

**SYNTHESIS AND CHARACTERIZATION OF NOVEL BIOLOGICALLY
ACTIVE BORON-CONTAINING ANALOGUES OF CAPSAICIN**

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A thesis submitted to the Department of Chemistry & Biochemistry Mount Allison
University in partial fulfillment of the requirements for the Bachelor of Science
degree with Honours in Chemistry



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Abstract

The anti-microbial and anti-cancer activities of the natural product capsaicin and related amides are of growing interest to medicinal chemists. Similarly, boron-containing compounds have been shown to have potent biological properties, with four boron-containing pharmaceuticals currently available on the market. As such, a number of boron-containing capsaicin analogues were generated for future biological testing and are discussed herein. Imines were generated from the facile reactions of 3,4-dimethoxybenzaldehyde with Bpin-functionalized aniline derivatives. These imines were subsequently reduced to the corresponding amines using HBcat as a reducing agent. Finally, the amines were reacted with aliphatic acyl chlorides, readily affording the desired amides in moderate yields. All amides were characterized using ^1H NMR, $^{13}\text{C}\{^1\text{H}\}$ NMR, and FT-IR spectroscopy, as well as ^{11}B NMR spectroscopy where applicable.

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List of Abbreviations

δ	chemical shift
$^{\circ}\text{C}$	degrees Celsius
$^{13}\text{C}\{\text{H}\}$	proton-decoupled ^{13}C
ACS	American Chemical Society
Ar	aryl
br	broad (spectral)
CDCl_3	deuterated chloroform
CH_2Cl_2	dichloromethane
d	doublet (spectral)
eq	equivalents
FDA	US Food and Drug Administration
g	grams
h	hour(s)
HBpin	pinacolborane
HBcat	catecholborane
HCOOH	formic acid
Hz	Hertz
IR	infrared
J	coupling constant
m	multiplet (spectral)
m	moderate (spectral)

MeOH	methanol
min	minutes
mL	milliliters
mmol	millimoles
NaBH ₄	sodium borohydride
NMR	nuclear magnetic resonance
ov	overlapping (spectral)
PBA	phenylboronic acid
q	quartet (spectral)
quint	quintet (spectral)
ROS	reactive oxygen species
rt	room temperature
s	singlet (spectral)
s	strong (spectral)
t	triplet (spectral)
TRPV1	transient receptor potential cation channel subfamily V member 1
w	weak (spectral)

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Table 1.1: Anti-microbial activity of select compounds reported by Ramsaywack *et al.* 13

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Chapter 1

Introduction

1.1 Chemotherapy

Nearly half of all Canadians are expected to be diagnosed with cancer during their lifetime. A quarter will die from the devastating disease.¹ Chemotherapy, the use of drugs in the treatment of disease, has long been an extremely popular form of cancer treatment. There are hundreds of chemotherapeutic agents used in the treatment of almost all types of cancer. Further, these compounds encompass several different classes of molecules, from the coordination complex cisplatin to the steroid prednisolone, along with a plethora of other organic and inorganic compounds (Figure 1.1). The biochemical scope of chemotherapy is also extremely broad, with drugs exhibiting several different mechanisms of action. Chemotherapeutic agents include DNA alkylating agents such as cyclophosphamide and melphalan, antimetabolites such as 5-fluorouracil and methotrexate, intercalating agents such as cisplatin and actinomycin D, and mitotic inhibitors such as paclitaxel and vincristine (Figure 1.1).² These particular examples, although somewhat arbitrary, are chosen specifically to illustrate the diversity of chemotherapeutic agents both structurally and mechanistically.

Despite the expansive scope of chemotherapeutic agents, they are not without their drawbacks. Cancer remains the leading cause of death in Canada.¹ This alone illustrates the need for continuous development of more effective cancer treatments. Further, while the overactive growth-signaling in cancer cells offers a number of targets for chemotherapy drugs, these processes are not exclusive to cancer cells. Thus, chemotherapy is typically viewed as preferential for, but not exclusive to, cancer cells.² The resultant side effects can be debilitating. Pearce *et al.*

reported that 86% of chemotherapy recipients experienced at least one side effect in a study that examined 449 participants over 5.64 months.³ Fatigue, vomiting, diarrhea, and constipation are just a small selection of these side effects, which have been shown to be of significant detriment to quality of life. More serious side effects can be permanent, and include damage to the kidneys, heart, lungs, and reproductive system. Clearly, selectivity is paramount in designing novel small-molecule cancer therapies.

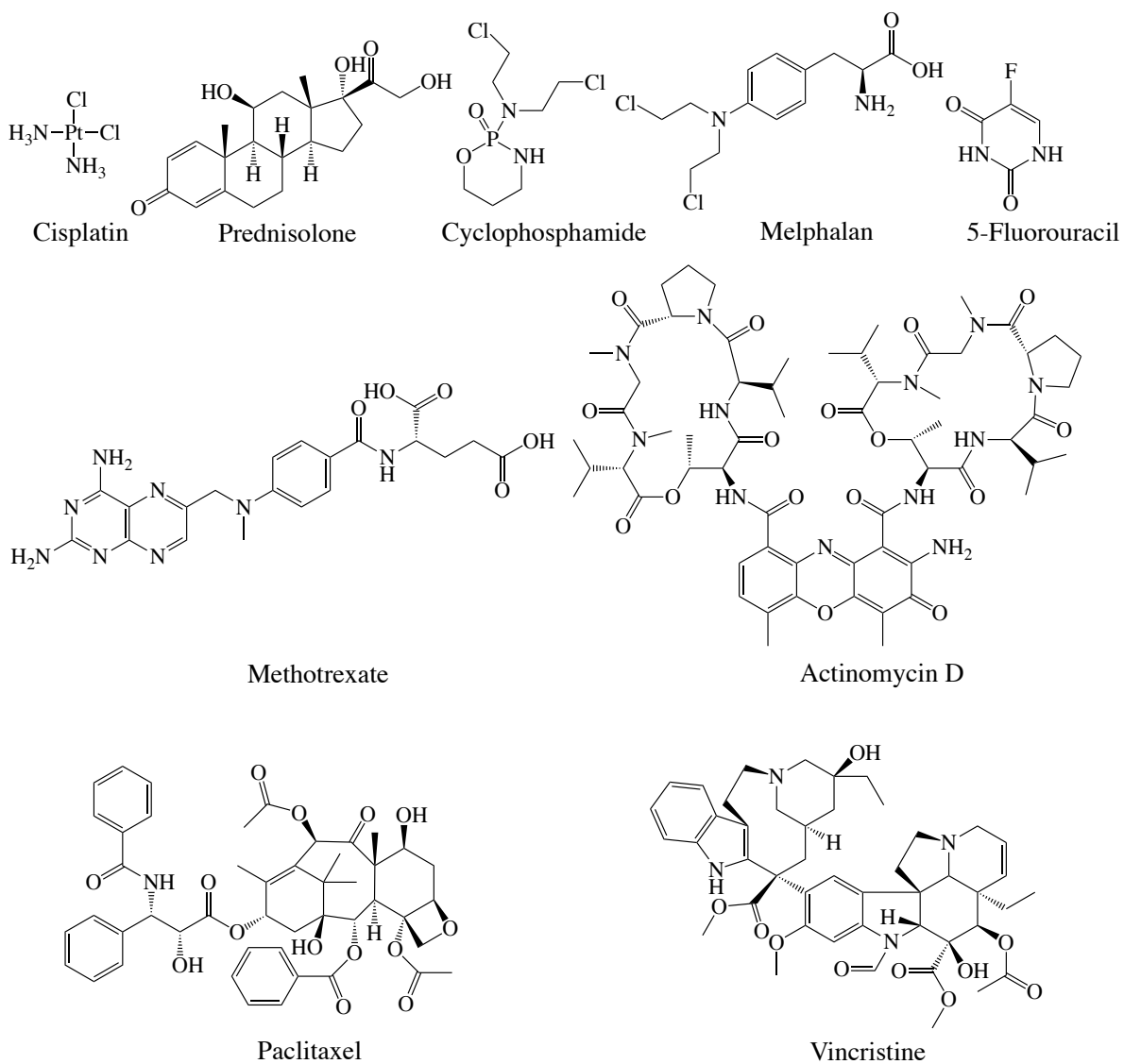


Figure 1.1: Chemical structures of select chemotherapeutic agents.

