehydes

S.No.	Product	cLogP	Yield (%)
1a		3.89	69
2a		4.42	68
3a		4.95	61
4a		5.48	30
5a		6.01	28
6a		6.54	51
7a		7.07	52
8a		7.60	67

4.1.2 Discussion of solubility. The partition coefficient (Log P) is a measurement of a compound's solubility in a hydrophobic and hydrophilic solvent, usually octanol ant water. This

value establishes a compound's hydrophilicity and gives an insight to how a drug will be metabolized in the body. High Log P values indicate that a compound is hydrophobic "water fearing" and is more likely to absorb/permeate through the lipid bilayers. A low score for the Log P value indicates that the drug is hydrophilic "water loving" and is more favored being that the drug will metabolize through the blood serum. Within the pharmaceutical industry an acceptable cLog P values is anything below a 5.0.

In regards to the solubility of the benzaldehydes, the solubility is completely dependent on the ether chain attached to the ring. Before the ether chain was added onto 4-hydroxybenzaldehye, its cLogP value was 1.44, making it a hydrophilic compound. As the chain increased with carbons the value of cLogP increased. For that reason we can assume the additional carbons make the compounds more hydrophobic.

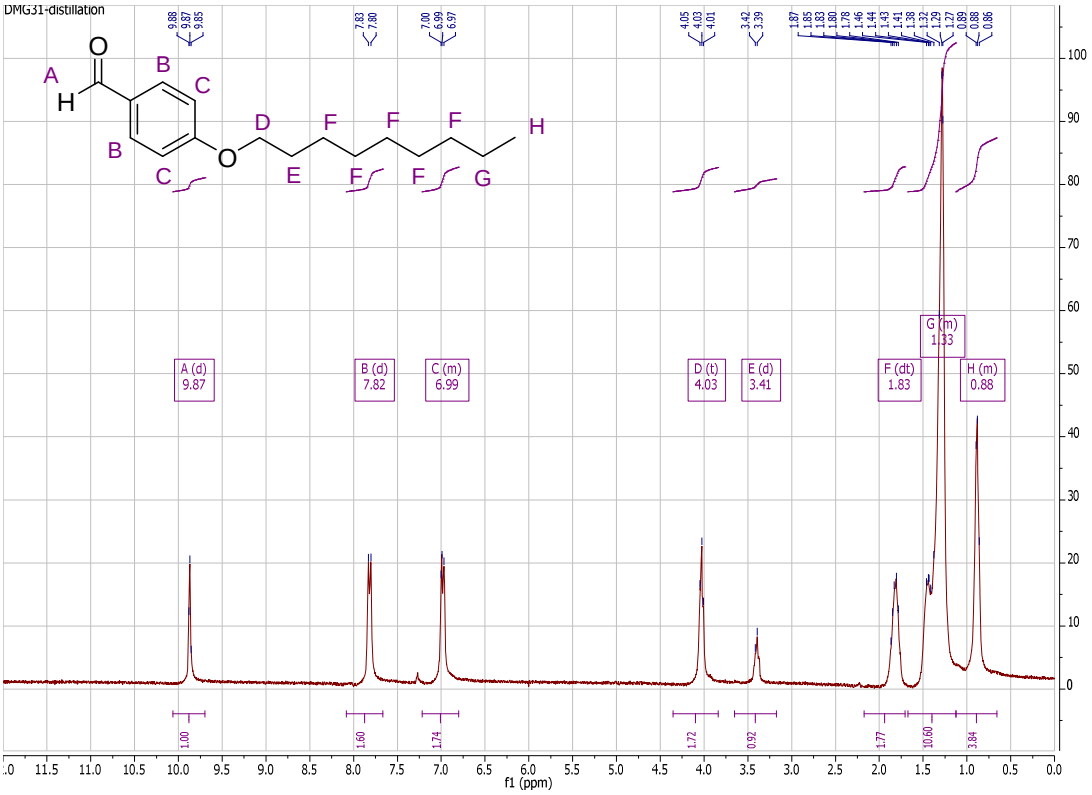


Figure 4. [1]H NMR of 4-(nonyloxy)benzaldehyde

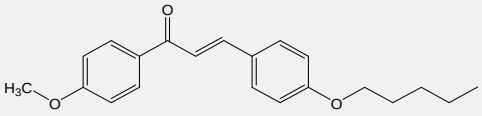
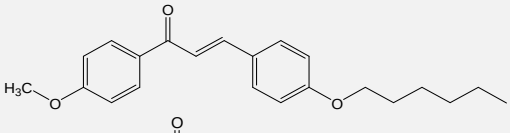
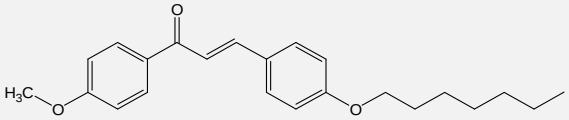
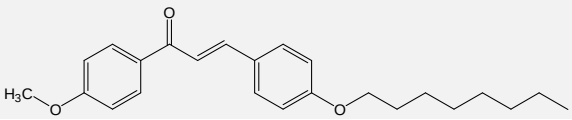
4.1.3 Discussion of ^{1}H NMR. The hydrocarbons on the ether chain, protons E-H, would have a chemical shift found between 0-3 ppm. Proton E is a doublet at 3.41 ppm, protons F shows a doublet of triplets at 1.83, proton G is a multiplet at 1.33 and proton H is a multiplet at 0.88 ppm. The hydrogen closest to the oxygen atom, proton D, had a chemical shift more downfield at 4.03 ppm resulting in a triplet because of the deshielding from its neighboring oxygen atom. Moving down the spectra towards the aromatic ring, the hydrogen on the benzene ring protons B shows a doublet at 7.82 ppm and proton C is a multiplet at 6.99 ppm. The aldehydic hydrogen, proton A, had the highest frequency at 9.87 ppm as a doublet because of the strong dipole moment from the carbonyl.

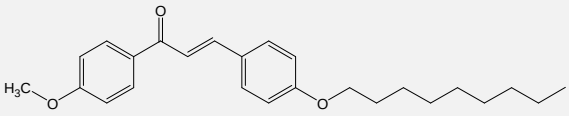
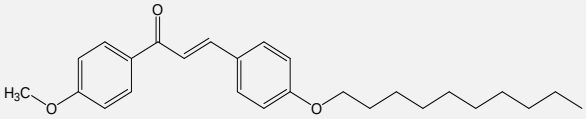
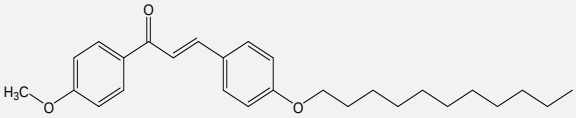
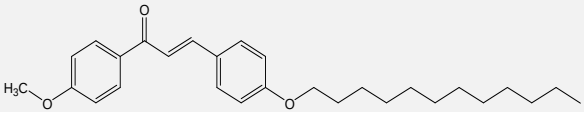
4.2 Results and Discussion of 4-alkoxymethoxychalcone Synthesis

4.2.1 Yields of 4-alkoxymethoxychalcones. Synthetic yields including cLogP values calculated from the 4-alkoxymethoxychalcones. Refer to Figure 2 for numbering sequence.

Table 2

Yields for 4-alkxoymethoxychalcones

S.No.	B-ring 4'-	A-ring 4-	Product	Yield (%)	cLogP
1b	OCH_3	C_5H_{11}		68	5.13
2b	OCH_3	C_6H_{13}		81	5.59
3b	OCH_3	C_7H_{15}		70	6.05
4b	OCH_3	C_8H_{17}		58	6.52

5b	OCH_3	C_9H_{19}		68	6.98
6b	OCH_3	$C_{10}H_{21}$		91	7.45
7b	OCH_3	$C_{11}H_{23}$		76	7.91
8b	OCH_3	$C_{12}H_{25}$		70	8.37

4.2.2 Discussion of solubility. In regards to the solubility of the methoxychalcones, it is assumed that the longer the ether chain the more nonpolar the compound is than the compounds with the shorter chains. Confirming this statement is the cLogP value from Table 2. The solubility value, when compared to its respected benzaldehyde starting material shows an increase in cLlogP value. This indicates that these compounds are more likely to metabolize through the lipid bilayers and would not be considered a target drug due to its high Log P values.

4.2.3 Discussion of ^{1}H and ^{13}C NMR. To confirm that the methoxychalcones were synthesized we ran both a ^{1}H NMR as well as a ^{13}C NMR to compare them to their corresponding benzaldehyde starting material (compounds 1a-8a). Figure 5 is the full spectrum of the proton NMR for the nonane methoxychalcone. Figure 6 the highlights the aliphatic region of the compound while Figure 7 highlights the aromatic region. This compound was ran in deuterated chloroform ($CDCl_3$) and the solvent peaks appear at 7.25 ppm. Within the aliphatic proton G, the methoxy proton is a triplet with a chemical shift at 4.0 ppm. Proton H is the methoxy proton attached to ring A is a singlet with a chemical shift at 3.9 ppm. Both the methoxy protons are slightly downfield than that of the methyl protons because of the deshielding affect oxygen has on the nucleus. In the ether chain are multiplets consisting of

protons I, K, J and L. Proton I is a CH_2 group at 1.80 ppm, proton K are CH_2 groups that are not equivalent but will show the same chemical shifts at 1.29 ppm. Proton J is another CH_2 group at 1.45 and proton L is the last peak at 0.9.

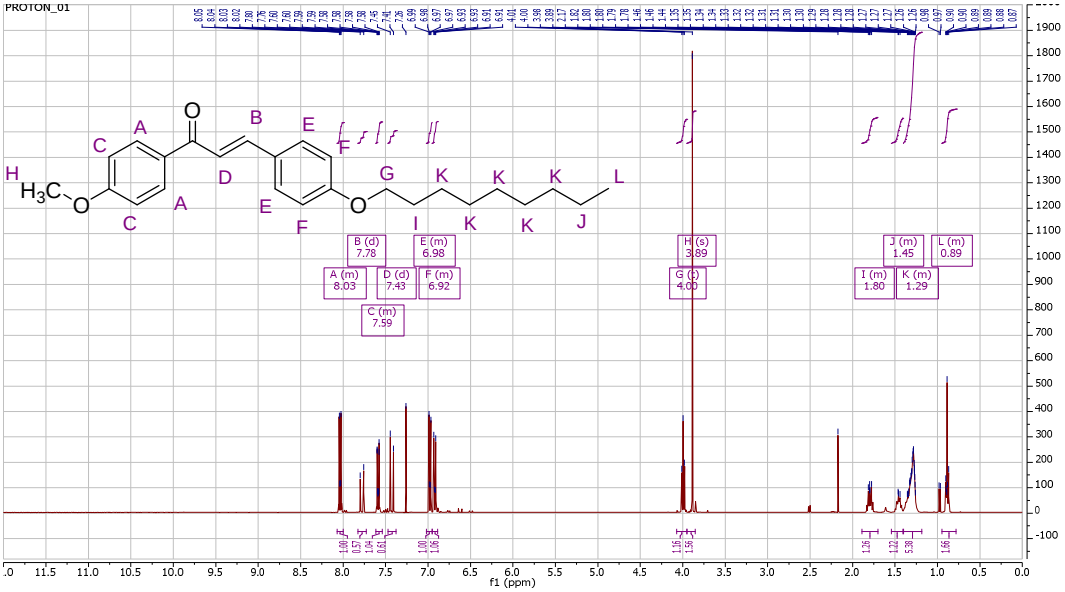


Figure 5. ^{1}H NMR of (E)-1-(4-methoxyphenyl)-3-(4-(nonyloxy)phenyl)prop-2-en-1-one.

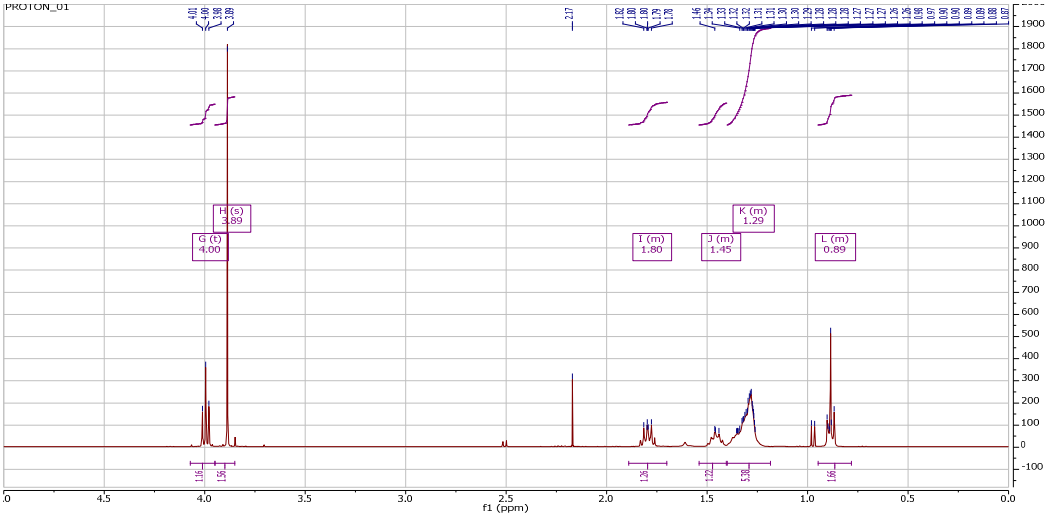


Figure 6. ^{1}H NMR aliphatic region of (E)-1-(4-methoxyphenyl)-3-(4-(nonlyoxy)phenyl)prop-2-en-1-one.

In the aromatic region there are a series of doublets. Both benzene rings have two sets of doublets that are difficult to label each protons chemical shift, but the vinyilic protons have

doublets at 7.78 ppm (proton B) and 7.43 ppm (proton D). Normally vinyilic protons appear between 4.6-5.7 ppm. To differentiate between the peaks that coupled in the aromatic region, a two-dimensional nuclear resonance spectroscopy (2D NMR) was perform, specifically a correlation spectroscopy (COSY) (Figure 8). Protons A and C are located on benzene ring A, proton C is a doublet at 7.59 ppm and proton A is another doublet at 8.03 ppm. On the benzene ring B are protons E and F, proton E is a doublet at 6.98 ppm and F is another doublet at 6.92 ppm.

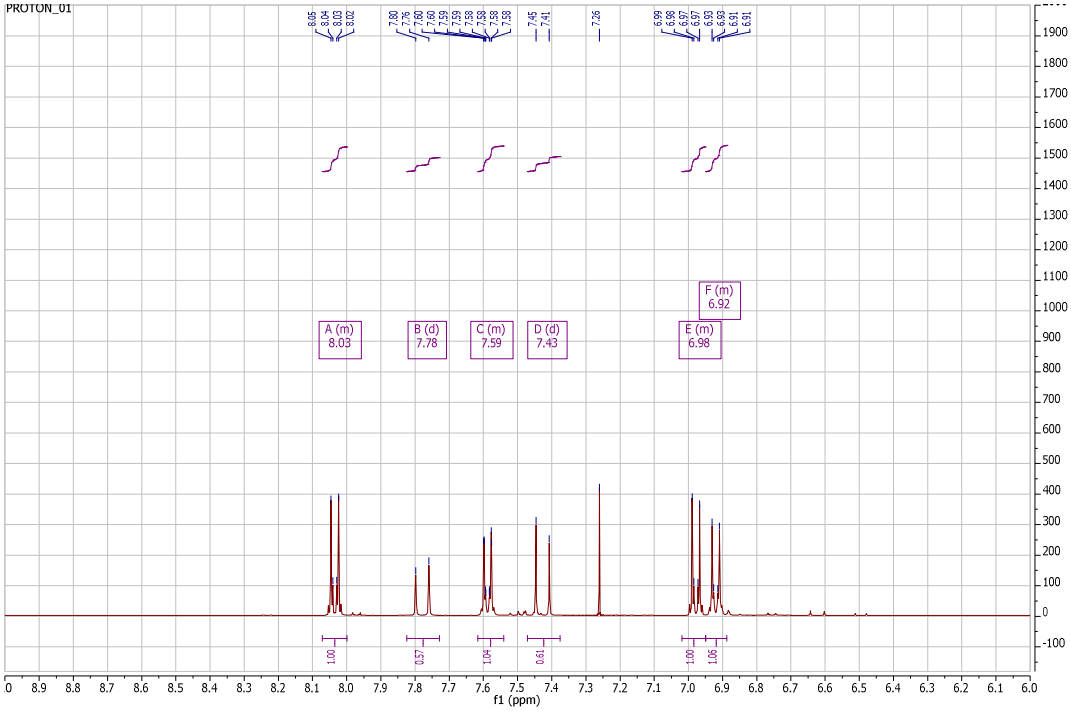


Figure 7. ^{1}H NMR aromatic region of (E)-1-(4-methoxyphenyl)-3-(4-(nonlyoxy)phenyl)prop-2-en-1-one.

The ^{13}C NMR allowed us to see how the chemical backbone was arranged, and what functional groups are represented. The different peaks represent the varying environments of the carbons. Figure 9 is the representative ^{13}C NMR of the nonane methoxychalcone. It has total of twenty five carbons in the chemical formula.