Further, some aggressive tumors can become resistant to chemotherapy. Resistance can be either inherent, due to some genetic characteristic, or acquired upon exposure to a drug, much like in the case of antibiotic resistance.⁴ Combination drug therapies are commonly employed to address this issue, but this can often lead to multi-drug resistance, with devastating consequences. Thus, the exploration of new classes of compounds as potential chemotherapy agents, paralleling the continuous development of antibiotics, is a particularly significant area of research in medicinal chemistry. This concept is aptly illustrated by exploring the increasing interest in phytochemicals such as capsaicin, and recent success of organoboron compounds for cancer treatment.

1.2 Capsaicinoids as Anti-Cancer Agents

Capsaicinoids, such as capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin, are natural products found in hot chili peppers.^{5,6} They consist of a vanillyl moiety attached to an aliphatic chain by an amide linkage and are stable in both polar and nonpolar environments.⁷ Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), seen in Figure 1.2, is the primary active spicy ingredient in chili peppers. The compound has several attributes that are promising for the pharmaceutical industry, such as anti-microbial and anti-inflammatory properties. Additionally, capsaicin is a known analgesic, exhibiting its effects by acting as an agonist of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor.⁸ The irritating nature of capsaicin causes excitement of sensory neurons, followed by a prolonged refractory period, resulting in pain reduction.⁹ These properties have been known for centuries, though more recently, capsaicin has been shown to exhibit anti-cancer properties, inhibiting cell proliferation in breast,¹⁰ liver,¹¹ and bone cancer,¹² as well as in melanoma.¹³ Capsaicin has also been shown to cause apoptosis in up to 80% of active prostate

cancer cells growing in mice, with tumors shrinking to one-fifth of their untreated size.^{8,14} Similarly, oral administration of capsaicin was shown to decrease the size of breast cancer tumors in mice, and to inhibit the development of pre-neoplastic breast lesions by up to 80%.¹⁵ More importantly, capsaicin selectively inhibits only malignant cell lines, but not normal cell lines, and thus bears low toxicity toward healthy cells.¹⁶ A number of studies have shown the anti-cancer properties of capsaicin to involve the generation of reactive oxygen species (ROS), increase in intracellular Ca^{2+} concentration, mitochondrial depolarization, and caspase 3 and 9 activation.^{17,18}

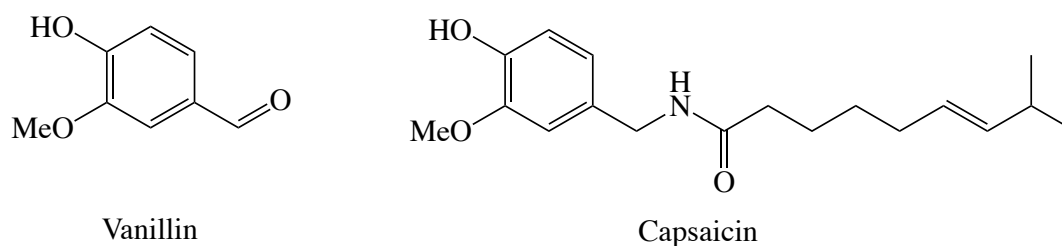
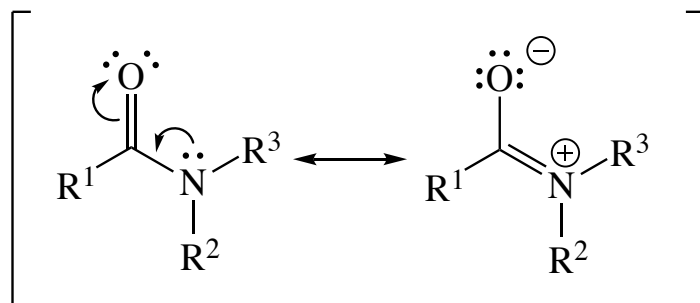


Figure 1.2: Chemical structures of vanillin and capsaicin.

Capsaicinoids contain amide functional groups, which have the general structure $\text{R}^1(\text{CO})\text{NR}^2\text{R}^3$, where R^1 , R^2 , and R^3 are organic substituents or hydrogen. In 2007, the ACS Green Chemistry Institute ranked amide formation avoiding poor atom economy reagents as the highest priority area of research.¹⁹ Amides can be found in countless synthetic organic molecules, and are easy to synthesize from several reported methodologies. One notable example is the Schotten-Baumann reaction, first reported by German chemists Carl Schotten and Eugen Baumann, which produces amides from the reaction of amines and acyl chlorides under basic conditions.^{20,21} Readers are encouraged to explore several excellent reviews for a more comprehensive investigation on amide synthesis.^{22,23} Amides are also desirable due to their high stability. Amide

nitrogen atoms are much less nucleophilic than those of amines as the lone pair electrons are delocalized through multiple resonance forms (Scheme 1.1). This also reduces the electrophilicity of the carbonyl carbon relative to aldehydes and ketones.



Scheme 1.1: Amide resonance forms.

Amides are highly pervasive in nature. Most notably from a biological standpoint, amide linkages (peptide bonds) between individual amino acids form the backbone of proteins in biological systems. As a result of their ease of synthesis, high stability, and biological relevance, amides have been of significant interest to the pharmaceutical industry for several decades. A 1999 analysis of the Comprehensive Medicinal Chemistry database revealed that more than 25% of known drugs contain amide groups, while amide bond formation was used in 66% of drug candidate syntheses according to a study of the prominent pharmaceutical companies GlaxoSmithKline, AstraZeneca and Pfizer.^{24,25} Amide groups are particularly prevalent in local anesthetic drugs, including lidocaine,²⁶ bupivacaine,²⁶ ropivacaine,²⁶ articaine,²⁷ etidocaine,²⁸ mepivacaine,²⁸ and prilocaine.²⁸ These amides are excellent alternatives to the ester category of local anesthetics which are more prone to causing allergic reactions.²⁹

1.3 Organoboron Chemistry

Organoboron compounds have been ubiquitous as industrial reagents and catalysts for decades. By definition these compounds contain a carbon-boron bond, which is of low polarity due to the similar electronegativities of the two elements.³⁰ Incorporation of a boron atom in an organic molecule also presents a unique characterization opportunity as ¹¹B is NMR active, having a natural abundance of 80.4% and a nuclear spin of 3/2.³⁰

1.3.1 Boronic Acids and Boronate Esters

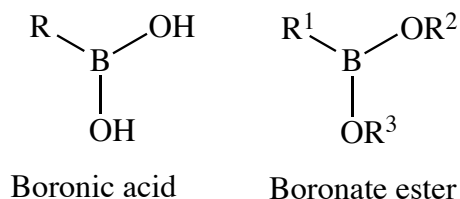
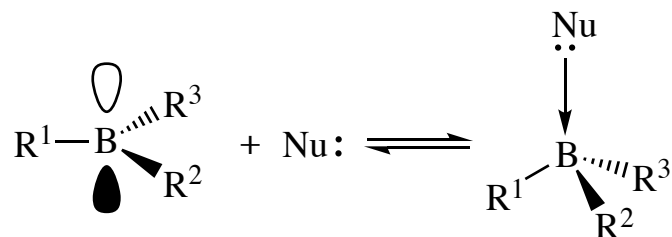


Figure 1.3: Chemical structures of boronic acids and boronate esters.

Boronic acids and boronate esters are common forms of organoboron molecules. These compounds contain a trisubstituted boron atom with two hydroxyl (boronic acid) or alkoxy (boronate ester) groups, and an alkyl or aryl group (Figure 1.3).³⁰ They contain an sp² hybridized trigonal planar boron(III) atom with an empty p-orbital. Thus, they are electrophiles, and behave as Lewis acids (Scheme 1.2).³⁰ The oxygen atoms of these molecules can donate electrons to boron's empty p-orbital, giving the B-O bond π-character, and weakening Lewis acidity.³⁰ This offers an excellent opportunity to tune the affinity of these molecules for particular biological targets. Boronic acids and boronate esters are relatively air and water stable. However, boronic acids can readily convert to boronic anhydrides upon drying.³⁰ While acyclic boronate esters can hydrolyze to boronic acids, some cyclic esters are resistant to hydrolysis. Two common variants

are pinacol ester (Bpin) and catechol ester (Bcat) from the class of boronate esters known as dioxaborolanes, in which the C-O-B-O-C linkage forms a five membered ring (Figure 1.4). The former is water stable, while the latter is susceptible to hydrolysis.



Scheme 1.2: sp^2 Hybridized boron atom acting as a Lewis acid.

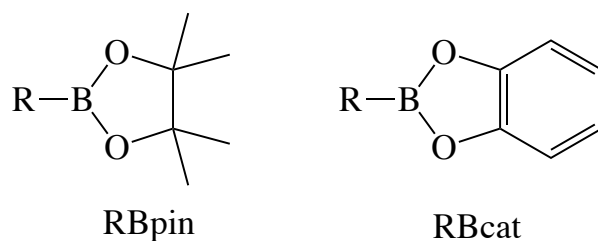


Figure 1.4: Chemical structures of RBpin and RBcat.

1.3.2 Organoboron Compounds as Therapeutics

Small boron-containing compounds are of interest to researchers for their medicinal properties.^{31,32} Anti-microbial activities for boron-containing compounds were first demonstrated in a study of 80 different diazaborines by Gronowitz and coworkers.^{33,34} Since then, boronic acids and boronate esters have displayed particularly promising biological activities. Imines containing boronate esters have been used to prepare various pharmacologically relevant compounds, and the boron groups have been shown to be responsible for the biological activities of these compounds on several occasions.³⁵⁻³⁷ A relevant example of this phenomenon has been noted for boron-containing benzylamine derivatives reported by Vogels *et al.* (Figure 1.5).³⁸ The biological activity of boron containing compounds has been suggested to result from the Lewis acidity of the boron

atom, which can reversibly form dative bonds with nucleophiles, such as hydroxyl groups in serine and bases in DNA.³⁹

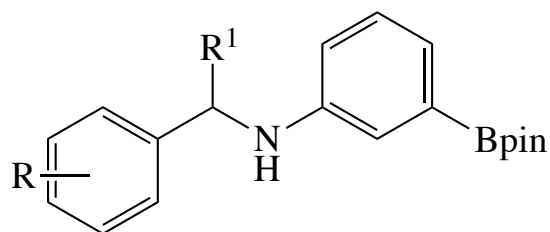


Figure 1.5: Benzylamine derivatives reported by Vogels *et al.*

Organoboron compounds have recently gained traction in the pharmaceutical industry, with four major therapeutic agents being approved by the FDA since the turn of the century. Bortezomib (Velcade), shown in Figure 1.6, was the first proteasome inhibitor approved as an anti-cancer agent, and one of three currently on the market. It was first approved in 2003 for the treatment of relapsed or refractory multiple myeloma, and as a first-line medication shortly thereafter.^{40,41} Bortezomib is a competitive inhibitor of the 26S proteasome. This proteasome is an enzyme complex that regulates protein degradation.⁴² Ubiquitinated proteins involved in cell cycle control, cell signaling, and apoptosis are degraded by this proteasome.⁴³ It contains a 20S core particle, which includes the active sites which hydrolyze substrate peptide bonds.^{44,45} The mechanism of action of bortezomib involves the binding of the boron atom to the catalytic site of this proteasome via a threonine residue. The crystal structure of bortezomib in complex with a yeast 20S proteasome has been elucidated.⁴⁶ It shows a terminal threonine residue bound to the boron atom via its hydroxylate oxygen, and hydrogen bonding between the terminal amino group and the boronic acid hydroxyl group (Figure 1.7). As a result of its novel mechanism of action, bortezomib has shown great clinical significance in treating otherwise refractory multiple

myelomas.⁴² Encouragingly, cancerous cells are more sensitive to bortezomib and other reversible proteasome inhibitors than are other cells. While normal cells can typically recover from the reversible effects of proteasome inhibition, cancerous cells lose checkpoint mechanisms during tumorigenesis, making them more susceptible to more long lasting effects of proteasome inhibition.⁴² Bortezomib is typically administered intravenously on an outpatient basis on days 1, 4, 8 and 11 of a 21 day cycle, with gaps in treatment strategically placed, allowing for the recovery of normal cells and minimization of side effects, without compromising the anti-cancer effects.⁴²

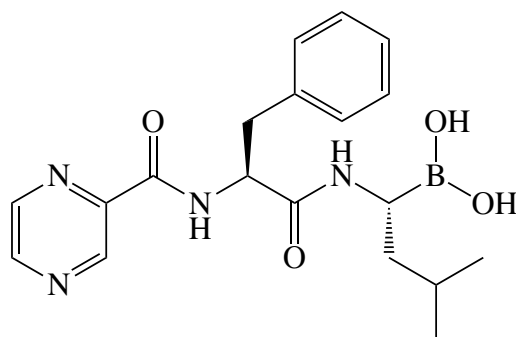


Figure 1.6: Chemical structure of bortezomib.

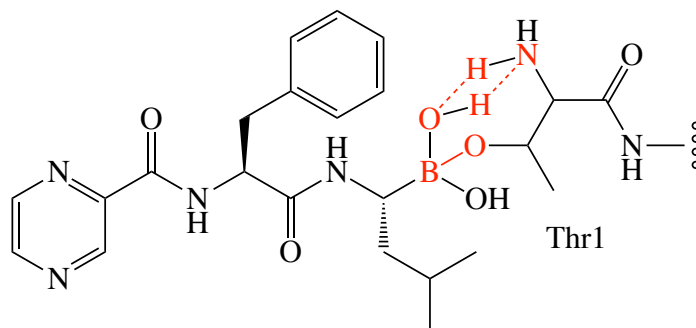


Figure 1.7: Interaction of bortezomib with Thr1 of a yeast 20S proteasome via its boronic acid moiety.

Despite the positive attributes and widespread success of bortezomib, it is not without its limitations. First and foremost, not all patients respond to it as a first-line therapy.⁴⁷ Furthermore, most patients who initially respond positively eventually develop drug resistance.⁴⁵ Finally, bortezomib causes peripheral neuropathy in 30-40% of patients, and thrombocytopenia in approximately 30% of patients, both of which are dose-limiting side effects.⁴⁸⁻⁵⁰ It is also associated with other unwanted symptoms, such as fatigue and gastrointestinal distress. As such, the search for effective proteasome inhibitors is ongoing, with boron remaining a central focus. In fact, in 2015, a second organoboron proteasome inhibitor was approved by the FDA.⁵¹ Ixazomib (Ninlaro), shown in Figure 1.8, shares a mechanism of action with bortezomib, though at high doses, it has also been shown to inhibit other proteolytic sites of the 26S proteasome.⁵² Ixazomib is the first available orally administered protease inhibitor, and is taken as a prodrug, ixazomib citrate (Figure 1.8). This boronate ester is hydrolyzed to the biologically active boronic acid under biological conditions.⁵³ Interestingly, it dissociates from the Thr1 residue of the 26S proteasome with a half-life of 18 minutes, compared to 110 minutes for bortezomib.⁵² It is easy to construct an argument for the superiority of ixazomib over bortezomib, given that it possesses greater anti-tumor activity and is associated with a lower incidence of peripheral neuropathy.^{52,53} Most significantly, ixazomib has been shown to elicit a positive response from patients resistant to bortezomib.⁵⁴

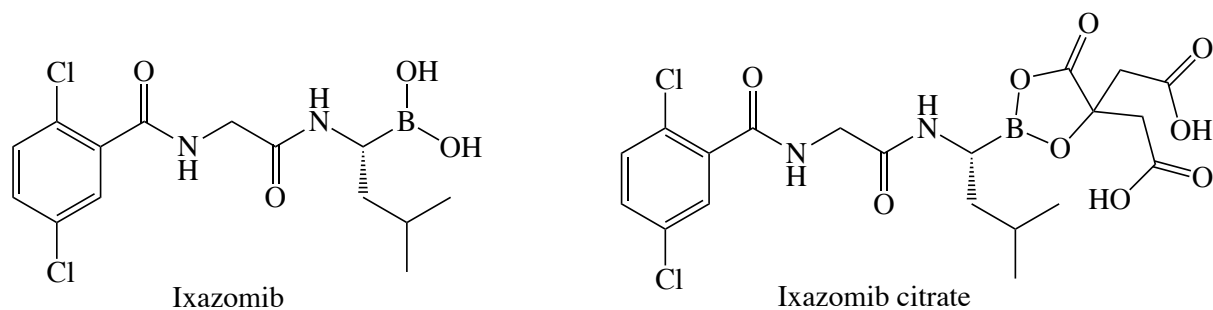


Figure 1.8: Chemical structures of ixazomib and ixazomib citrate.