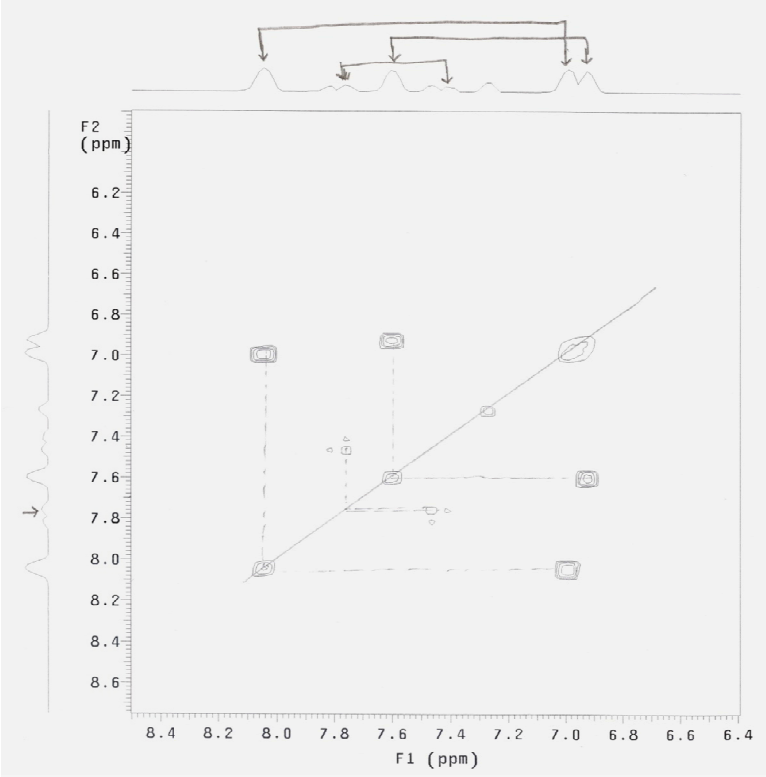


Figure 8. 2D NMR COSY of (E)-1-(4-methoxyphenyl)-3-(4-(nonyloxy)phenyl)prop-2-en-1-one.

Within the structure should be eighteen different carbon environments which should be indicated by eighteen peaks. Starting with the alkane chain there are seven different chemical environments. There are two methoxy carbons that are slightly down field around 55.2 ppm and 68.2 ppm. The very last peak is the CH_3 group at, the end of the chain in which shows up at 13 ppm. Three of the carbons within the chain have the same environment and show up around 29.3 ppm. The four carbons on the chain appear more downfield between 35-0 ppm. The alkene carbons have two different environments. The α carbon shows up around 126.9 ppm and the β carbon appears at 143.5 ppm. The carbonyl is showcased down field around 188.3 ppm. The aromatic rings will have a representation of four peaks because there are two sets of carbons that have the same environment. This is true for both ring systems in the compound.

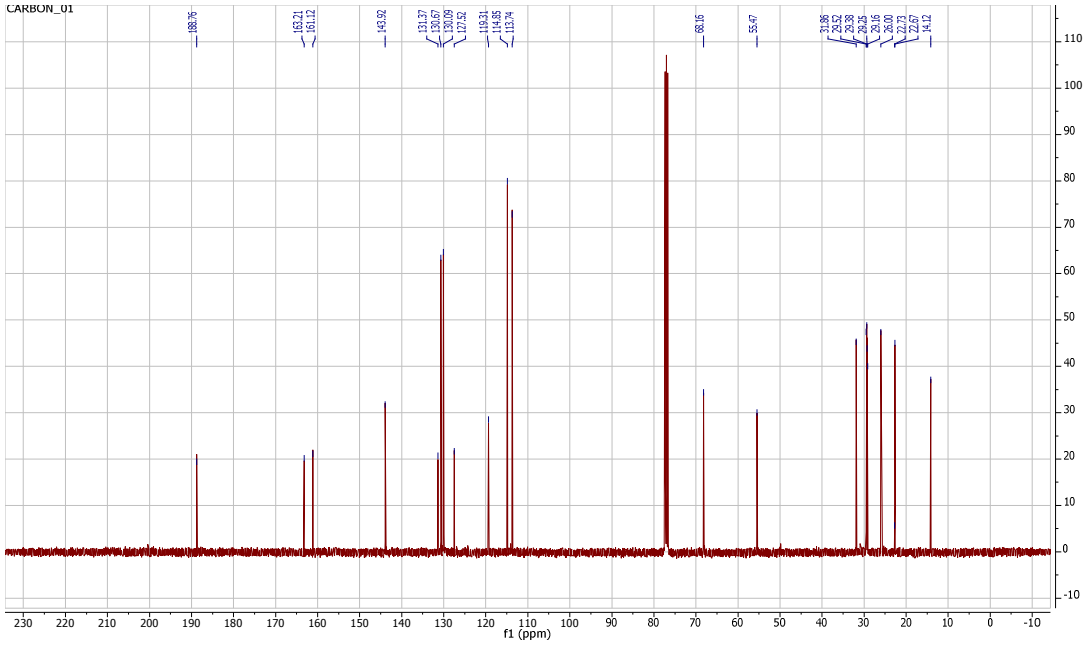


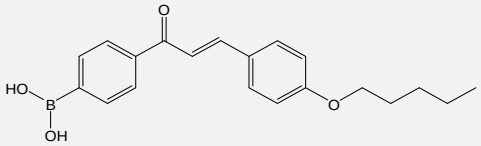
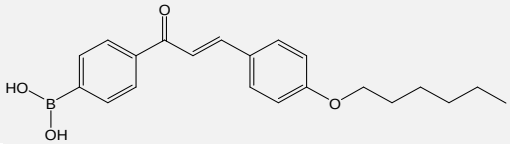
Figure 9. ^{13}C NMR of (E)-1-(4-methoxyphenyl)-3-(4-(nonyloxy)phenyl)prop-2-en-1-one.

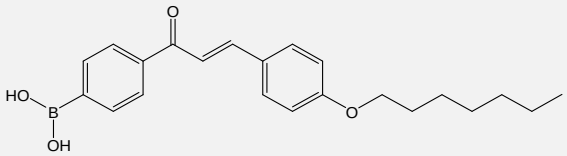
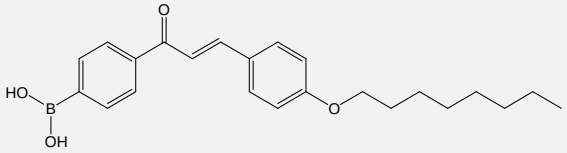
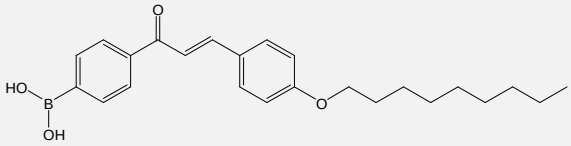
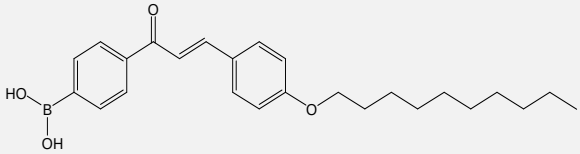
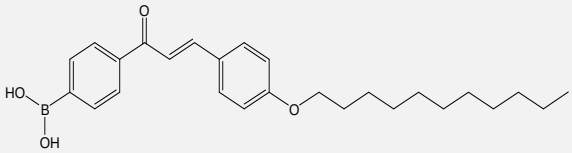
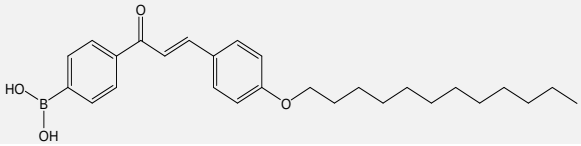
4.3 Results and Discussions of 4-alkoxyboronic acid chalcone Synthesis

4.3.1 Yields of 4-alkoxyboronic acid chalcones. Synthetic yields including cLogP values calculated from the 4-alkoxyboronic acid chalcones. Refer to Figure 2 for numbering sequence

Table 3

Yields for 4-alkoxyboronic acid chalcones

S.No.	B-ring 4'-	A-ring 4-	Product	Yield (%)	cLogP
1c	$B(OH)_2$	C_5H_{11}			3.30
2c	$B(OH)_2$	C_6H_{13}		64	3.77

3c	$B(OH)_2$	C_7H_{15}		88	4.23
4c	$B(OH)_2$	C_8H_{17}		58	4.69
5c	$B(OH)_2$	C_9H_{19}		67	5.16
6c	$B(OH)_2$	$C_{10}H_{21}$		84	5.52
7c	$B(OH)_2$	$C_{11}H_{23}$		82	6.09
8c	$B(OH)_2$	$C_{12}H_{25}$		75	6.55

4.3.2 Discussion of solubility. The solubility of the boronic acid chalcones follows the trend with that of the others, as the chain increases in carbons the solubility increases. However because of the boronic acid group on the other side of the compound the cLogP value significantly dropped when compared to the methoxychalcones. This validates that by adding the boronic acid functional group, the compounds become more soluble allowing it to have more bioavailability. These compounds would be promising in the pharmaceutical industry due to its low cLogP values indicating that they would metabolize through the blood serum.

4.3.3 Discussion of ^{1}H and ^{13}C NMR. The boronic acid chalcones were all ran in deuterated methanol which has two peaks with chemical shifts of 4.8 ppm and 3.3 ppm. Similar to the methoxy chalcones' proton NMRs, Figure 10 showcases the full proton NMR, Figure 11 is

the aliphatic region, and Figure 12 is the aromatic region. The chemical shifts are somewhat similar to that of the methoxy chalcone in the aliphatic region with the exception of only expecting one methoxy proton with a chemical shift around 4.0 ppm being that the boronic acid chalcones have hydroxyl protons attached to its second ring instead of an extra methoxy group. The same follows true for the aromatic region, both the vinylic protons and aromatic protons have similar chemical shifts with exception of now having an extra peak that appears at 8.01 ppm representing the hydroxyl protons on the boron. Literature confirms that when boronic acid is attached to a benzene ring, there is an expected chemical shift of 7.25-8.29 ppm (Bruns, Sinnwell, & Voss, 2003).

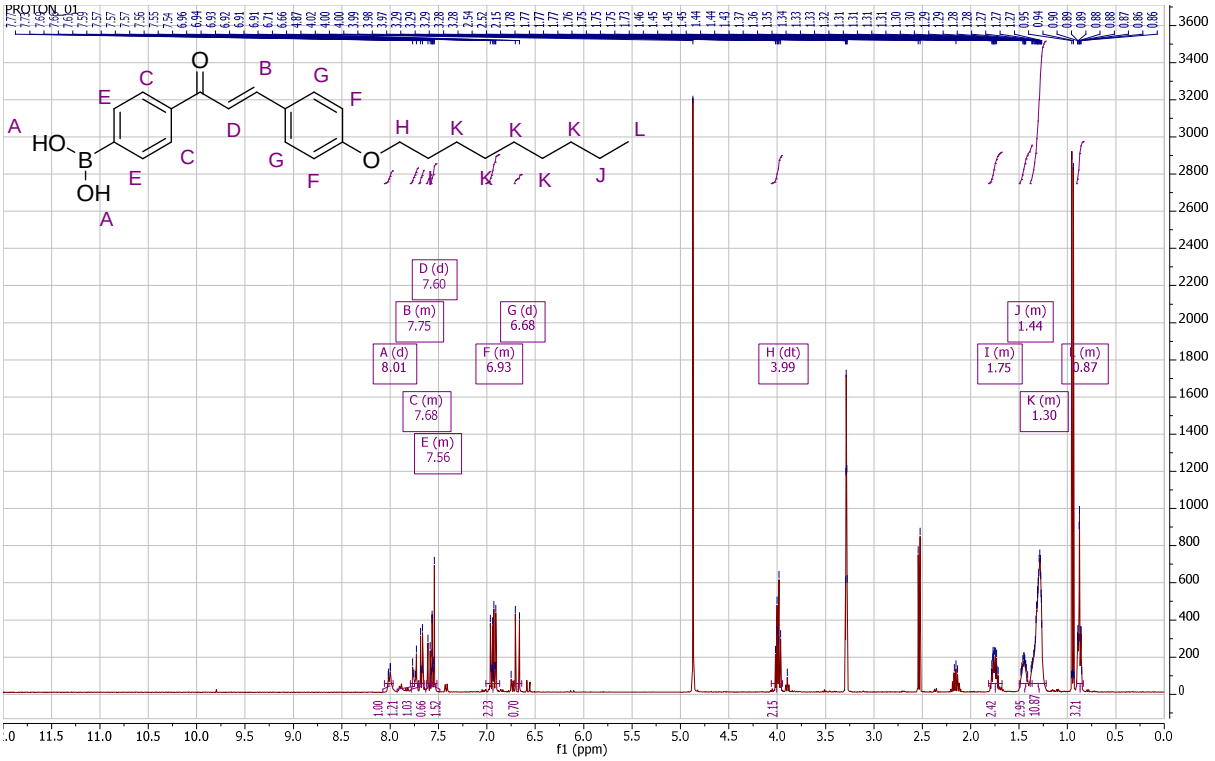


Figure 10. ^{1}H NMR of 4-((E)-3-(4-(nonyloxy)phenyl)acryloyl)phenylboronic acid.

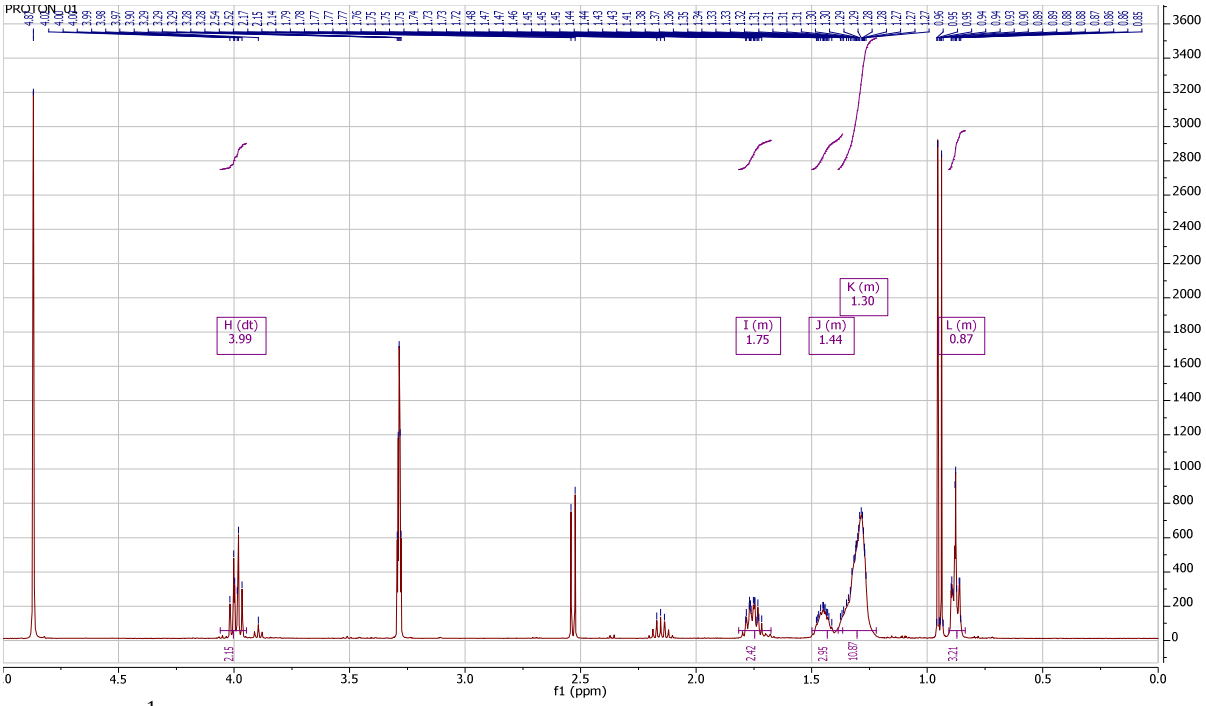


Figure 11. ^{1}H NMR aliphatic region of 4-((E)-3-(4-(nonyloxy)phenyl)acryloyl)phenylboronic acid.

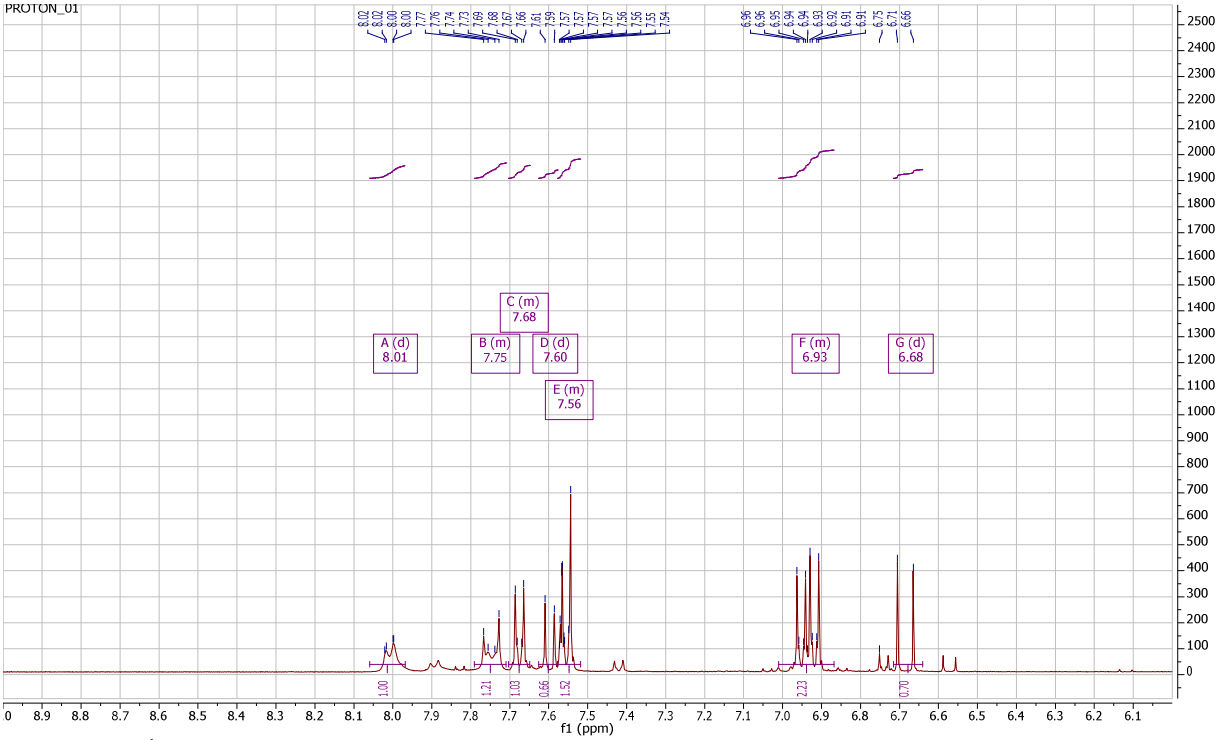


Figure 12. ^{1}H NMR aromatic region of 4-((E)-3-(4-(nonyloxy)phenyl)acryloyl)phenylboronic acid.

Figure 13 is the representative ^{13}C NMR of the nonane boronic acid chalcone.Peaks are not as pronounced due to the solubility of the compound in the solvent. Again similar to that of the methoxy chalcone we expect to see twenty five peaks for each of the carbons in the compound, but eighteen different environments. The only difference is the slight down field shift of the peaks that might be due to the boron. The biggest difference between the ^{13}C NMR of the methoxy and boronic acid chalcones is the carbonyl peak. In the methoxy spectrum the carbonyl peak appears at 188.59 ppm but now in the boronic acid spectrum has a down field shift at 203.63 ppm. The presence of only one methoxy carbon instead of two signifies that there is another difference between both the methoxy and boronic acid spectrums.

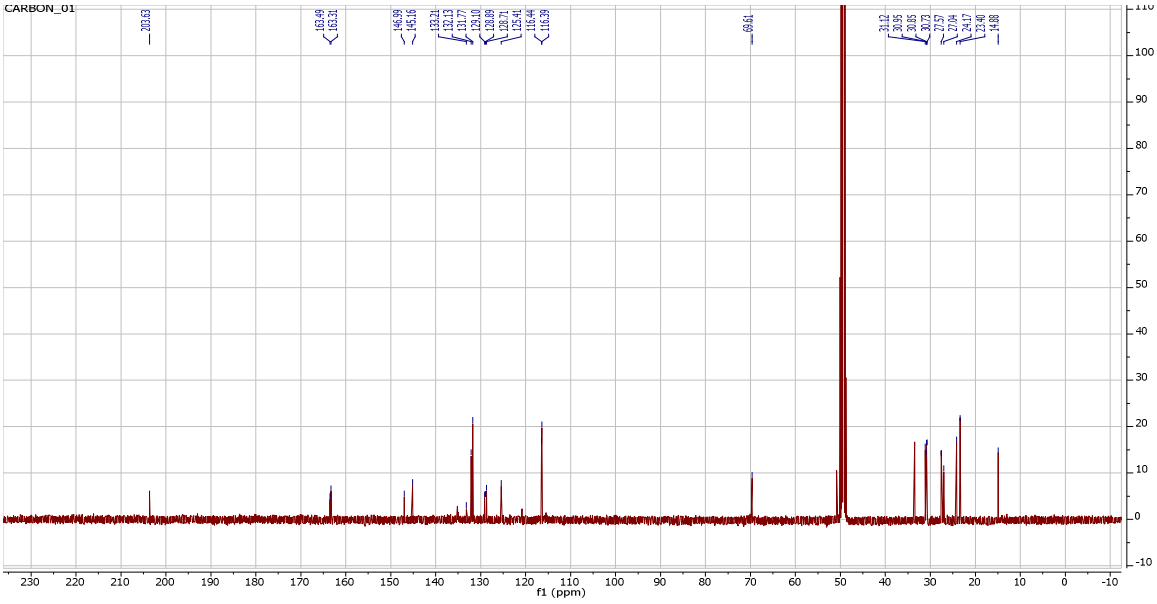


Figure 13. ^{13}C NMR of ((E)-3-(4-(nonyloxy)phenyl)arcyloyl)phenylboronic acid

By comparing the NMR data from both the ^{1}H NMR and ^{13}C NMR of each chalcone confirms t that there is a difference between the methoxychalcones and the boronic acid chalcones. This difference can be made by the aliphatic regions of the ^{1}H NMR and by different carbonyl shifts in the ^{13}C NMR.

CHAPTER 5

Conclusion and Future Research

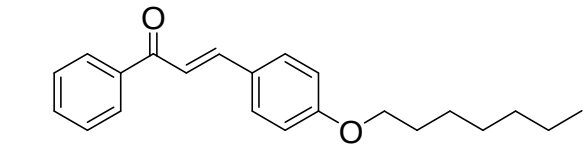
We have reported an attempt to synthesize twenty four chalcone derivatives. To the best of our knowledge, thirteen of our chalcone derivatives have never being reported, this investigation namely, five methoxy chalcones (4b-8b) and eight boronic acid chalcones (1c-8c). The benzaldehyde compounds had much success with the Williamson Ether synthesis. An extra step was added to ensure that the compounds were pure; the distillation via Kugelrohr. The benzaldehydes that were synthesized are commercially available, but do not have any reported melting point from their respected companies.

Out of the three reactions, the boronic acid chalcones took the most effort to recover. The degree of difficulty came about when it came time to recrystallize the compounds. This was partially due to the solubility of the compound and because of that three of the compounds were not recovered. Another issue we encountered when synthesizing both sets of chalcones was having starting material in the products. Evidence of the starting material, mainly benzaldehye, showed up in the NMR spectra and could be the reason to why recrystallizing the compound had a degree of difficulty. To deal with this issue an excess of acetophenone could be used instead of equal molar quantity.

Once we recovered the three boronic acid chalcones lost in recrystallization, (1c, 4c and 8c) we want to add on with the discovery and add the butane and propane boronic acid chalcones to the library, neither of which have been reported. The next step for both sets of chalcones is to send them to the National Institute of Health Developmental Therapeutics Program to be screened on cancer cell lines. This step will help with the development of a structure-activity

relationship and to see if boronic acid will indeed have more biological availability than that of a methoxy group as well as see if the ether chain has any affect on cancer.

During this research, we also encountered a crystal form of a chalcone that we attempted to synthesize in the past (Figure 14). This too gives great insight to the characteristics of chalcones. In the future we have hopes to further study this crystal and attempt to form crystals with the other chalcones.



(*E*)-3-(4-(heptyloxy)phenyl)-1-phenylprop-2-en-1-one

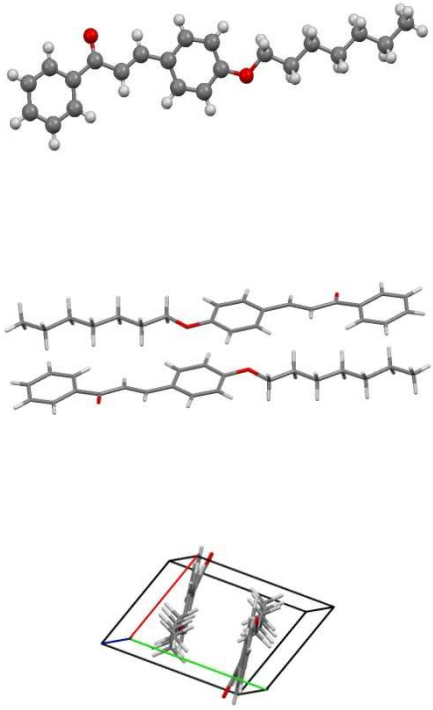


Figure 14. Chalcone crystal structures.

References

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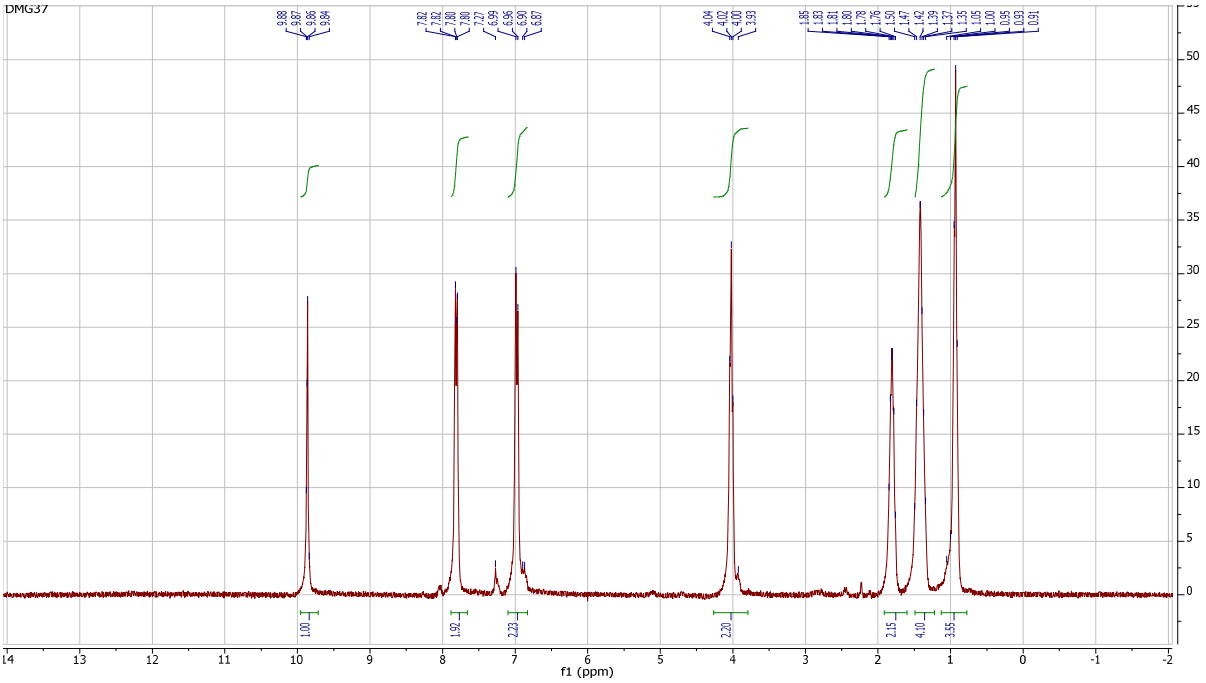
Appendix A

^{1}H NMR

4-(pentyloxy)benzaldehyde (1a)



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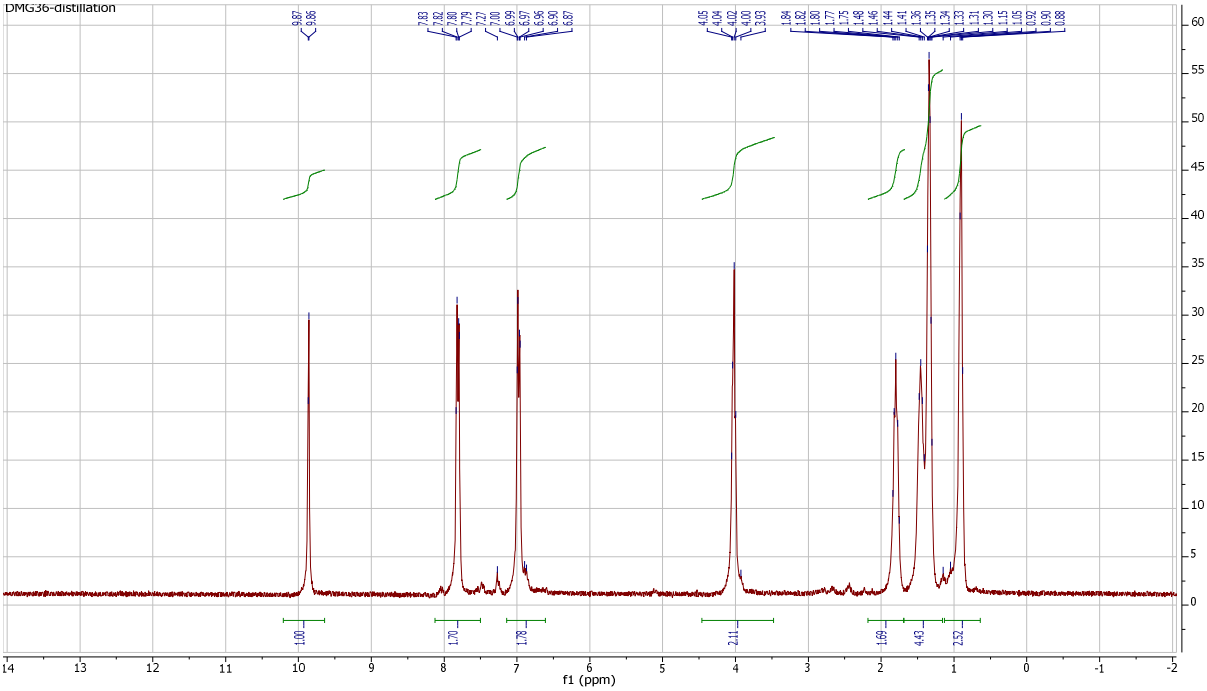
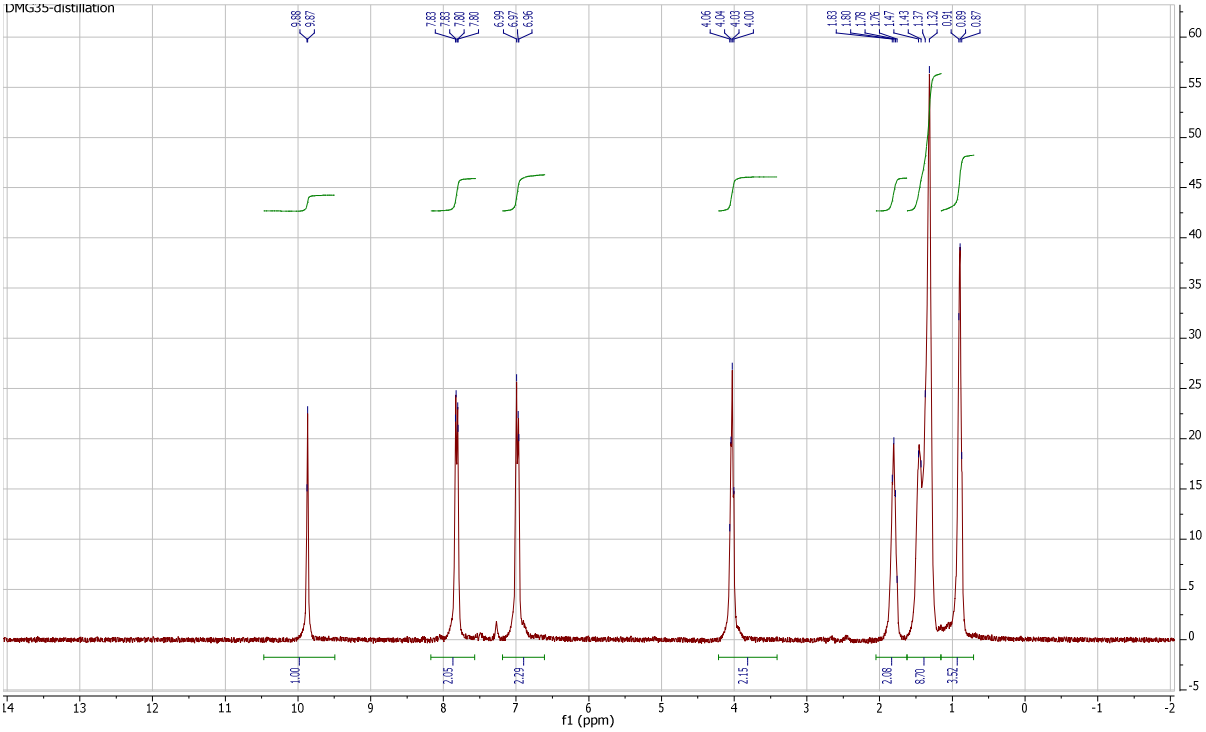


4-(heptyloxy)benzaldehyde (3a)