Along with the success story of boron as an anti-cancer agent, the anti-microbial properties of boron containing compounds have also been exploited in another pair of FDA approved molecules. Tavaborole (Kerydin) was approved by the FDA as an anti-fungal agent for the treatment of onychomycosis in 2014,^{55,56} and two years later, crisaborole (Eucrisa) was approved by the FDA as a topical medication for the treatment of atopic dermatitis (Figure 1.9).⁵⁷

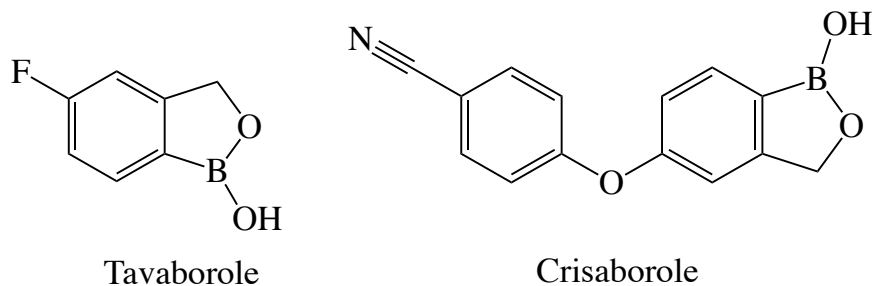


Figure 1.9: Chemical structures of tavaborole and crisaborole.

With the recent successes of boron-containing therapeutics, organoboron compounds have become increasingly attractive to medicinal chemists. α -Aminoboronic acids (Figure 1.10), the class of molecules to which bortezomib and ixazomib belong, are of particular interest for the pharmaceutical industry for their proteasome-inhibiting properties.^{58,59} Further, heterocyclic boronic acid derivatives, the class of molecules to which tavaborole and crisaborole belong, have been shown to display biological activity against *S. aureus* (Figure 1.10).⁶⁰ Yet another promising perspective on the potential of boronic acid-containing therapeutics has arisen from a study by Kumar *et al.*⁶¹ Chalcones (Figure 1.11) have been shown to be active against human breast cancer, though they are also highly toxic to normal breast tissues. However, the functionalization of these chalcones with boronic acids (Figure 1.12), induced selectivity towards cancerous cells,

significantly decreasing the toxicity of the compounds towards normal cells. An excellent review on the medicinal properties of boron-containing compounds can be found in reference 58.

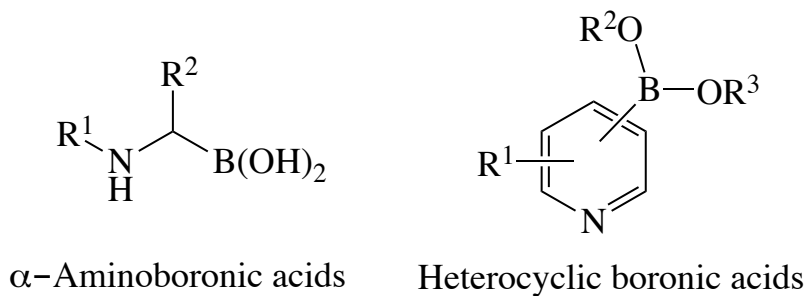


Figure 1.10: Structures of biologically active classes of boronic acids.

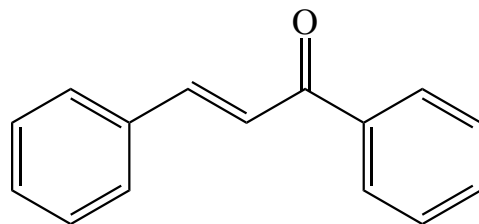


Figure 1.11: Chemical structure of chalcone.

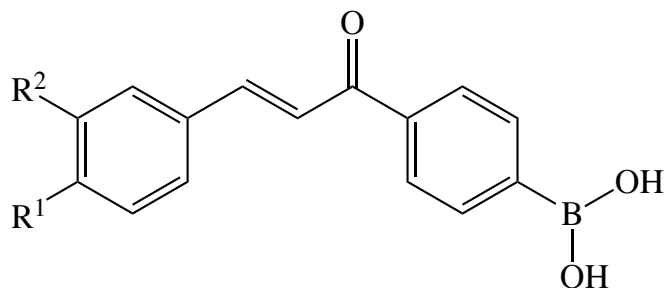


Figure 1.12: Chalcones bearing boronic acid moieties reported by Kumar *et al.*

1.3.3 Boron-Containing Capsaicin Derivatives

Compounds derived from the structures of both small-molecule boron species and capsaicin derivatives have been reported by Westcott and coworkers. This is extremely significant

as chemotherapeutic agents with multiple biological targets and mechanisms of action are tremendously desirable given the propensity for certain cancers to become resistant. One such study by Ramsaywack *et al.* generated compounds containing Bpin in the terminal position of a variable length saturated aliphatic substituent of a capsaicin-derived molecule (Figure 1.13).⁶² This particular study examined the anti-microbial activity of these compounds (Table 1.1). The study was promising, with a number of boron-containing compounds outperforming capsaicin itself.

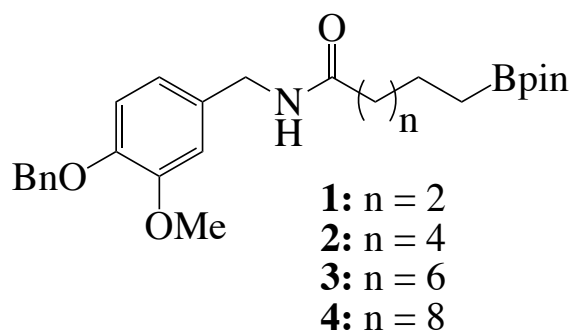


Figure 1.13: Select boron-containing analogues of capsaicin reported by Ramsaywack *et al.*

Table 1.1: Anti-microbial activity of select compounds reported by Ramsaywack *et al.*

	<i>E. faecium</i>	VRE	<i>S. aureus</i>	MRSA	<i>C. albicans</i>	<i>S. cerevisiae</i>
Compound	IC ₅₀ ($\mu\text{mol/mL}$)	IC ₅₀ ($\mu\text{mol/mL}$)	IC ₅₀ ($\mu\text{mol/mL}$)	IC ₅₀ ($\mu\text{mol/mL}$)	IC ₅₀ ($\mu\text{mol/mL}$)	IC ₅₀ ($\mu\text{mol/mL}$)
1	Inactive	Inactive	105.9	107.1	Inactive	Inactive
4	228.6	276.7	279.5	244.7	Inactive	150.6
Capsaicin	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

Note: Inhibition of less than 20% (*E. faecium*, VRE, *S. aureus*, MRSA) and 25% (*C. albicans*, *S. cerevisiae*) at 200 $\mu\text{mol/mL}$ considered inactive.

This project deals with the synthesis of novel compounds from the combination of these structural motifs in an effort to enhance their anti-cancer properties. Synthesized compounds contain Bpin on a phenyl group attached to the benzylic nitrogen of the vanillamine moiety, and a long chain aliphatic segment added via an acyl chloride, resulting in a tertiary amide (Figure 1.14).

These compounds have been designed to undergo biological testing. It is hypothesized that the addition of a Bpin group to the molecule will increase its biological activity, and that the location of this moiety will be significant, as will be the length of the aliphatic chain.

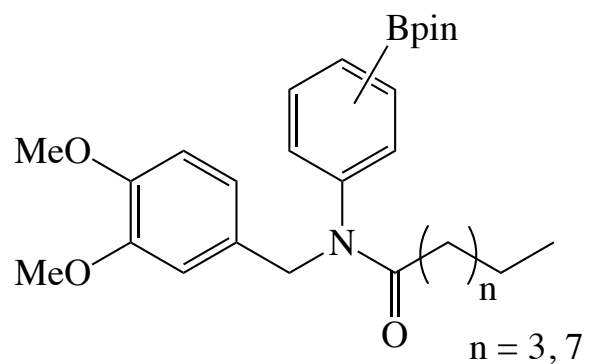
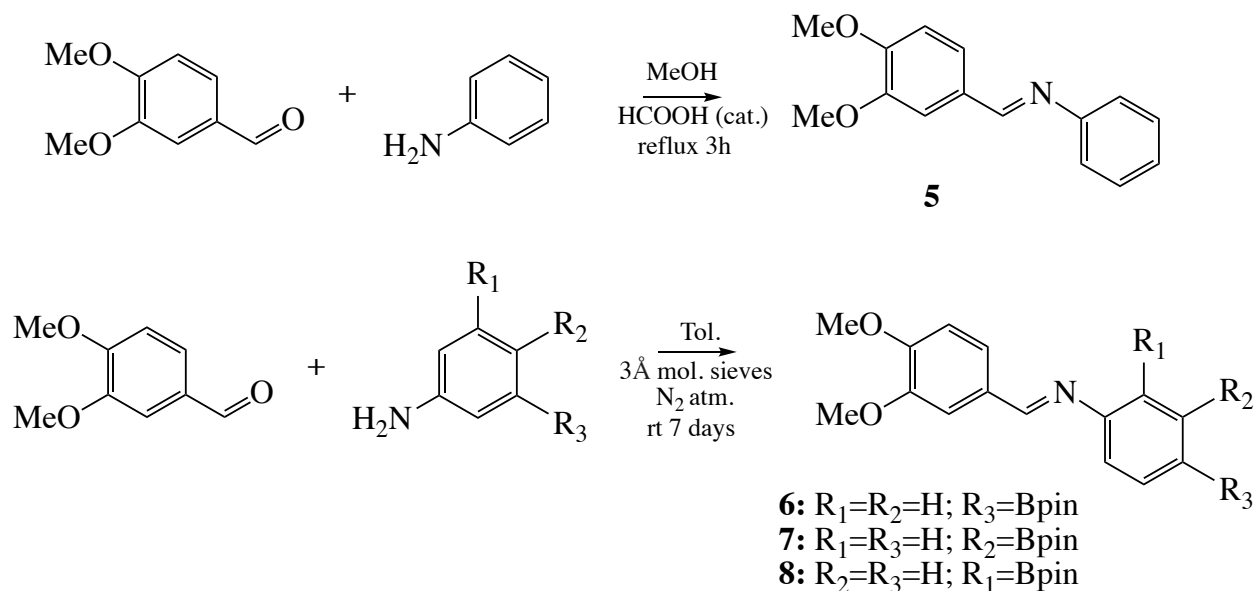