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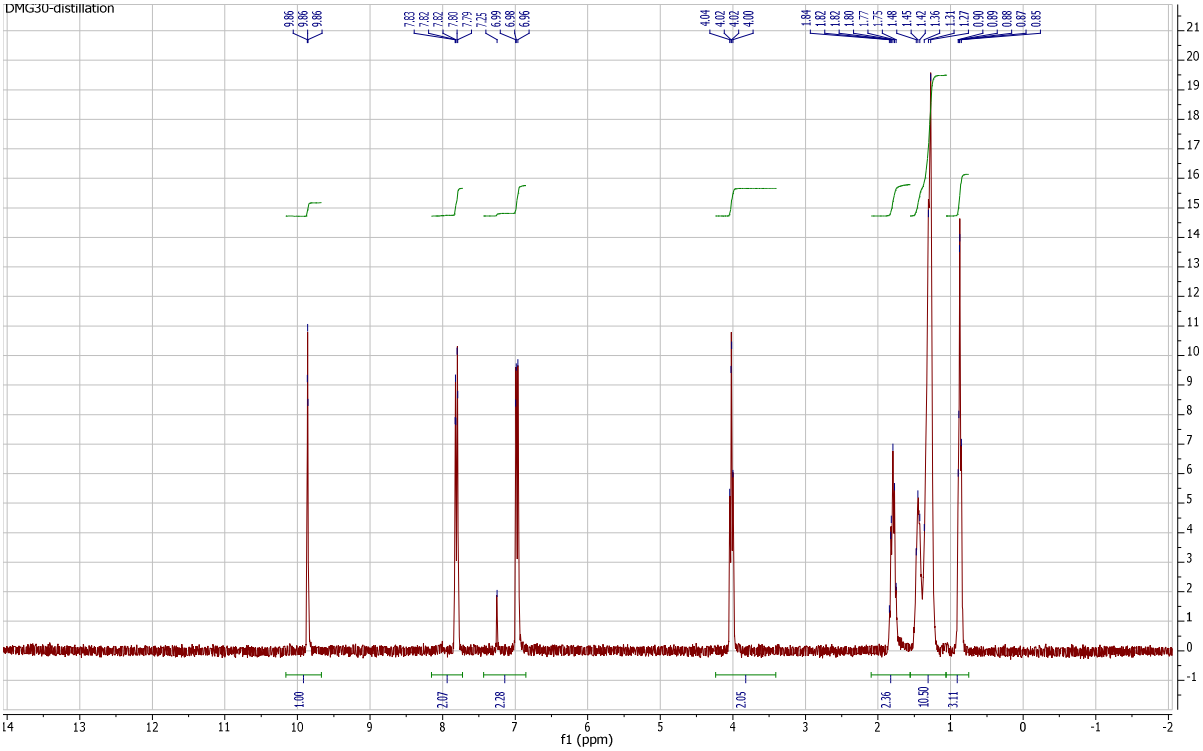

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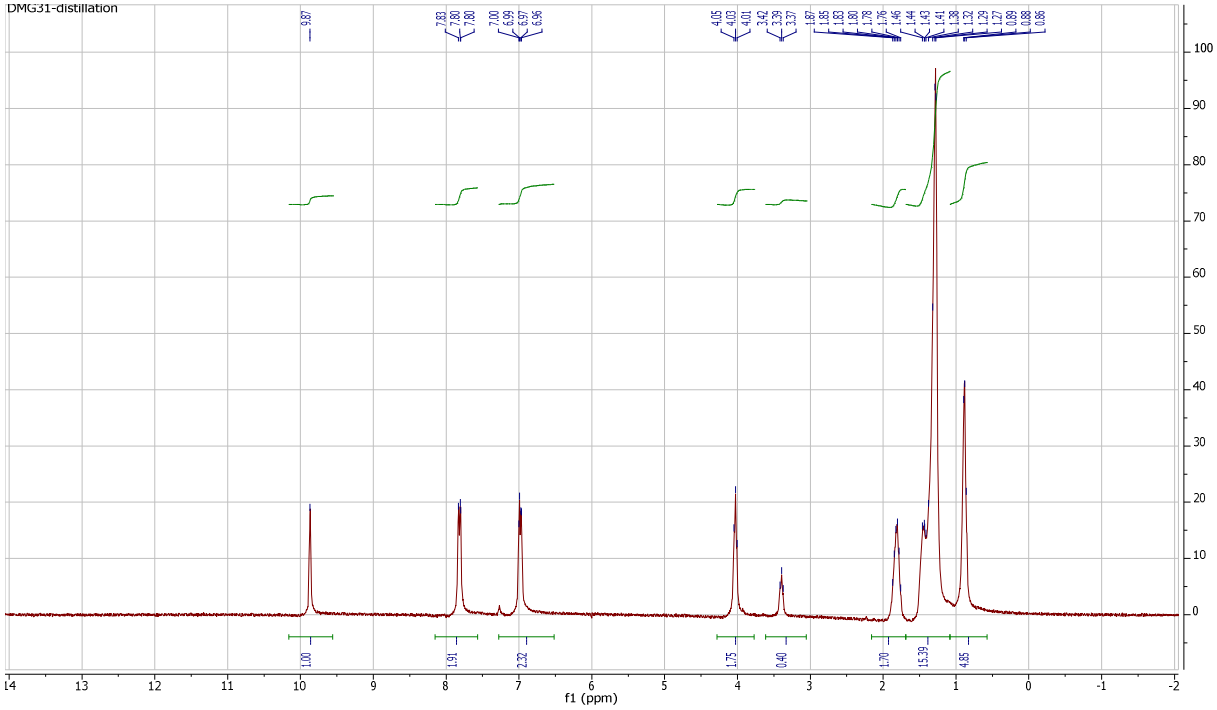

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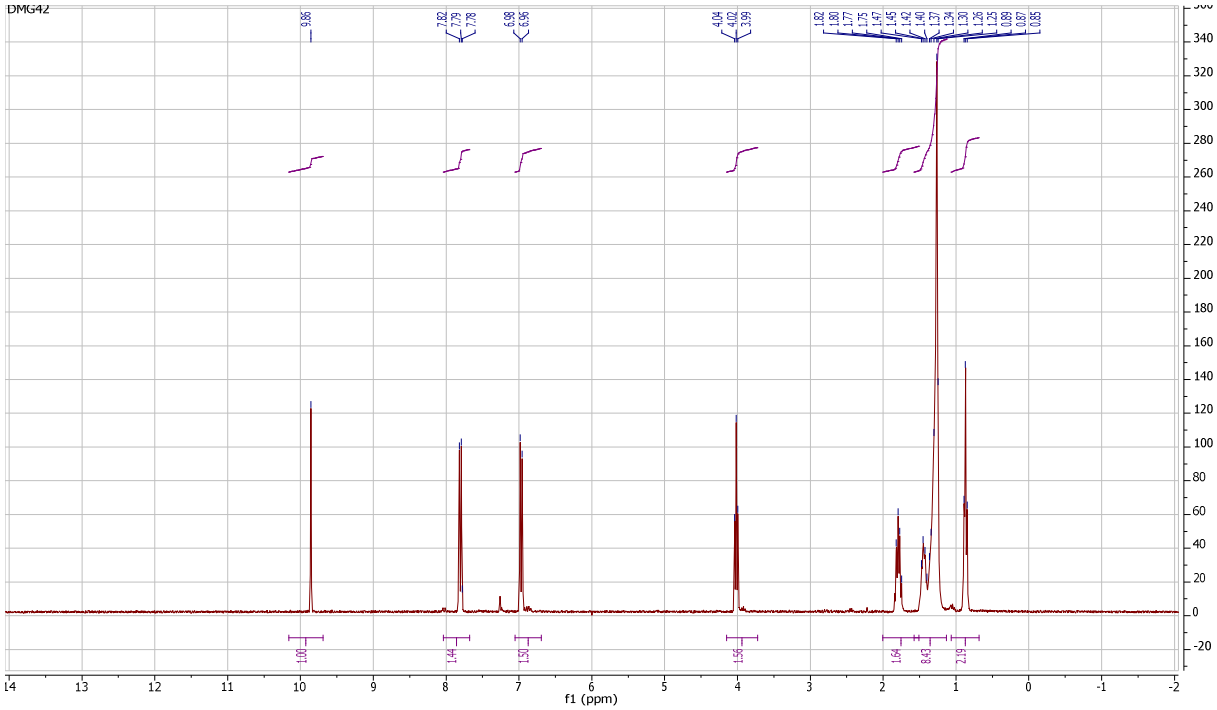

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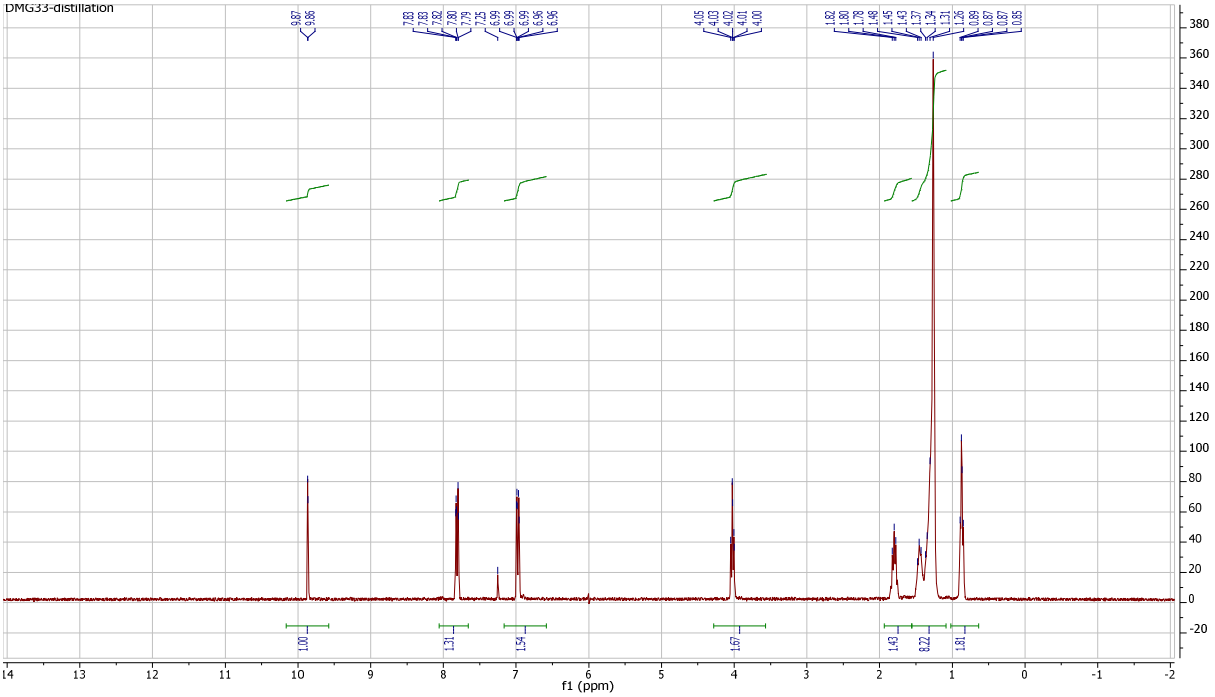

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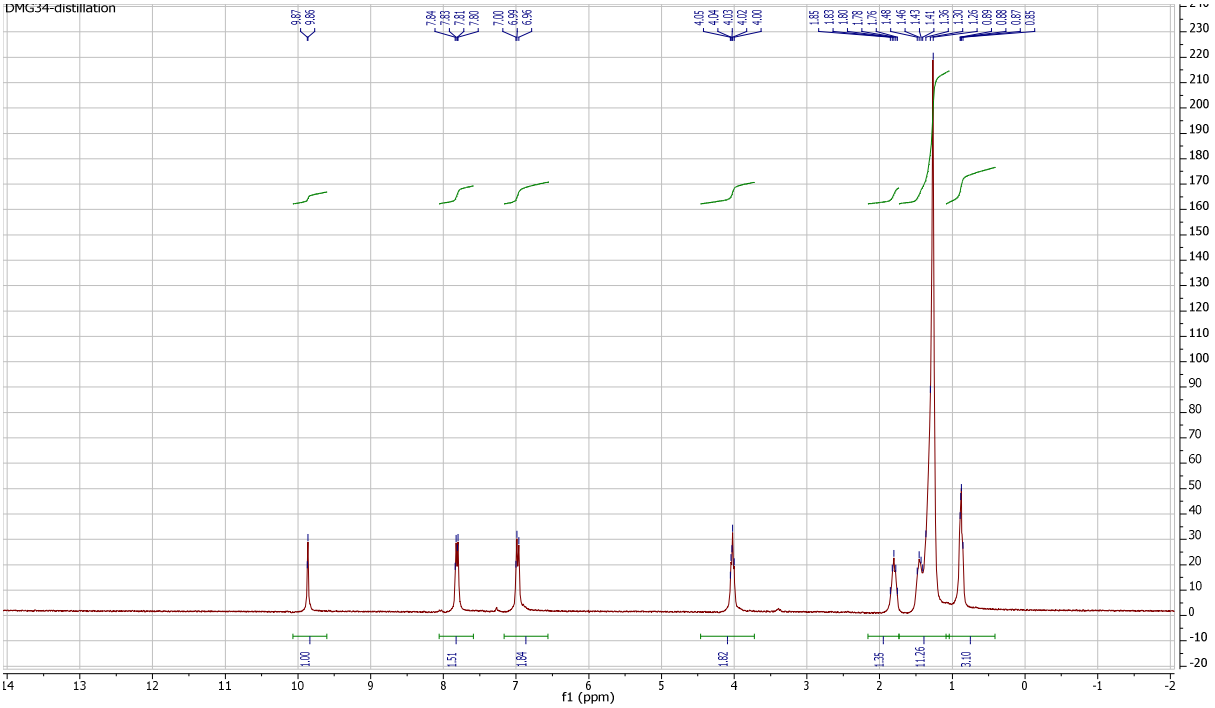
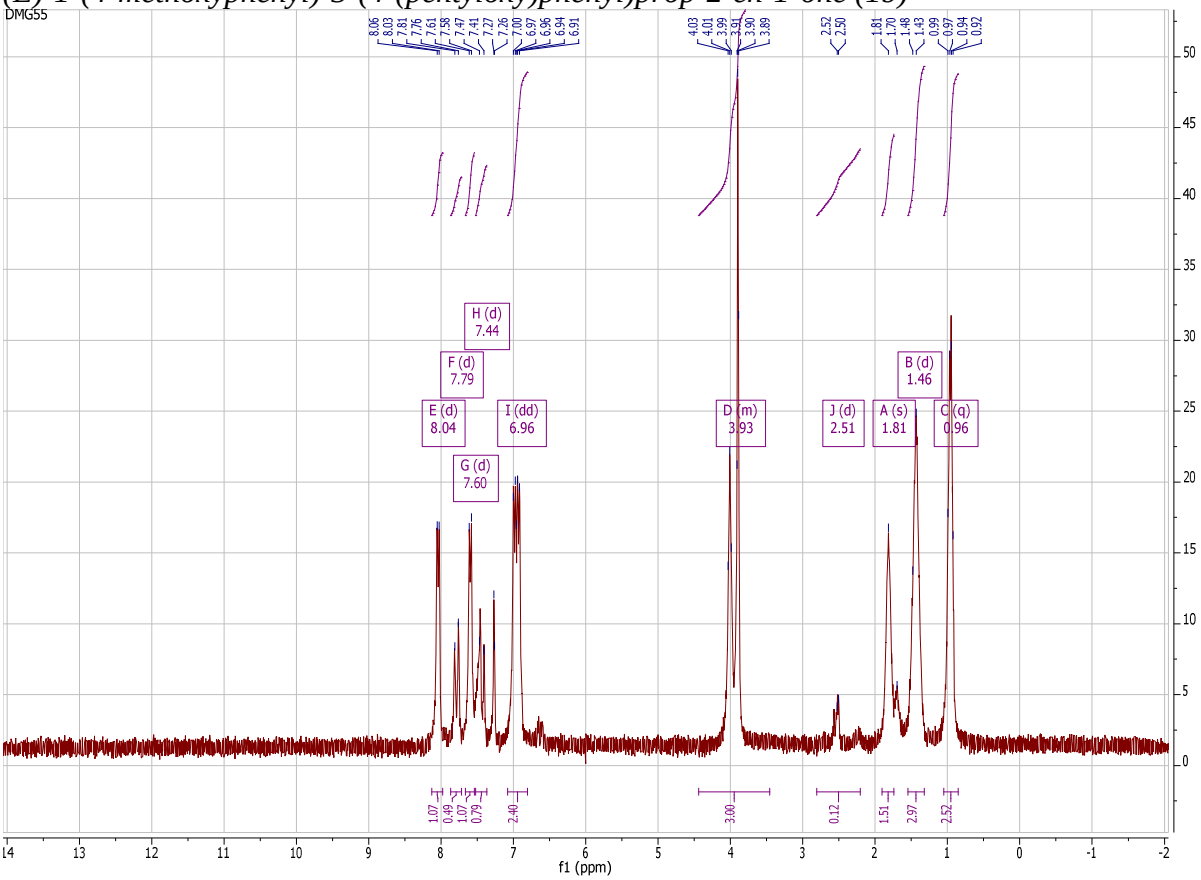


(E)-1-(4-methoxyphenyl)-3-(4-(pentyloxy)phenyl)prop-2-en-1-one (1b)



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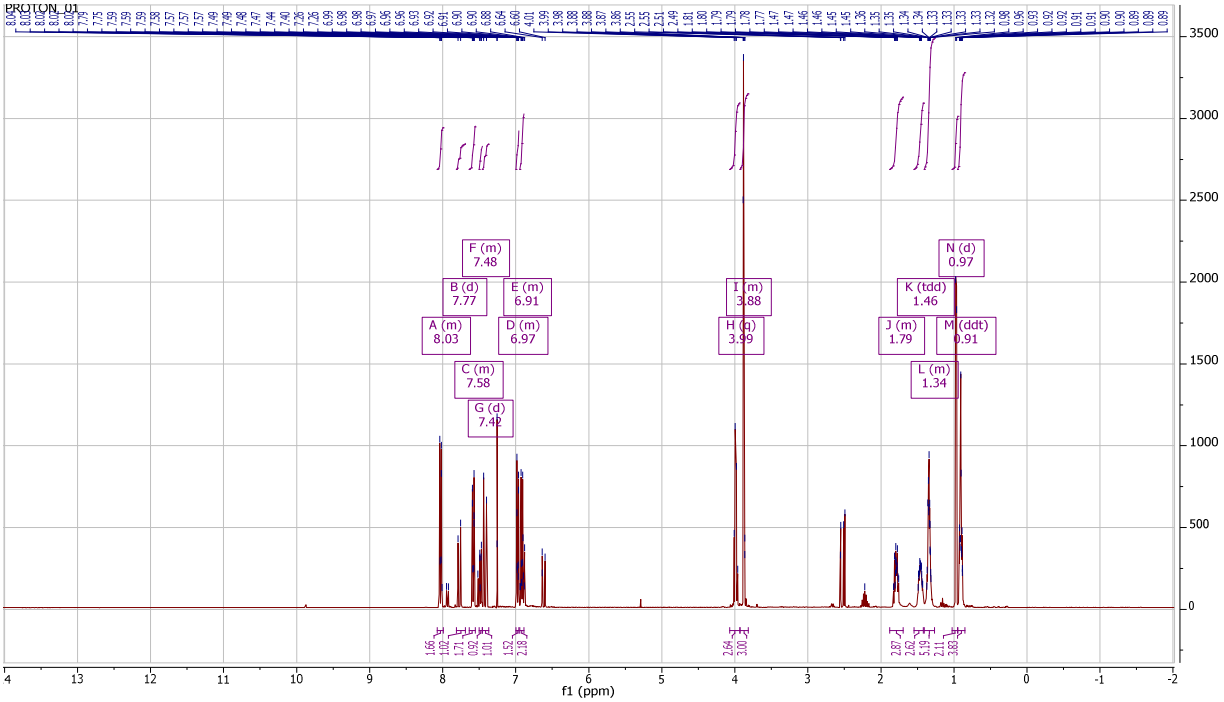

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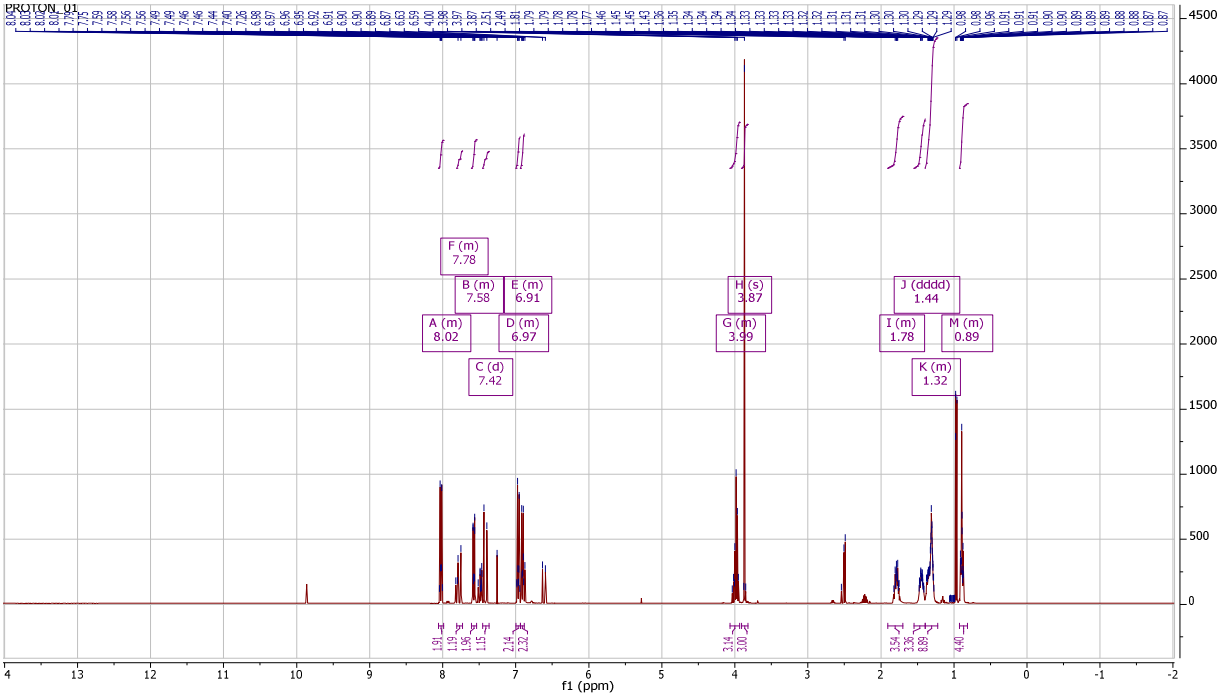

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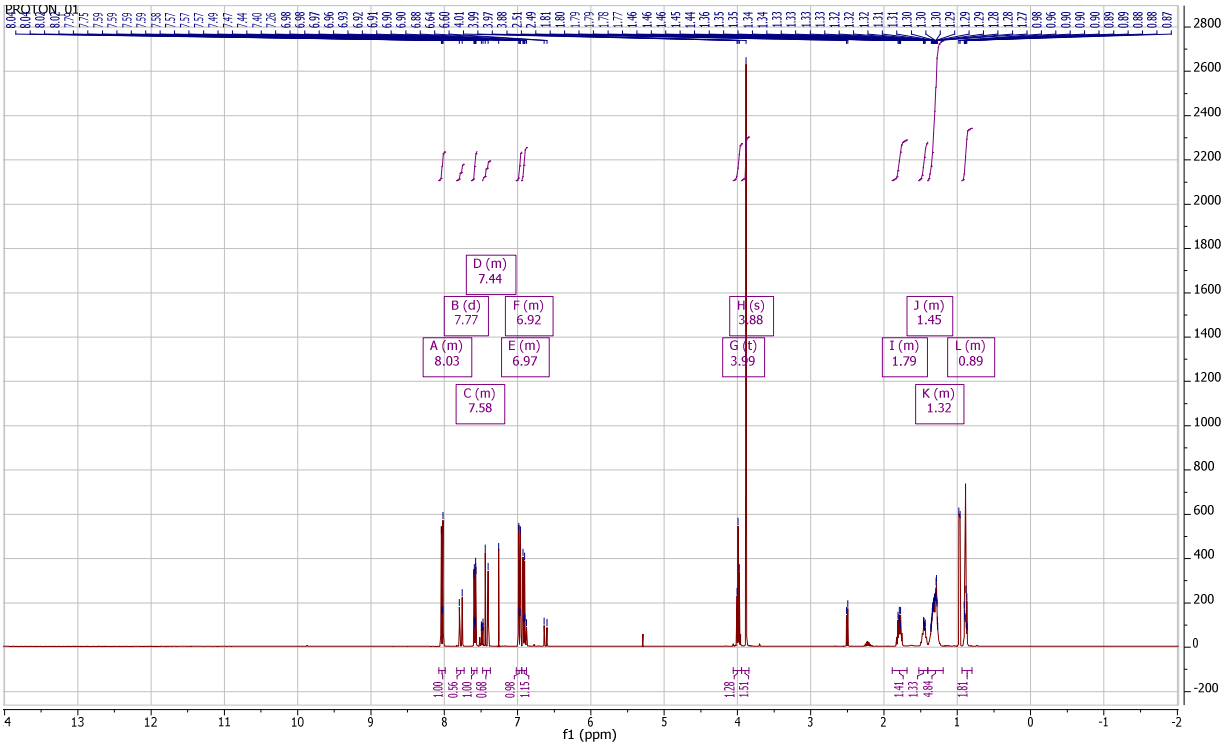

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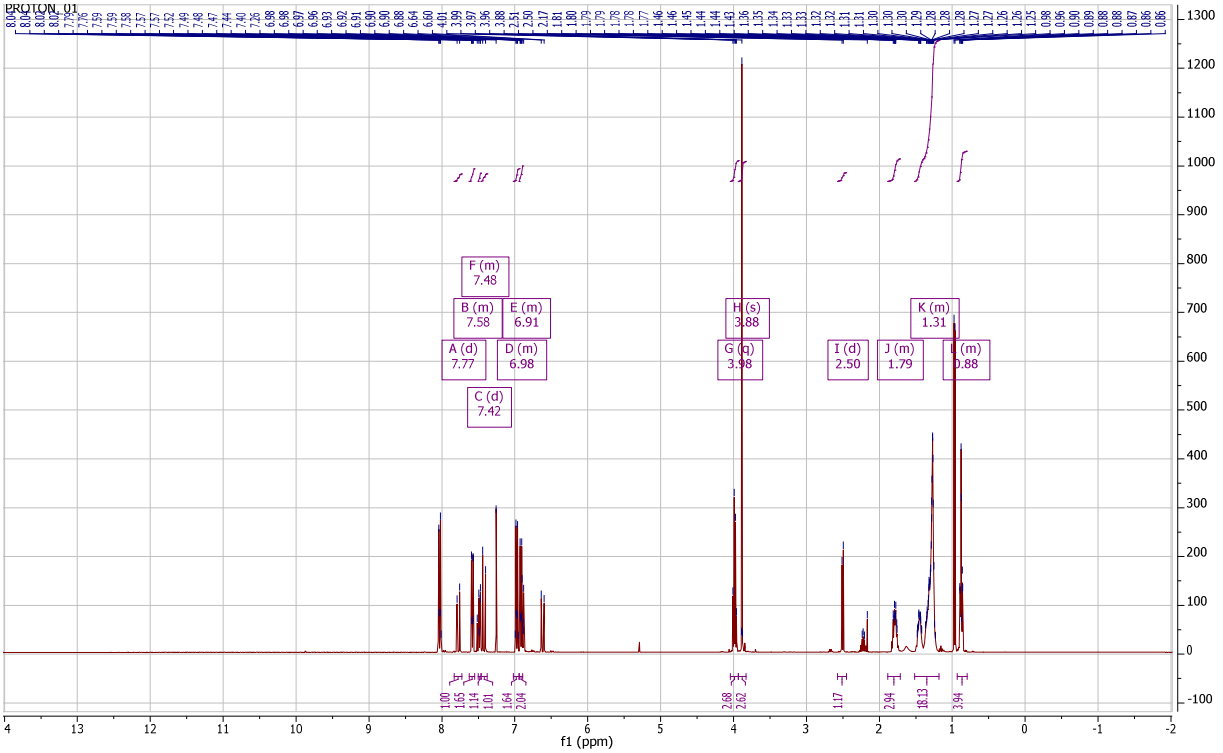

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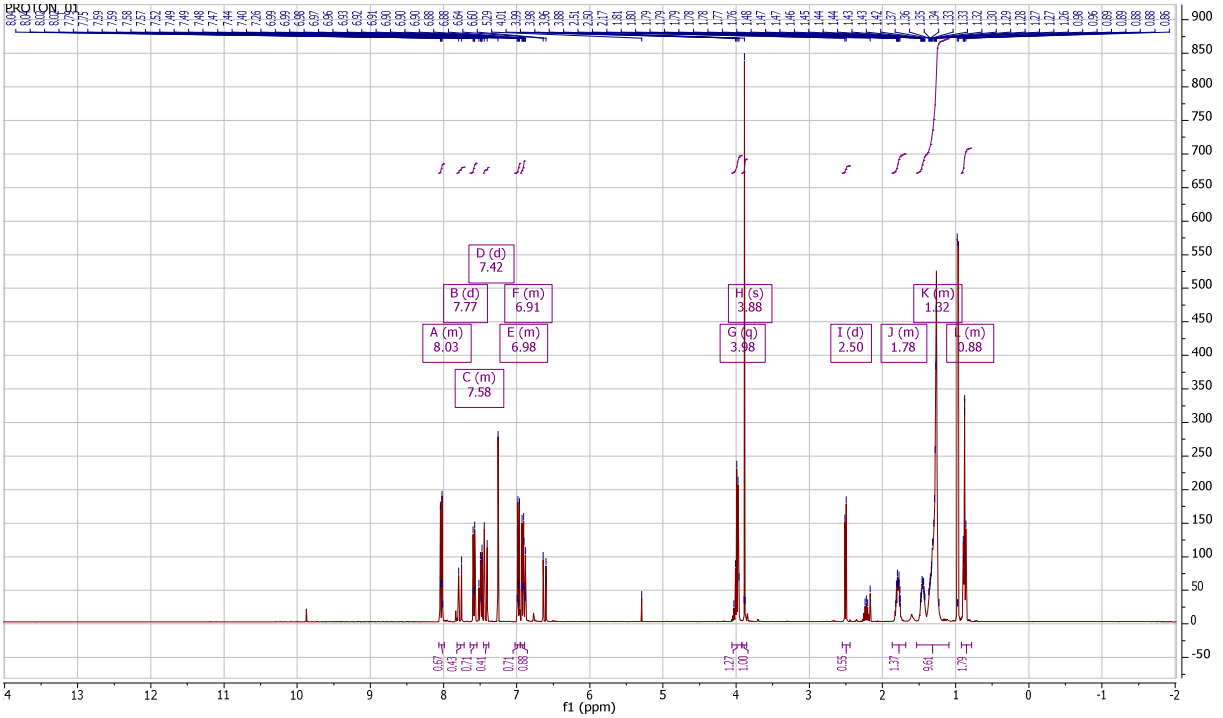
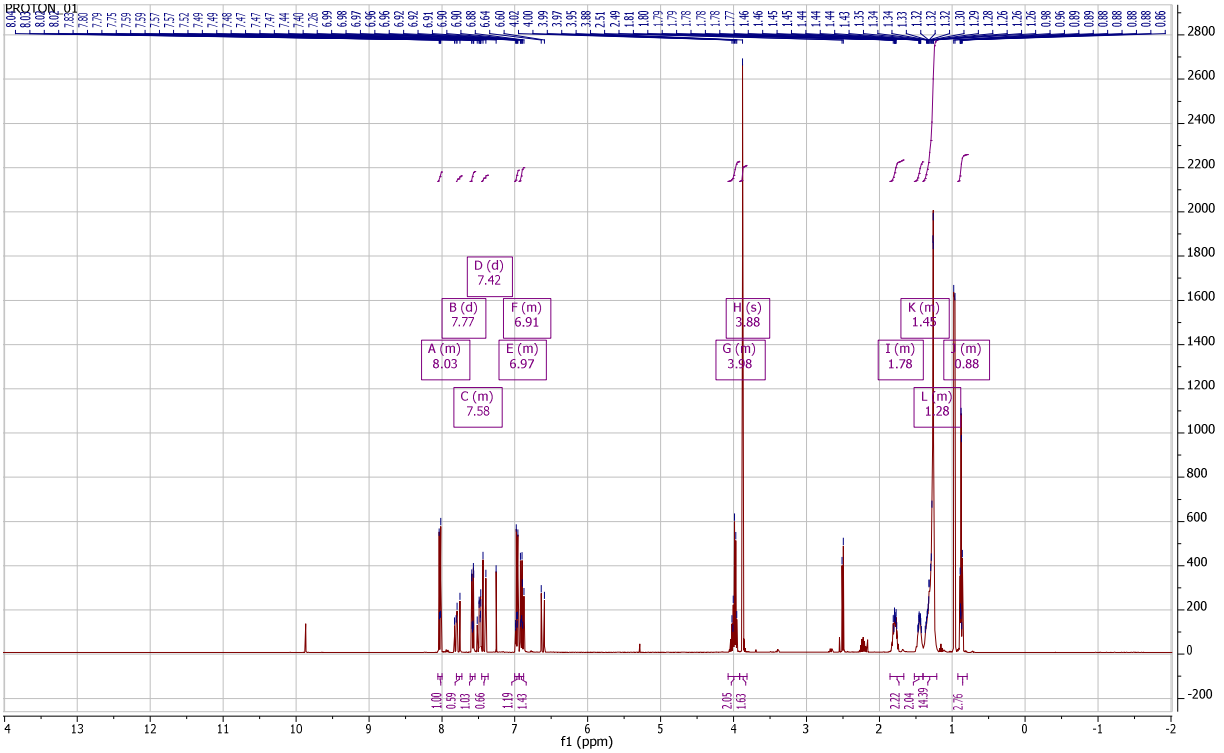
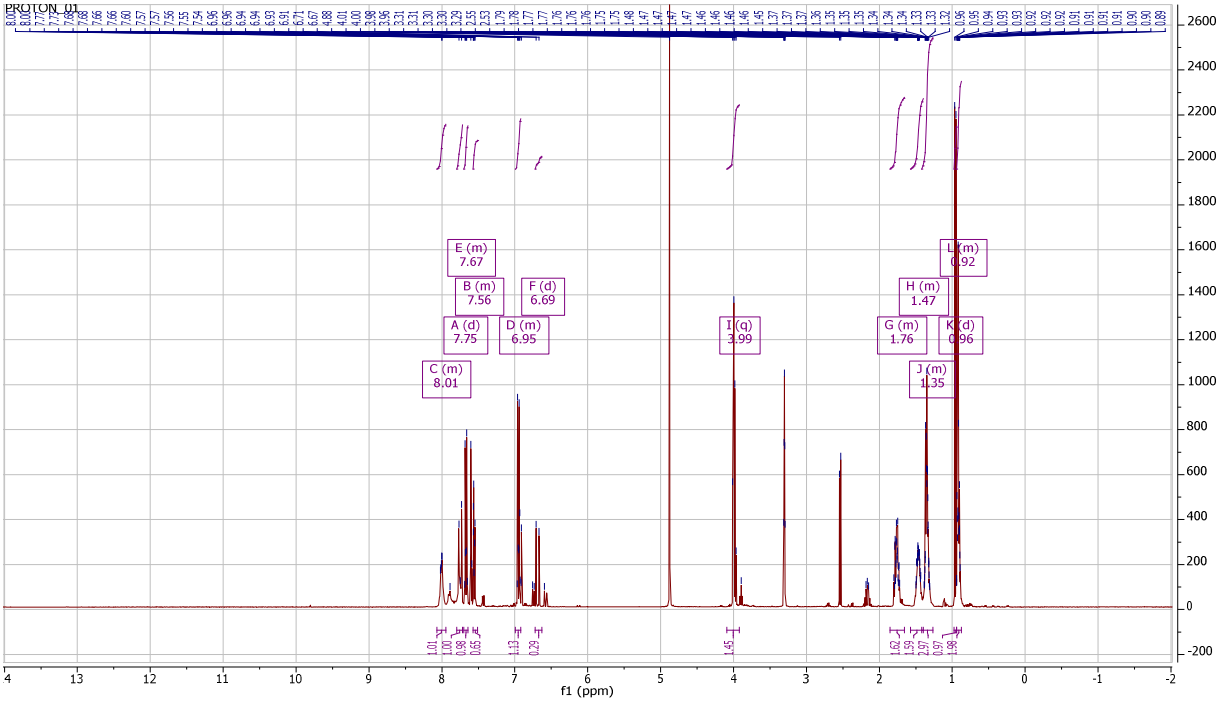