Figure 1.14: Target molecules in this study.

Chapter 2

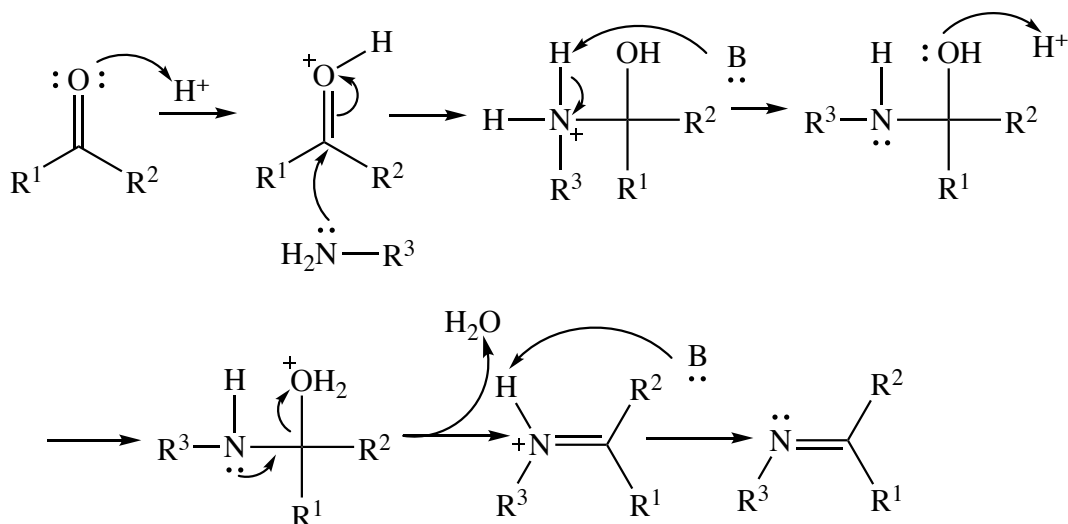
Results and Discussion

2.1 Imine Formation



Scheme 2.1: Generation of imines in this study.

Amides can be generated from a series of reactions in which the first step is imine formation. Indeed, a number of imines were generated in this study (Scheme 2.1). These molecules can be synthesized from the reaction of aldehydes and primary amines. The mechanism of this reaction involves the nucleophilic attack at the carbonyl carbon of the aldehyde by the amino nitrogen of the amine, followed by loss of water, as seen in Scheme 2.2.⁶³

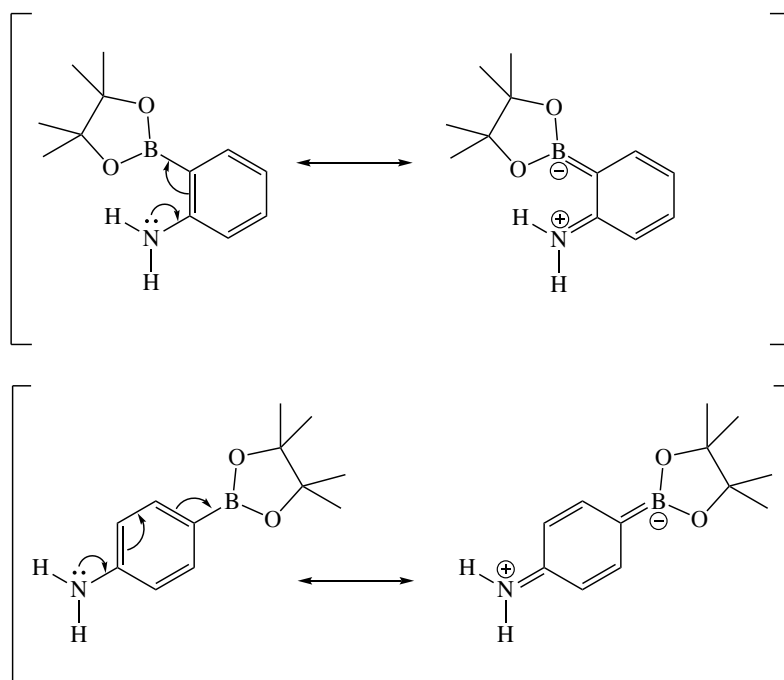


Scheme 2.2: Imine formation reaction mechanism.

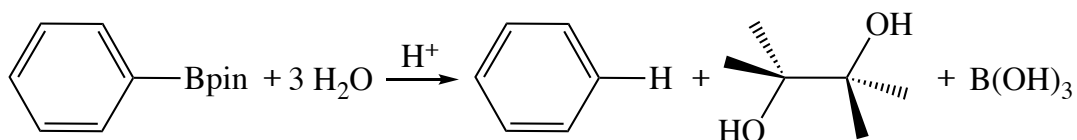
The synthesis of **5** was accomplished by heating the appropriate reagents at reflux in methanol for 3 hours. This particular reaction was readily reproducible with 100% conversion, and isolation was straightforward, requiring only the removal of solvent under vacuum, and resulting in consistently high yields. In contrast, the synthesis of Bpin-containing imines **6**, **7**, and **8** proved much more challenging. Initial attempts to synthesize **6** from the same conditions as **5** yielded the desired product with approximately 40% conversion, as estimated from the ^1H NMR spectrum. This is attributed to the electron withdrawing nature of the Bpin group, which has a deactivating effect on the amine through resonance when in the ortho and para positions (Scheme 2.3). With the addition of a catalytic amount of formic acid and an increase in the reaction time, conversion approached 85%, though the purity suffered considerably. The primary degradation product is believed to be pinacol, as evidenced by the recurrence of a peak near 1.23 in the ^1H NMR spectrum. This suggests that the Bpin moiety is undergoing protodeboronation (Scheme 2.4). As protodeboronation can be acid catalyzed, the reactions were attempted in the absence of formic

acid, though conversion was hampered significantly as anticipated. The conversion was increased and the decomposition was eliminated by exchanging methanol for toluene. Conversions in excess of 90% could ultimately be attained reproducibly by allowing the reactions to proceed in toluene under inert atmosphere with molecular sieves for 5-7 days. Analogous to **5**, isolation of **6** simply involved the removal of solvent under vacuum, and high yields were readily attainable.

The series of conditions used to generate **7** largely mirrored those used to generate **6**. Correspondingly, a peak near 1.23 in the ^1H NMR spectra was obtained from initial reaction trials in methanol under ambient conditions, suggesting that the meta Bpin derivative is not immune to the protodeboronation reaction. Fortunately, **7** could be generated with high purity and high yields from the same conditions used to generate **6**. Curiously, the conversion of **7** only slightly outperformed that of **6** at any given point in the reaction. This is peculiar as the meta Bpin group does not withdraw electron density from the amine through resonance as does the para Bpin group. It is plausible that the steric implications of the meta Bpin are more significant than anticipated.