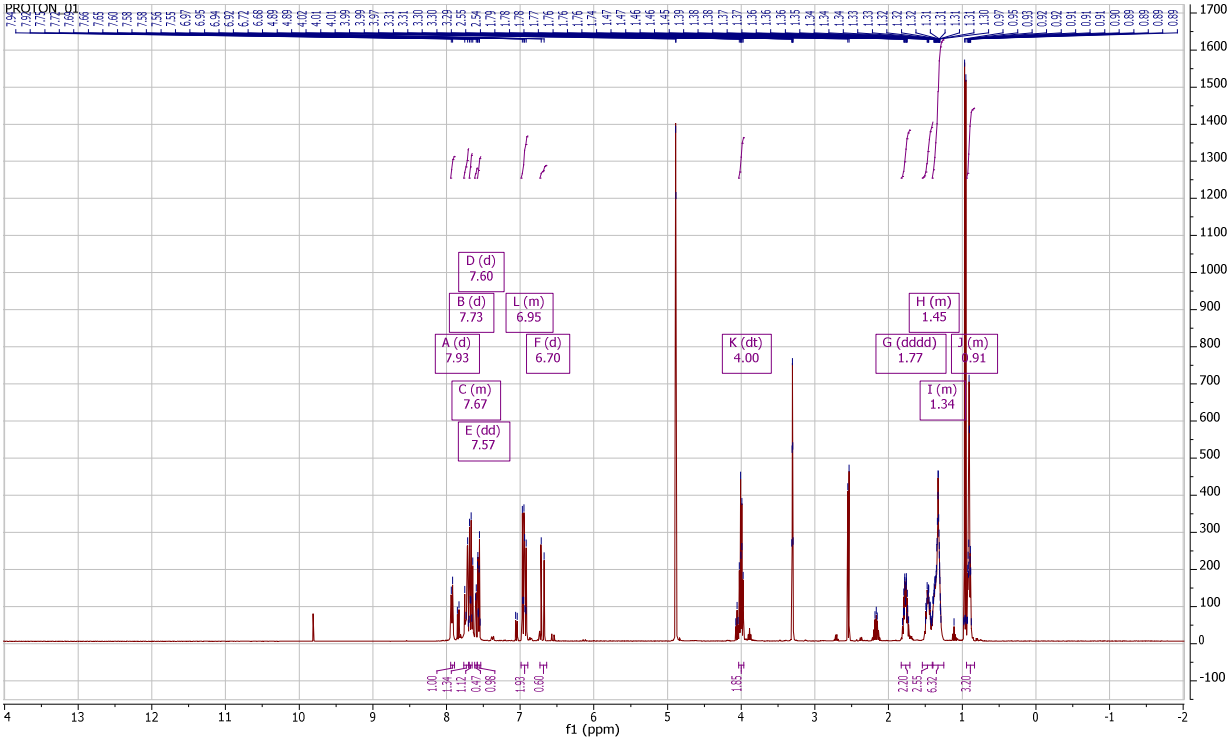
(E)-3-(4-(dodecyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (8b)



4-((E)-3-(4-(hexyloxy)phenyl)acryloyl)phenylboronic acid (2c)



4-((E)-3-(4-heptyloxy)phenyl)acryloyl)phenyloboronic acid (3c)



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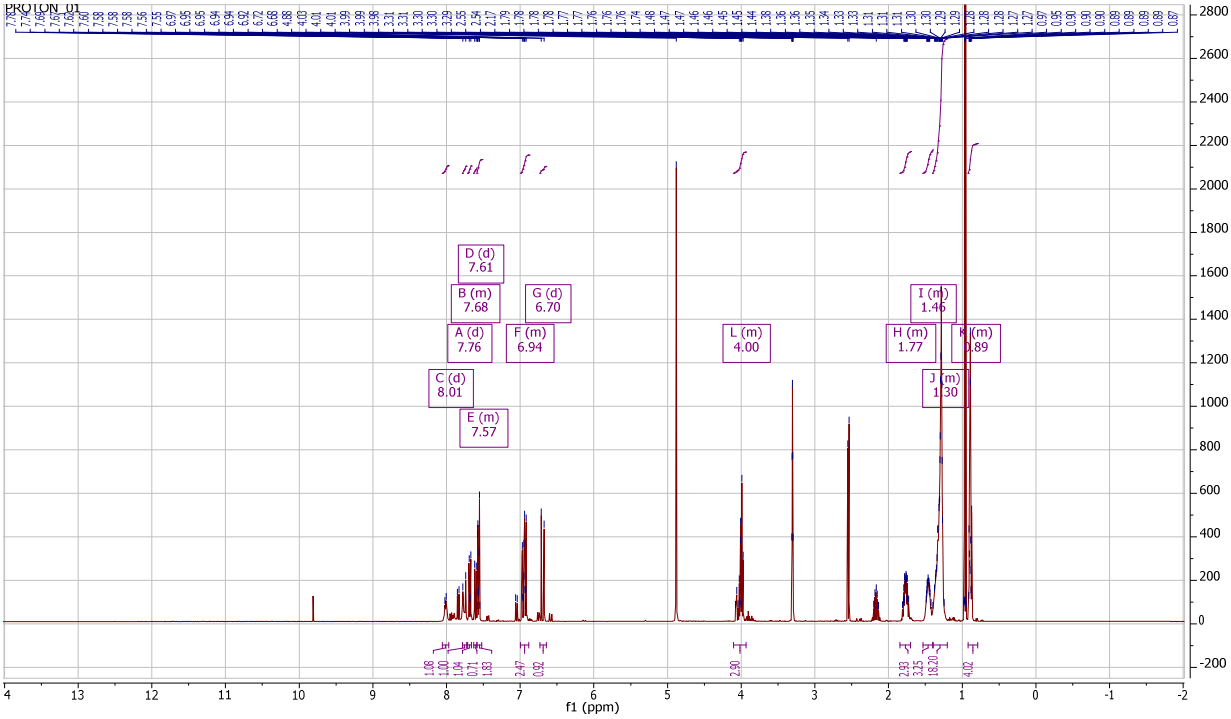

Appendix B

^{13}C NMR

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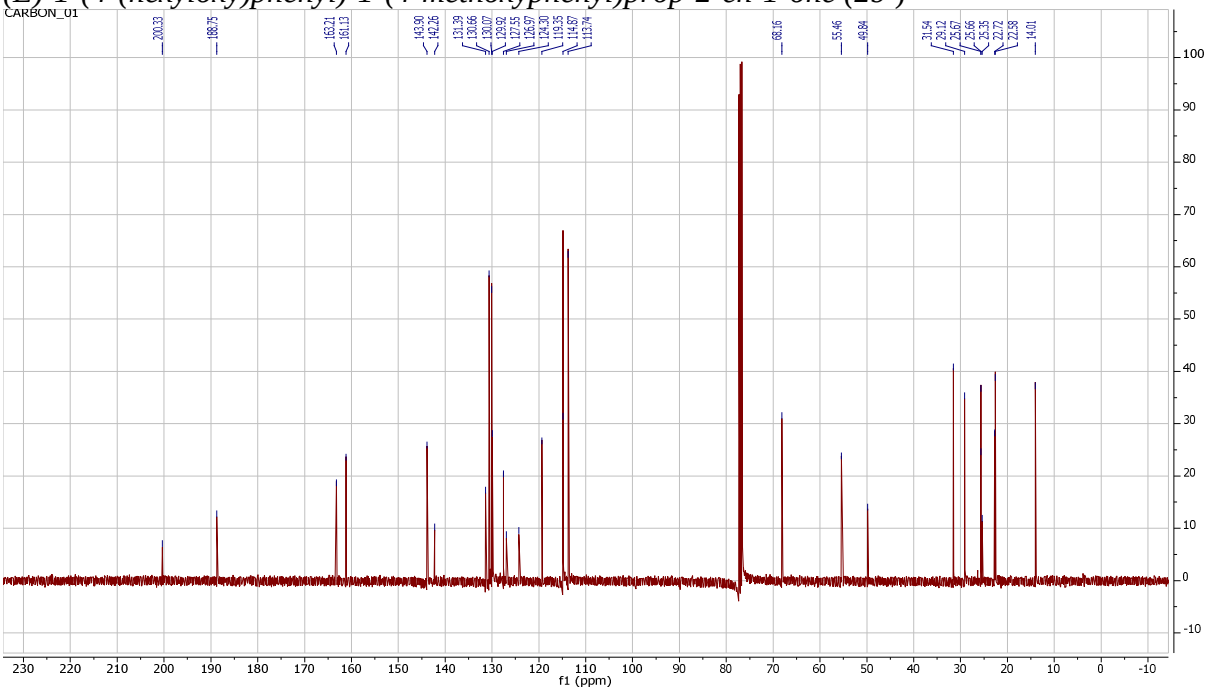

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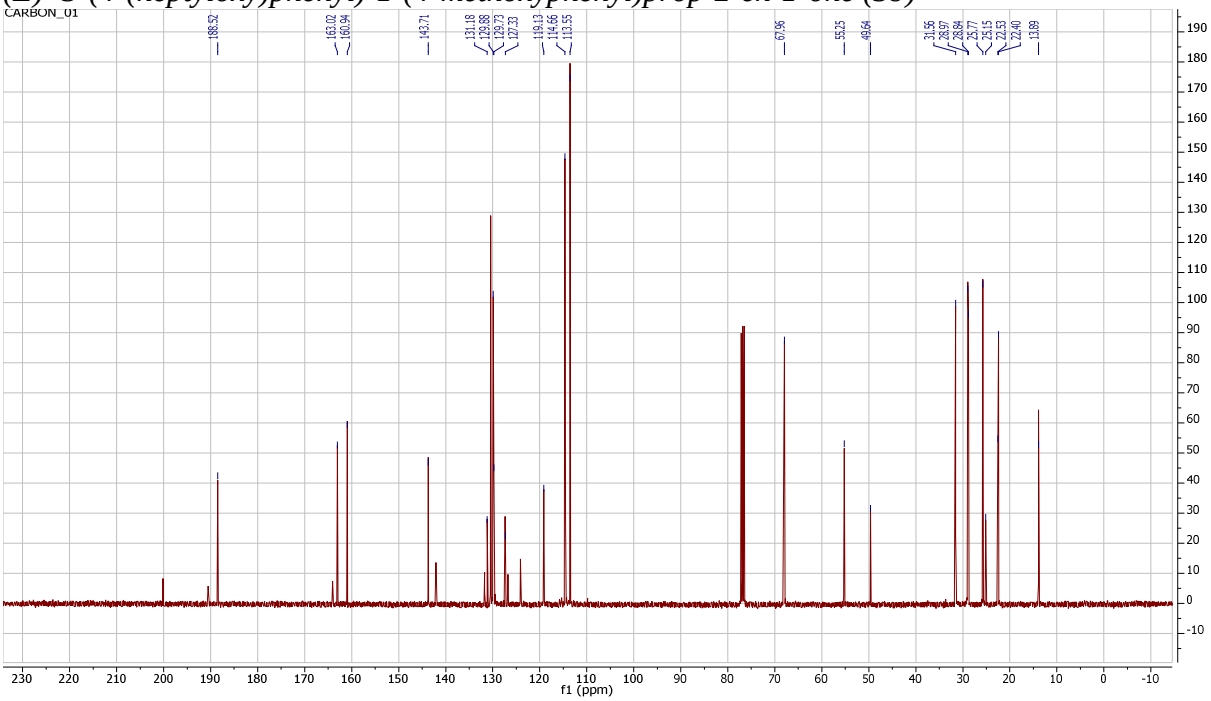
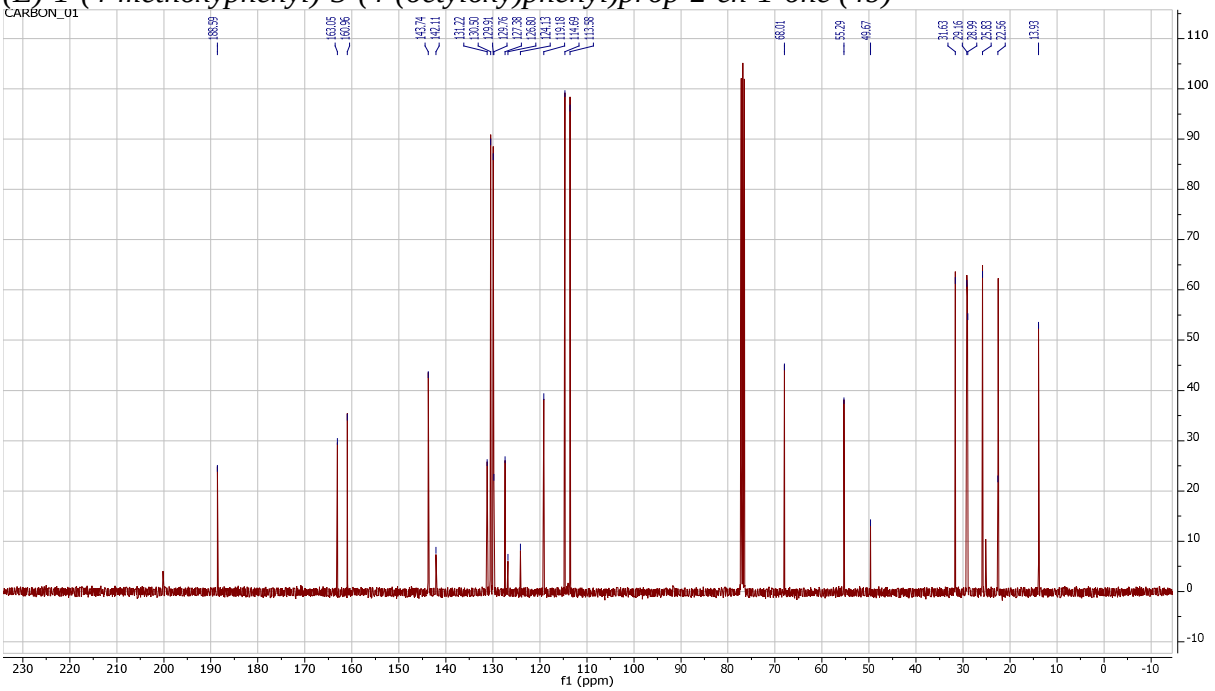
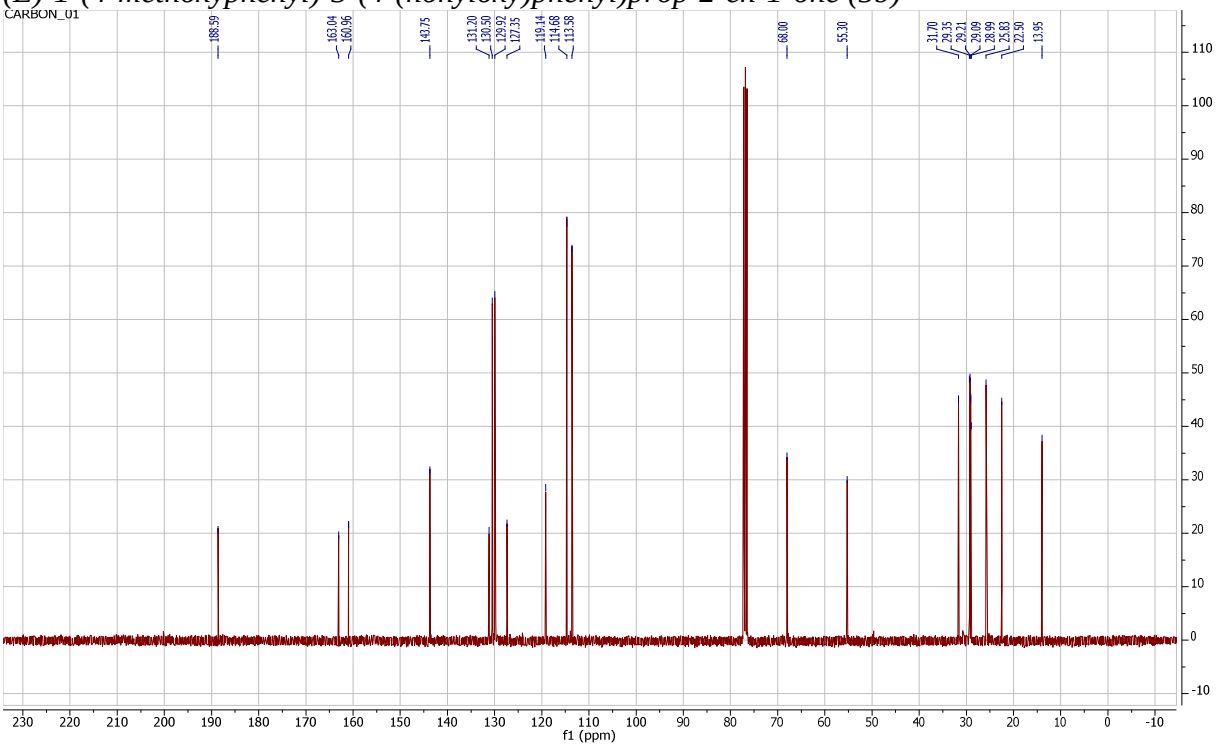


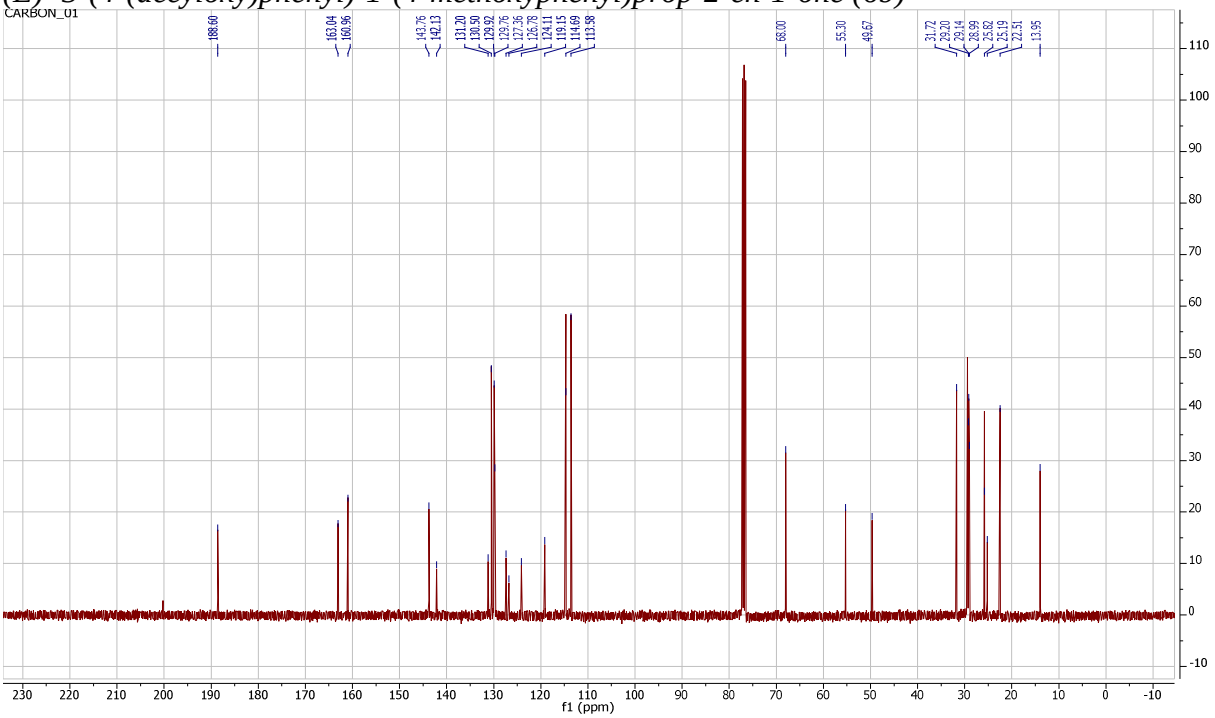
(E)-1-(4-methoxyphenyl)-3-(4-(octyloxy)phenyl)prop-2-en-1-one (4b)



(E)-1-(4-methoxyphenyl)-3-(4-(nonyloxy)phenyl)prop-2-en-1-one (5b)



(E)- 3-(4-(decyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (6b)



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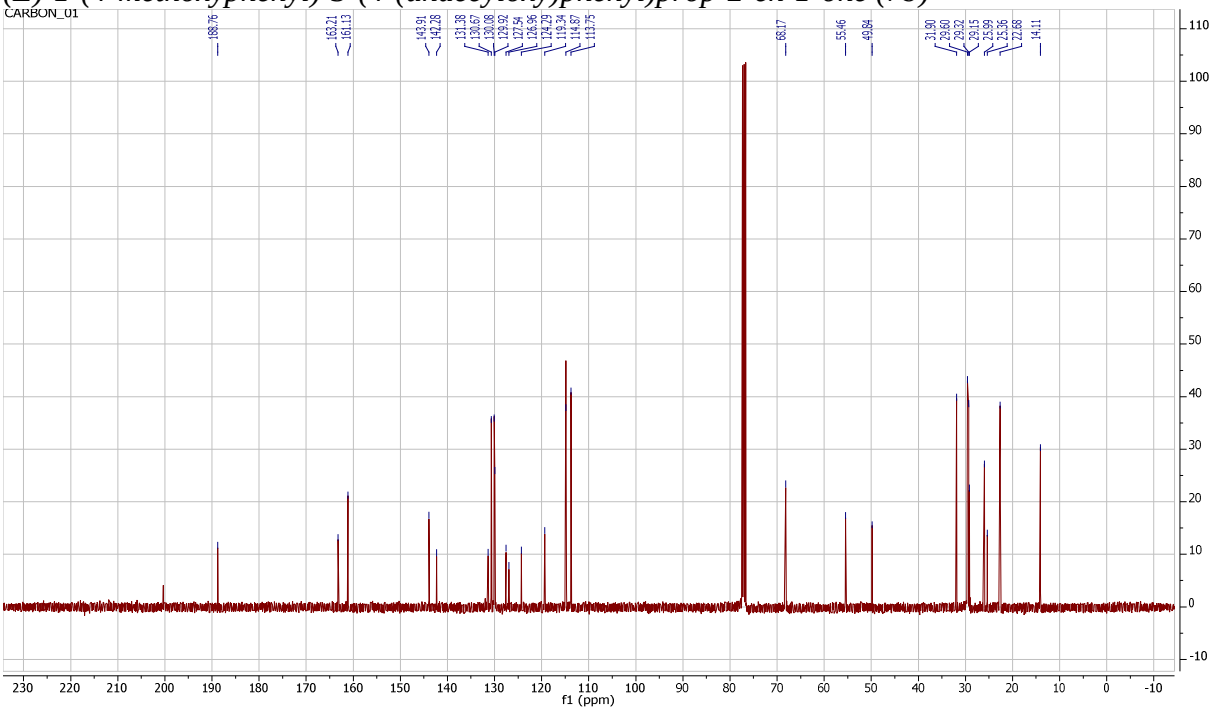
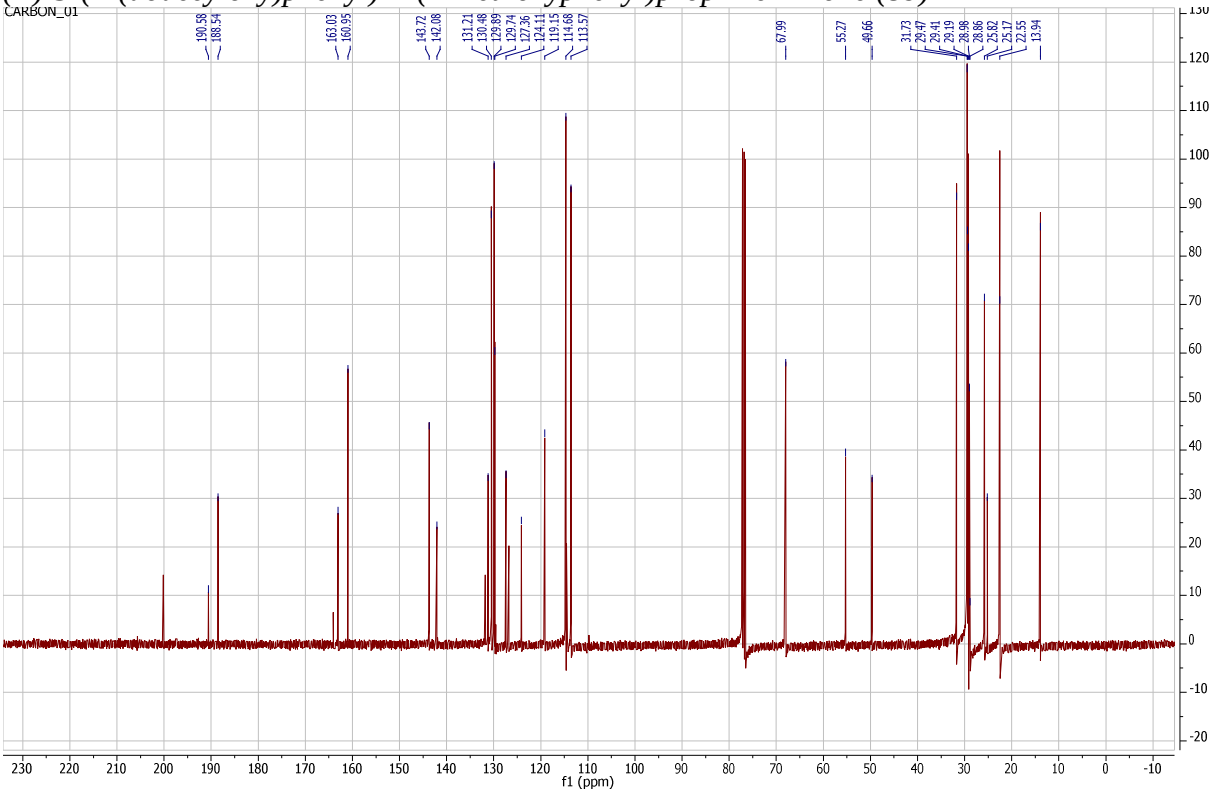
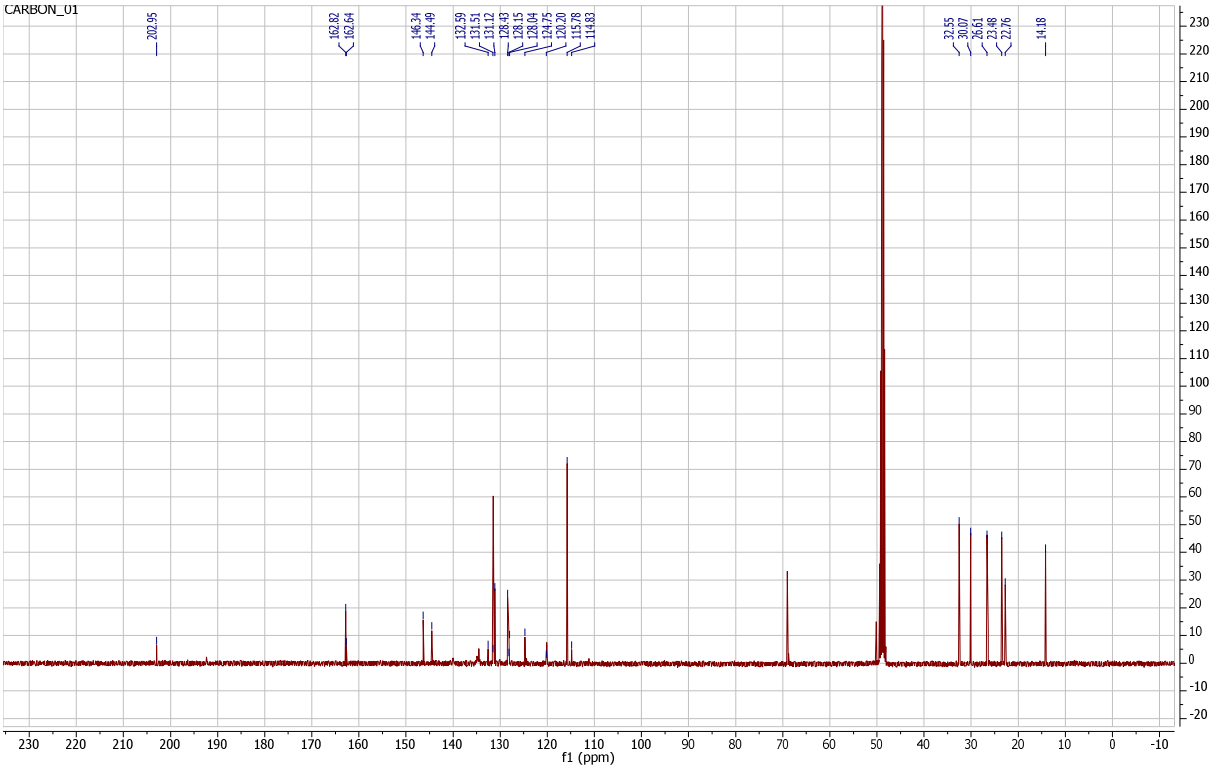


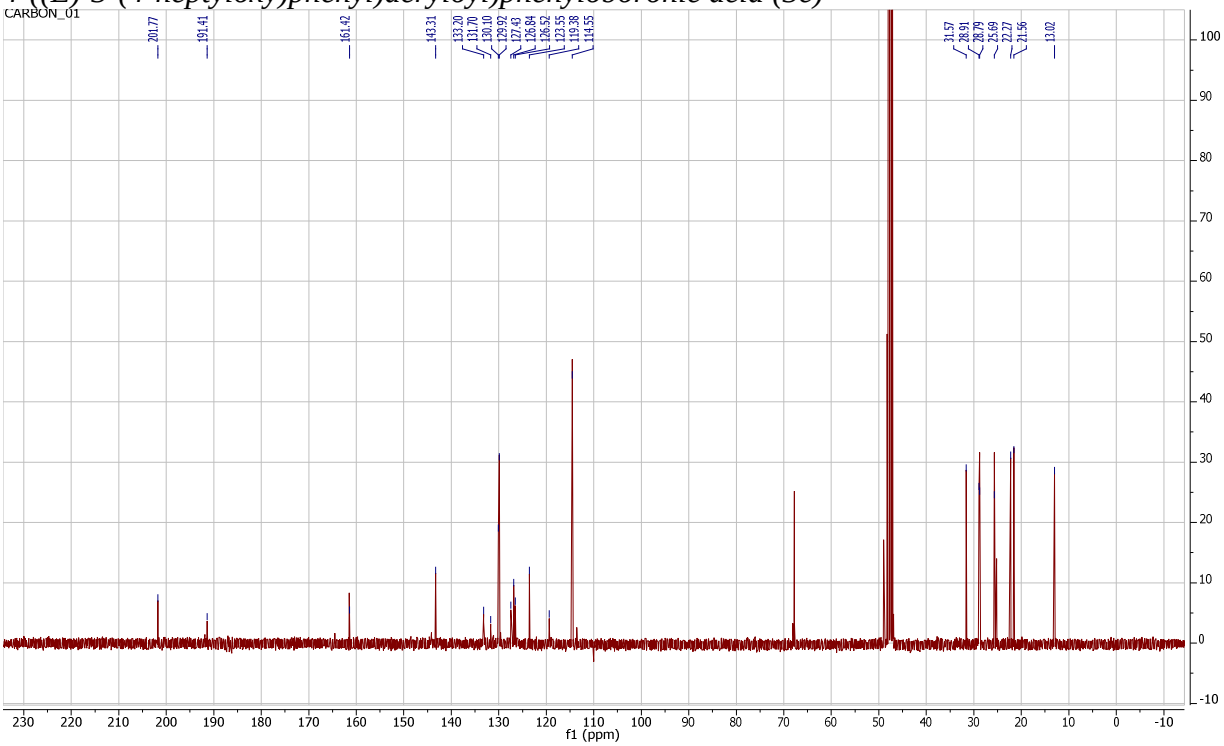
(E)-3-(4-(dodecyloxy)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (8b)