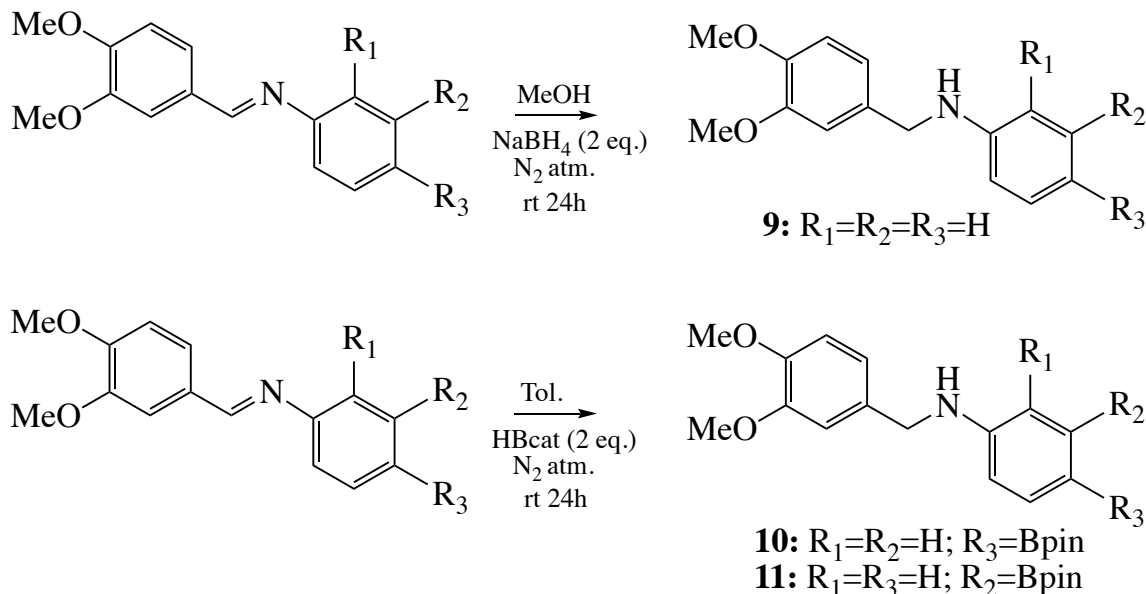
Scheme 2.3: Deactivation of amino group through resonance of 2- and 4-aminophenylboronic acid pinacol ester.



Scheme 2.4: Protodeboronation of phenylboronic acid pinacol ester.

Unsurprisingly, the imine derived from 3,4-dimethoxybenzaldehyde and 2-aminophenylboronic acid pinacol ester (**8**) was the most challenging to generate. The reaction conditions that successfully yielded the para- and meta-substituted imines (**7** and **8**) resulted in conversion of approximately 60% in this case. This is attributed to the electron withdrawing effect of Bpin as seen with 4-aminophenylboronic acid pinacol ester, as well as the increased steric hindrance imposed by the ortho Bpin group.

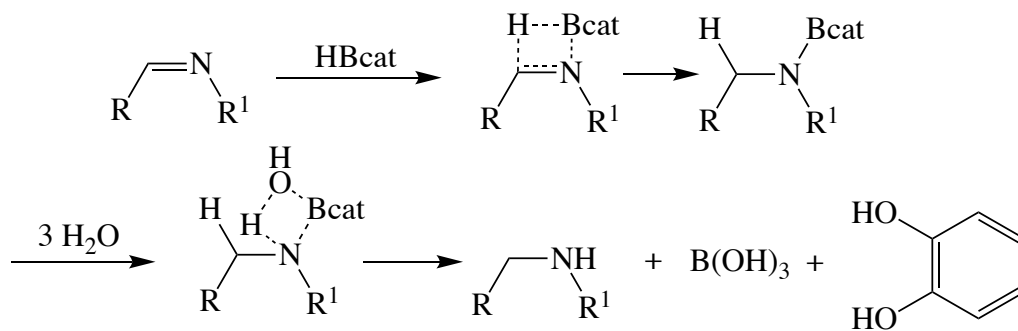
2.2 Reductive Amination



Scheme 2.5: Generation of amines in this study.

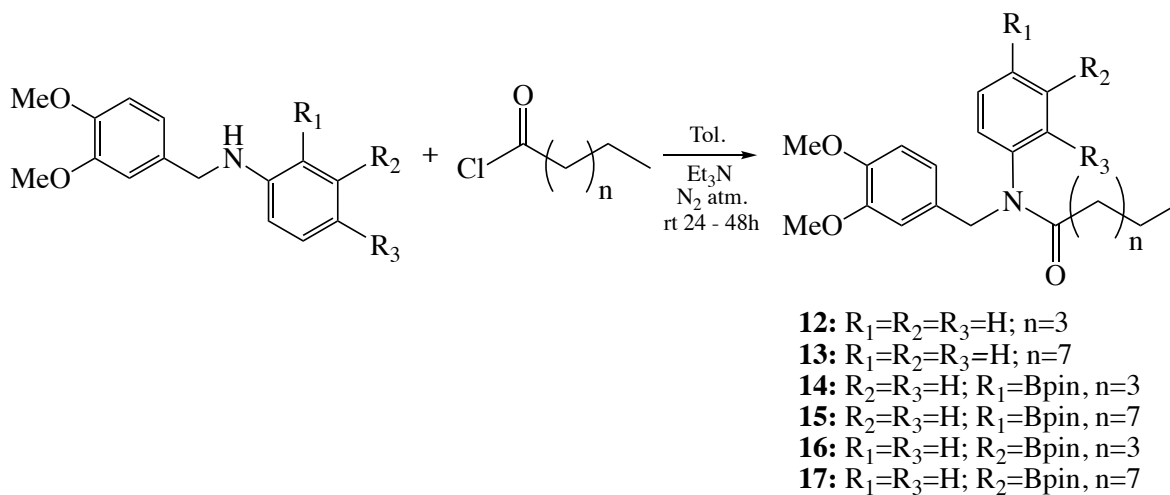
The reduction of the aforementioned imines leads to the corresponding amines, the immediate precursors to the desired amides. Most commonly, these reactions are carried out using sodium borohydride as a reducing agent. This reaction produces a secondary amine along with a series of water-soluble boric acid derivatives. The control amine (**9**) was readily produced from the corresponding imine (**5**) and sodium borohydride in methanol and successfully isolated from the organic layer of a dichloromethane and water extraction, while the syntheses of Bpin-functionalized amines (**10**, **11**) were more troublesome. Once again, cleavage of the Bpin group presumed to arise from the protodeboronation reaction made it difficult to isolate a pure product. Compound **10** was isolated when the reaction was carried out under inert atmosphere, while cleavage was still apparent from 1H and ^{11}B NMR spectroscopy in attempts to generate **11**. It is hypothesized that the resonance displayed in Scheme 2.3 has a stabilizing effect on the phenyl-Bpin interaction when the Bpin group is in the ortho or para position, while meta substituted Bpin

groups are more prone to undergoing cleavage. Given the apparent tendency of the Bpin group to cleave in methanol but not toluene, it was extremely desirable to attempt to generate **11** by reducing **7** in toluene. Due to the insolubility of sodium borohydride in organic solvents, the procedure had to be adjusted. Organoboranes were thus used as reducing agents, allowing the reaction to be carried out in toluene. These reactions proceed via a hydroboration mechanism, and dissociation of the boron atom from the amino nitrogen is readily achieved by addition of water (Scheme 2.6). Interestingly, the use of pinacolborane resulted in no conversion at all whereas the use of the more reactive catecholborane resulted in complete conversion to **11**, the desired product. It should be noted that **10** could also be generated reproducibly and with high purity from reduction using catecholborane in toluene. Isolation of **10** and **11** required an extraction using dichloromethane and water, followed by recrystallization from hot hexanes. The latter of these steps served to remove a boron salt generated from the catecholborane.



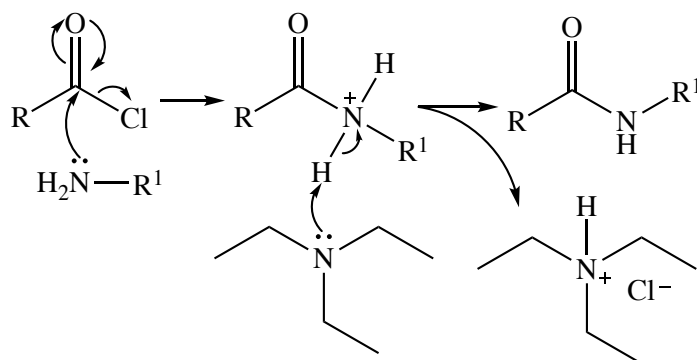
Scheme 2.6: Reduction by hydroboration reaction mechanism.