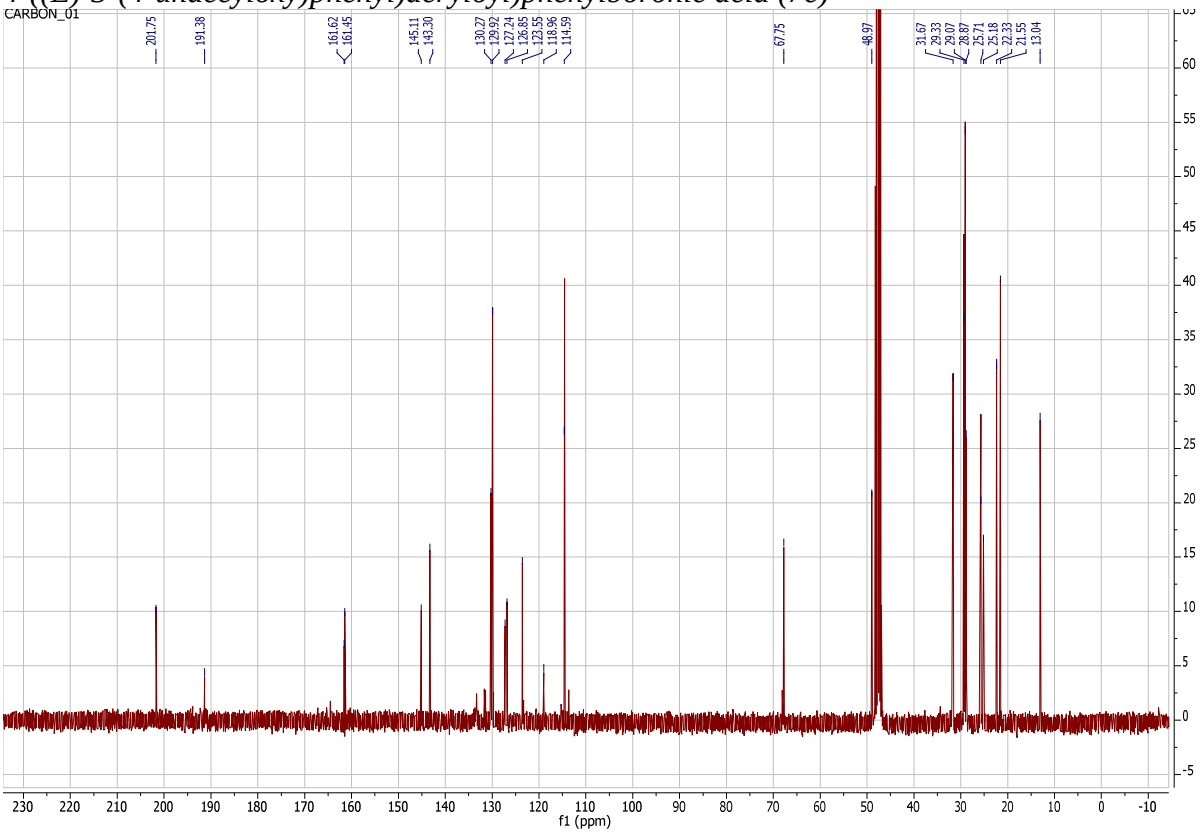
4-((E)-3-(4-(hexyloxy)phenyl)acryloyl)phenylboronic acid (2c)



4-((E)-3-(4-heptyloxy)phenyl)acryloyl)phenyloboronic acid (3c)



4-((E)-3-(4-undecyloxy)phenyl)acryloyl)phenylboronic acid (7c)



Appendix C

Chalcone Crystal Tables

Table 1: Data collection details for Franks2.

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frame	Time/s	λ/Å	Voltage/kV	Current/mA	Tem/K
Omega	44.765	-20.00	340.00	0.00	35.02	0.50	360	10.00	0.70973	50	1.0	200.00
Omega	44.765	-20.00	340.00	120.00	35.02	0.50	360	10.00	0.70973	50	1.0	200.00
Omega	44.765	-20.00	340.00	240.00	35.02	0.50	360	10.00	0.70973	50	1.0	200.00

A total of 1080 frames were collected. The total exposure time was 3.00 hours. The integration of the data using a triclinic unit cell yielded a total of 8223 reflections to a maximum θ angle of 25.05° (0.84 Å resolution), of which 3228 were independent (average redundancy 2.547, completeness = 98.0%, R_{int} = 5.44%, R_{sig} = 8.92%) and 2386 (73.92%) were greater than $2\sigma(F^2)$.The final cell constants of a = 5.6069(9) Å, b = 7.7822(13) Å, c = 22.864(4) Å, α = 81.101(5)°, β = 85.571(5)°, γ = 69.879(4)°, volume = 925.2(3) $Å^3$, are based upon the refinement of the XYZ-centroids of 2559 reflections above 20 σ(I) with 5.404° < 2θ < 49.74°.Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.627. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9648 and 0.9885.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{22}H_{26}O_2$.The final anisotropic full-matrix least-squares refinement on F^2 with 228 variables converged at R1 = 6.51%, for the observed data and wR2 = 20.77% for all data. The goodness-of-fit was 1.190. The largest peak in the final difference electron density synthesis was 0.552 $e^-/Å^3$ and the largest hole was -0.276 $e^-/Å^3$ with an RMS deviation of 0.116 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.157 g/cm^3 and F(000), 348 e^-.

Table 2. Sample and crystal data for Franks2.

Identification code	Franks2
Chemical formula	$C_{22}H_{26}O_2$
Formula weight	322.43
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal size	0.16 x 0.26 x 0.50 mm
Crystal habit	colorless plate

Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.6069(9) Å	α = 81.101(5)°
	b = 7.7822(13) Å	β = 85.571(5)°
	c = 22.864(4) Å	γ = 69.879(4)°
Volume	925.2(3) $Å^3$	
Z	2	
Density (calculated)	1.157 Mg/cm^3	
Absorption coefficient	0.072 mm^{-1}	
F(000)	348	

Table 3. Data collection and structure refinement for Franks2.

Diffractometer	Bruker Smart X2S Diffractometer	
Radiation source	microfocus sealed tube, Mo K_α	
Theta range for data collection	0.90 to 25.05°	
Index ranges	-6<=h<=6, -9<=k<=9, -27<=l<=27	
Reflections collected	8223	
Independent reflections	3228 [R(int) = 0.0544]	
Coverage of independent reflections	98.0%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9885 and 0.9648	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3228 / 0 / 228	
Goodness-of-fit on F^2	1.190	
Final R indices	2386 data; I>2σ(I)	R1 = 0.0651, wR2 = 0.1697
	all data	R1 = 0.0854, wR2 = 0.2077
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0979P)^2+0.0000P]$ where $P=(F_o^2+2F_c^2)/3$	

Extinction coefficient	0.0570(120)
Largest diff. peak and hole	0.552 and -0.276 eÅ^{-3}
R.M.S. deviation from mean	0.116 eÅ^{-3}

Table 4. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for Franks2.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C11	0.6979(3)	0.2351(2)	0.61650(8)	0.0373(5)
C12	0.8440(4)	0.2089(2)	0.66932(9)	0.0401(5)
C10	0.8257(3)	0.1746(2)	0.56517(8)	0.0421(5)
O1	0.2981(2)	0.31056(16)	0.46311(5)	0.0443(4)
O2	0.1747(3)	0.1737(2)	0.75749(6)	0.0669(5)
C1	0.2058(5)	0.2485(3)	0.08678(10)	0.0809(11)
C2	0.0852(4)	0.2923(3)	0.14694(9)	0.0610(6)
C3	0.2731(4)	0.2277(2)	0.19622(8)	0.0480(5)
C4	0.1557(4)	0.2757(2)	0.25614(8)	0.0462(5)
C5	0.3482(3)	0.2293(2)	0.30457(8)	0.0437(5)
C6	0.2296(3)	0.2862(2)	0.36364(8)	0.0424(5)
C7	0.4238(4)	0.2392(2)	0.41054(8)	0.0412(5)
C8	0.4414(3)	0.2829(2)	0.51157(8)	0.0360(5)
C9	0.7019(4)	0.1964(2)	0.51296(8)	0.0425(5)
C13	0.7633(4)	0.2386(2)	0.72417(9)	0.0406(5)
C14	0.9482(4)	0.2096(2)	0.77038(9)	0.0440(5)
C15	0.8612(4)	0.2268(2)	0.83310(8)	0.0417(5)
C16	0.6110(4)	0.3095(3)	0.85062(9)	0.0494(6)
C17	0.5449(4)	0.3288(3)	0.90944(9)	0.0585(6)
C18	0.7295(5)	0.2628(3)	0.95184(10)	0.0613(6)
C19	0.3094(3)	0.3496(2)	0.56215(8)	0.0401(5)
C20	0.4342(3)	0.3248(2)	0.61376(8)	0.0390(5)
C21	0.9803(4)	0.1774(3)	0.93508(9)	0.0593(6)
C22	0.0452(4)	0.1600(3)	0.87671(9)	0.0502(6)

Table 5. Bond lengths (Å) for Franks2.

C11-C10	1.386(3)	C11-C20	1.403(3)
C11-C12	1.460(2)	C12-C13	1.327(3)
C12-H13	0.934(19)	C10-C9	1.386(2)
C10-H10	0.949	O1-C8	1.365(2)
O1-C7	1.434(2)	O2-C14	1.226(2)
C1-C2	1.519(3)	C1-H1A	0.98
C1-H1B	0.98	C1-H1C	0.98
C2-C3	1.508(2)	C2-H2A	0.99
C2-H2B	0.99	C3-C4	1.516(3)
C3-H3A	0.99	C3-H3B	0.99
C4-C5	1.521(2)	C4-H4A	0.99
C4-H4B	0.99	C5-C6	1.518(2)
C5-H5A	0.99	C5-H5B	0.99
C6-C7	1.502(2)	C6-H6A	0.99
C6-H6B	0.99	C7-H7A	0.99
C7-H7B	0.99	C8-C9	1.383(3)
C8-C19	1.394(2)	C9-H9	0.95
C13-C14	1.475(2)	C13-H12	0.95(2)
C14-C15	1.490(3)	C15-C16	1.384(3)
C15-C22	1.399(2)	C16-C17	1.384(3)
C16-H16	0.95	C17-C18	1.382(3)
C17-H17	0.95	C18-C21	1.385(3)
C18-H18	0.95	C19-C20	1.372(2)
C19-H19	0.95	C20-H20	0.95
C21-C22	1.371(3)	C21-H21	0.95
C22-H22	0.95		

Table 6. Bond angles (°) for Franks2.

C10-C11-C20	117.38(16)	C10-C11-C12	118.82(17)
C20-C11-C12	123.75(17)	C13-C12-C11	129.55(19)
C13-C12-H13	117.3(11)	C11-C12-H13	113.1(11)
C9-C10-C11	122.48(17)	C9-C10-H10	118.8
C11-C10-H10	118.7	C8-O1-C7	118.07(14)
C2-C1-H1A	109.5	C2-C1-H1B	109.5
H1A-C1-H1B	109.5	C2-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
C3-C2-C1	113.5(2)	C3-C2-H2A	108.9

C1-C2-H2A	108.9	C3-C2-H2B	108.9
C1-C2-H2B	108.9	H2A-C2-H2B	107.7
C2-C3-C4	113.85(18)	C2-C3-H3A	108.8
C4-C3-H3A	108.8	C2-C3-H3B	108.8
C4-C3-H3B	108.8	H3A-C3-H3B	107.7
C3-C4-C5	114.00(17)	C3-C4-H4A	108.8
C5-C4-H4A	108.8	C3-C4-H4B	108.8
C5-C4-H4B	108.8	H4A-C4-H4B	107.6
C6-C5-C4	113.52(16)	C6-C5-H5A	108.9
C4-C5-H5A	108.9	C6-C5-H5B	108.9
C4-C5-H5B	108.9	H5A-C5-H5B	107.7
C7-C6-C5	112.37(15)	C7-C6-H6A	109.1
C5-C6-H6A	109.1	C7-C6-H6B	109.1
C5-C6-H6B	109.1	H6A-C6-H6B	107.9
O1-C7-C6	108.46(14)	O1-C7-H7A	110.0
C6-C7-H7A	110.0	O1-C7-H7B	110.0
C6-C7-H7B	110.0	H7A-C7-H7B	108.4
O1-C8-C9	124.51(17)	O1-C8-C19	115.95(15)
C9-C8-C19	119.54(16)	C8-C9-C10	119.06(18)
C8-C9-H9	120.5	C10-C9-H9	120.5
C12-C13-C14	119.98(18)	C12-C13-H12	121.8(11)
C14-C13-H12	118.2(11)	O2-C14-C13	120.41(18)
O2-C14-C15	119.19(16)	C13-C14-C15	120.39(17)
C16-C15-C22	118.12(18)	C16-C15-C14	124.01(17)
C22-C15-C14	117.85(18)	C15-C16-C17	120.99(18)
C15-C16-H16	119.5	C17-C16-H16	119.5
C18-C17-C16	120.0(2)	C18-C17-H17	120.0
C16-C17-H17	120.0	C17-C18-C21	119.6(2)
C17-C18-H18	120.2	C21-C18-H18	120.2
C20-C19-C8	120.69(17)	C20-C19-H19	119.7
C8-C19-H19	119.7	C19-C20-C11	120.81(17)
C19-C20-H20	119.6	C11-C20-H20	119.6
C22-C21-C18	120.18(19)	C22-C21-H21	119.9
C18-C21-H21	119.9	C21-C22-C15	121.1(2)
C21-C22-H22	119.5	C15-C22-H22	119.5

Table 7. Anisotropic atomic displacement parameters ($Å^2$) for Franks2.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C11	0.0381(11)	0.0313(8)	0.0435(11)	-0.0044(7)	-0.0017(9)	-0.0132(8)
C12	0.0350(12)	0.0382(9)	0.0466(12)	-0.0038(8)	-0.0019(9)	-0.0124(8)
C10	0.0333(11)	0.0415(9)	0.0507(12)	-0.0119(8)	-0.0004(9)	-0.0094(8)
O1	0.0407(8)	0.0490(7)	0.0374(8)	-0.0082(6)	-0.0044(6)	-0.0059(6)
O2	0.0403(10)	0.1027(12)	0.0556(10)	-0.0106(8)	-0.0044(7)	-0.0207(8)
C1	0.120(3)	0.0757(16)	0.0502(15)	-0.0115(11)	-0.0160(14)	-0.0329(16)
C2	0.0783(17)	0.0532(11)	0.0493(13)	-0.0081(10)	-0.0188(12)	-0.0151(11)
C3	0.0554(13)	0.0416(10)	0.0454(12)	-0.0049(8)	-0.0060(10)	-0.0138(9)
C4	0.0508(13)	0.0389(9)	0.0455(12)	-0.0044(8)	-0.0085(10)	-0.0098(9)
C5	0.0453(12)	0.0409(9)	0.0430(12)	-0.0065(8)	-0.0041(9)	-0.0113(9)
C6	0.0471(13)	0.0382(9)	0.0398(11)	-0.0050(8)	-0.0019(9)	-0.0115(9)
C7	0.0439(12)	0.0382(9)	0.0398(11)	-0.0096(8)	0.0034(9)	-0.0107(8)
C8	0.0401(11)	0.0301(8)	0.0372(10)	-0.0039(7)	-0.0022(8)	-0.0111(8)
C9	0.0402(12)	0.0430(9)	0.0439(11)	-0.0131(8)	0.0021(9)	-0.0113(8)
C13	0.0365(13)	0.0422(10)	0.0437(12)	-0.0013(8)	-0.0057(9)	-0.0149(9)
C14	0.0384(12)	0.0448(10)	0.0488(12)	-0.0009(8)	-0.0066(9)	-0.0151(9)
C15	0.0467(13)	0.0402(9)	0.0432(11)	-0.0018(8)	-0.0080(9)	-0.0212(9)
C16	0.0419(13)	0.0563(11)	0.0505(13)	-0.0072(9)	-0.0068(10)	-0.0160(9)
C17	0.0539(14)	0.0694(13)	0.0537(13)	-0.0145(10)	0.0014(10)	-0.0207(11)
C18	0.0736(17)	0.0729(14)	0.0446(12)	-0.0104(10)	-0.0018(11)	-0.0328(13)
C19	0.0346(11)	0.0402(9)	0.0420(11)	-0.0050(8)	-0.0004(8)	-0.0085(8)
C20	0.0378(11)	0.0401(9)	0.0369(10)	-0.0046(7)	0.0025(8)	-0.0115(8)
C21	0.0655(16)	0.0686(13)	0.0475(13)	0.0002(10)	-0.0155(11)	-0.0279(12)
C22	0.0470(13)	0.0539(11)	0.0502(13)	-0.0005(9)	-0.0103(10)	-0.0185(10)