2.3 Amidation



Scheme 2.7: Generation of amides in this study.

The target amides were then generated by allowing the appropriate amines to react with acyl chlorides (Scheme 2.7). Mechanistically, the carbonyl carbon of the acyl chloride undergoes nucleophilic attack by the amino nitrogen, generating a tertiary amide linkage (Scheme 2.8).⁶³ It is useful to incorporate a base in order to neutralize the HCl generated in the reaction. It is important that this base be sterically encumbered in order to suppress its nucleophilic behavior and inhibit it from attacking at the carbonyl carbon. Triethylamine was used exclusively as the base in these amidation reactions as it satisfies all the necessary criteria. Amides **12**–**17** were obtained by stirring the appropriate reagent in toluene at room temperature for 24–48 h. It should be noted that the 3-Bpin-functionalized derivatives **16** and **17** require further purification.



Scheme 2.8: Amidation reaction mechanism.

2.4 Characterization

All successfully generated compounds were analyzed by FT-IR, ^1H NMR, and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy, as well as ^{11}B NMR spectroscopy in the case of boron-containing molecules. Solids were further subjected to melting point analysis. The formation of imines could be detected by the disappearance of a signal at 9.8 ppm of the ^1H NMR spectrum corresponding to the aldehydic proton of 3,4-dimethoxybenzaldehyde in favour of a new peak at 8.4 ppm corresponding to the azomethine proton. This signal then shifts upfield to 4.3 ppm upon reduction of the imine to a secondary amine. The amides are identifiable by the observation of the appropriate integration ratios of the protons of the aliphatic motif from the acyl chloride to the aromatic motif of the precursor amine. ^{11}B NMR peaks around 29 are indicative of the boron atom of the Bpin group, and were observed for all relevant compounds.

Chapter 3

Conclusions and Future Directions

Six analogues of capsaicin have been synthesized. 3- and 4-Bpin-functionalized derivatives with aliphatic chain lengths of six and ten carbons were afforded in moderate yields, as were the corresponding non-boron compounds. All compounds were characterized by ^1H NMR, $^{13}\text{C}\{^1\text{H}\}$ NMR, and FT-IR spectroscopy, as well as ^{11}B NMR spectroscopy for boron-containing compounds. Unfortunately, the steric constraints and resonance effects formerly described precluded progress towards the 2-Bpin-functionalized amides at the imine step. It would be advisable for future work to explore methods of generating these particular compounds. Further, elemental analysis and X-ray crystallography should be carried out for full characterization of the compounds generated in this study. Finally, the biological potential of these molecules is of significance. Both anti-microbial and anti-cancer testing will be carried out in the future. The implications of the presence and regiochemistry of Bpin groups, as well as the length of the aliphatic chains are of particular interest.

Chapter 4

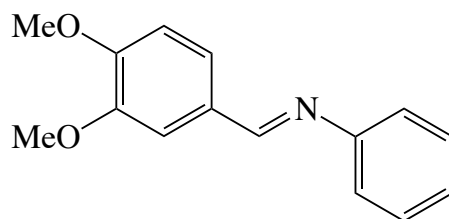
Experimental

4.1 General Procedures

All reagents and solvents were purchased from Aldrich Chemicals. ^1H NMR and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a Varian Mercury 200 plus FT NMR spectrometer. ^1H NMR chemical shifts are reported in ppm and referenced to residual protons in deuterated chloroform at 200 MHz, while $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are reported in ppm and referenced to residual carbon resonances at 50.3 MHz. ^{11}B NMR spectra were recorded on a JEOL JNM-GSX400 FT NMR spectrometer, and chemical shifts are reported in ppm at 128 MHz. FT-IR spectra were obtained with a Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer in ATR mode and signals are reported in cm^{-1} . Melting points were measured using a Stuart SMP30 mel-temp apparatus.

4.2 Imine Synthesis

5. Imine synthesis from 3,4-dimethoxybenzaldehyde and aniline



Small scale trial 1:

To a stirring MeOH (2 mL) solution of 3,4-dimethoxybenzaldehyde (0.09 g, 0.55 mmol) was added a MeOH (1 mL) solution of aniline (0.05 g, 0.55 mmol). The contents were heated at reflux for 3 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a yellow

oil. The structure of **5** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.⁶⁴

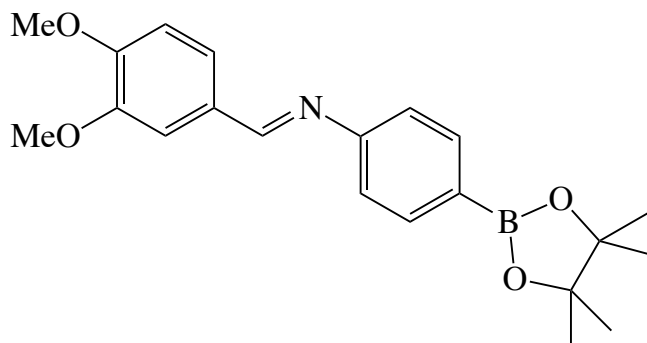
Large scale trial 1:

To a stirring MeOH (10 mL) solution of 3,4-dimethoxybenzaldehyde (2.00 g, 12.0 mmol) was added a MeOH (10 mL) solution of aniline (1.12 g, 12.0 mmol). The contents were heated at reflux for 3 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a yellow oil, which solidified within an hour. The structure of **5** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.⁶⁴ Yield: 2.56 g (88%); ^1H NMR (CDCl_3) δ : 8.36 (s, 1H, $\text{HC}=\text{N}$), 7.62 (d, $^4J = 2.0$ Hz, 1H, Ar), 7.43-7.32 (ov m, 3H, Ar), 7.29-7.16 (ov m, 3H, Ar), 6.93 (d, $^3J = 8.2$ Hz, 1H, Ar), 3.99 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3).

Large scale trial 2:

To a stirring MeOH (5 mL) solution of 3,4-dimethoxybenzaldehyde (1.12 g, 6.72 mmol) was added a MeOH (5 mL) solution of aniline (0.63 g, 6.72 mmol). The contents were heated at reflux for 3 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a yellow oil, which solidified within an hour. The structure of **5** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.⁶⁴

6: Imine synthesis from 3,4-dimethoxybenzaldehyde and 4-aminophenylboronic acid pinacol ester



Small scale trial 1:

To a stirring MeOH (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.25 mmol) was added a MeOH (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.25 mmol). The contents were heated at reflux for 3 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 40%.

Small scale trial 2:

To a stirring MeOH (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.23 mmol) was added a MeOH (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.23 mmol). HCOOH (1 drop) was added to the reaction mixture and the contents were heated at reflux for 7 h before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 75%.

Small scale trial 3:

To a stirring toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.24 mmol) was added a toluene (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.24 mmol). HCOOH (1 drop) was added to the reaction mixture, and the contents were heated at reflux for 6

h before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 80%.

Small scale trial 4:

To a stirring MeOH (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.24 mmol) was added a MeOH (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.24 mmol). HCOOH (1 drop) was added to the reaction mixture and the contents were heated at reflux for 7 h before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 60%.

Small scale trial 5:

To a toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.05 g, 0.28 mmol) was added a toluene (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.06 g, 0.28 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 90%.

Large scale trial 1:

To a toluene (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.23 g, 1.38 mmol) was added a toluene (9 mL) solution of 4-aminophenylboronic acid pinacol ester (0.31 g, 1.38 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a white solid. The structure of **6** was elucidated from ¹H NMR and ¹¹B NMR spectroscopy.

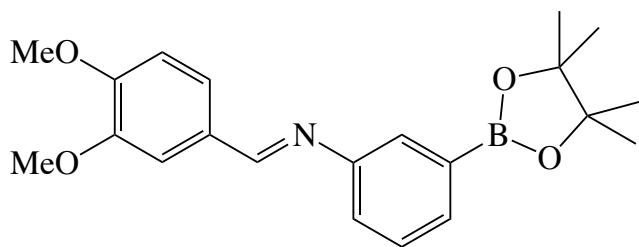
Large scale trial 2:

To a toluene (5 mL) solution of 3,4-dimethoxybenzaldehyde (0.39 g, 2.35 mmol) was added a toluene (8 mL) solution of 4-aminophenylboronic acid pinacol ester (0.51 g, 2.35 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a white solid. Yield: 0.69 g (80%); ¹H NMR (CDCl₃) δ: 8.35 (s, 1H, HC=N), 7.83 (dt, ³J = 8.2 Hz, ⁴J = 2.0 Hz, 2H, Ar), 7.61 (d, ⁴J = 2.0 Hz, 1H, Ar), 7.31 (dd, ³J = 8.4 Hz, ⁴J = 2.0 Hz, 1H, Ar), 7.18 (dt, ³J = 8.2 Hz, ⁴J = 2.0 Hz, 2H, Ar), 6.93 (d, ³J = 8.4 Hz, 1H, Ar), 3.99 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 1.35 (s, 12H, Bpin); ¹¹B NMR (CDCl₃) δ: 28 (br).

Large scale trial 3:

To a toluene (5 mL) solution of 3,4-dimethoxybenzaldehyde (0.39 g, 2.35 mmol) was added a toluene (8 mL) solution of 4-aminophenylboronic acid pinacol ester (0.51 g, 2.35 mmol). The reaction was allowed to proceed under inert atmosphere with 4Å molecular sieves for 8 days. Removal of solvent under vacuum yielded a white solid. The structure of **6** was elucidated from ¹H NMR and ¹¹B NMR spectroscopy. Yield: 0.63 g (73 %).

7: Imine synthesis from 3,4-dimethoxybenzaldehyde and 3-aminophenylboronic acid pinacol ester



Small scale trial 1:

To a stirring toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.25 mmol) was added a toluene (3 mL) solution of 3-aminophenylboronic acid pinacol ester (0.05 g, 0.25 mmol). The contents were heated at reflux for 6 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 20%.

Small scale trial 2:

To a stirring toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.26 mmol) was added a toluene (3 mL) solution of 3-aminophenylboronic acid pinacol ester (0.06 g, 0.26 mmol). HCOOH (1 drop) was added to the reaction mixture, and the contents were heated at reflux for 7 h, before being stored at 4°C for 20 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 90%.

Small scale trial 3:

To a toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.26 mmol) was added a toluene (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.06 g, 0.26 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 5 days. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 95%.

Large scale trial 1:

To a toluene (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.23 g, 1.38 mmol) was added a toluene (3 mL) solution of 3-aminophenylboronic acid pinacol ester (0.31 g, 1.38 mmol). The

reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a white solid. The structure of **7** was elucidated from ^1H NMR and ^{11}B NMR spectroscopy.

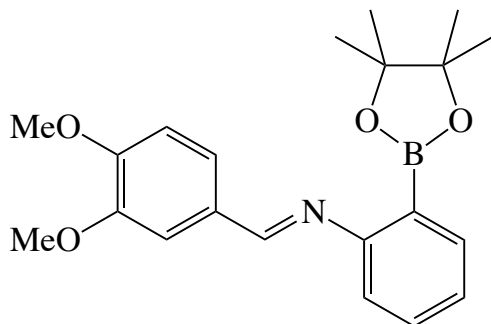
Large scale trial 2:

To a toluene (5 mL) solution of 3,4-dimethoxybenzaldehyde (0.39 g, 2.35 mmol) was added a toluene (5 mL) solution of 3-aminophenylboronic acid pinacol ester (0.51 g, 2.35 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a white solid. Yield: 0.72 g (84%); ^1H NMR (CDCl_3) δ : 8.41 (s, 1H, $\text{HC}=\text{N}$), 7.69-7.62 (ov m, 3H, Ar), 7.44-7.28 (ov m, 3H, Ar), 6.93 (d, $^3J = 8.2$ Hz, 1H, Ar), 3.99 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 1.36 (s, 12H, Bpin); ^{11}B NMR (CDCl_3) δ : 30 (br).

Large scale trial 3:

To a toluene (5 mL) solution of 3,4-dimethoxybenzaldehyde (0.39 g, 2.35 mmol) was added a toluene (5 mL) solution of 3-aminophenylboronic acid pinacol ester (0.51 g, 2.35 mmol). The reaction was allowed to proceed under inert atmosphere with 4Å molecular sieves for 8 days. Removal of solvent under vacuum yielded a white solid. The structure of **7** was elucidated from ^1H NMR and ^{11}B NMR spectroscopy. Yield: 0.69 g (80%).

8: Imine synthesis from 3,4-dimethoxybenzaldehyde and 2-aminophenylboronic acid pinacol ester



Small scale trial 1:

To a toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.05 g, 0.30 mmol) was added a toluene (1 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.30 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 60%.

Small scale trial 2:

To a toluene (1 mL) solution of 3,4-dimethoxybenzaldehyde (0.05 g, 0.30 mmol) was added a toluene (1 mL) solution of 4-aminophenylboronic acid pinacol ester (0.07 g, 0.30 mmol). The reaction was heated at reflux for 12 h. Removal of solvent under vacuum yielded a clear oil. ¹H NMR spectroscopy was indicative of conversion near 75%.

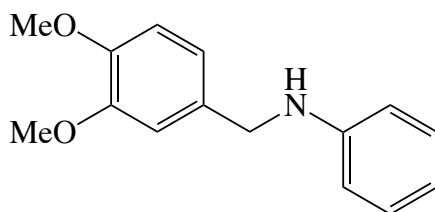
Small scale trial 3:

To a toluene (1.5 mL) solution of 3,4-dimethoxybenzaldehyde (0.05 g, 0.30 mmol) was added a toluene (1.5 mL) solution of 4-aminophenylboronic acid pinacol ester (0.07 g, 0.30 mmol). The reaction was carried out under microwave irradiation at 125°C for 2 h followed by 200°C for 2 h.

Removal of solvent under vacuum yielded a clear oil. ^1H NMR spectroscopy was indicative of conversion near 75%.

4.3 Reductive Amination

9: Reduction of 5



Small scale trial 1:

To a stirring MeOH (3 mL) solution of **5** (0.13 g, 0.55 mmol) was added NaBH_4 (0.04 g, 1.11 mmol). The contents were stirred for 18 h. Removal of solvent under vacuum yielded a white solid, which was washed with H_2O (3 x 10 mL). The structure of **9** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.^{65,66}

Large scale trial 1:

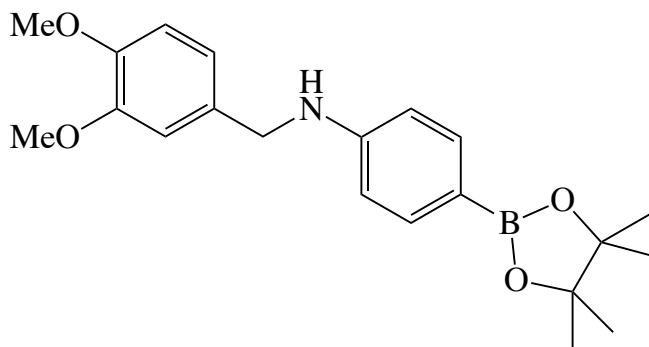
To a stirring MeOH (30 mL) solution of **5** (2.56 g, 10.6 mmol) was added NaBH_4 (0.82 g, 21.2 mmol). The contents were stirred for 18 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH_2Cl_2 (30 mL, 10 mL) and H_2O (30 mL) was performed. The structure of **9** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.^{65,66} Yield: 1.65 g (64%); mp: 79-80°C; FT-IR (ATR): 3363 (s), 3014 (w), 2935 (w), 2836 (w), 1602 (s), 1507 (s), 1463 (s), 1451 (m), 1431 (m), 1418 (m), 1366 (w), 1314 (s), 1285 (w), 1260 (s), 1227 (s), 1195 (w), 1179 (w), 1153 (m), 1138 (s), 1100 (m), 1067 (w), 991 (m), 946 (m), 873

(m), 858 (m), 838 (w), 810 (s), 766 (m), 749 (s), 694 (s), 634 (m), 598 (w); ^1H NMR (CDCl_3) δ : 7.26-7.15 (ov m, 2H, Ar), 6.95-6.63 (ov m, 6H, Ar), 4.26 (s, 2H, ArCH_2N), 3.96 (s, 1H, HN), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).

Large scale trial 2:

To a stirring MeOH (20 mL) solution of **5** (1.37 g, 5.69 mmol) was added NaBH_4 (0.43 g, 11.4 mmol). The contents were stirred for 18 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH_2Cl_2 (20 mL, 10 mL) and H_2O (20 mL) was performed. The structure of **9** was elucidated from ^1H NMR spectroscopy data, which matched previously published spectra.^{65,66}

10: Reduction of 6



Small scale trial 1:

To a stirring MeOH (3 mL) solution of **6** (0.05 g, 0.13 mmol) was added NaBH_4 (0.01 g, 0.26 mmol). The contents were stirred for 20 h, and an extraction using CH_2Cl_2 (30 mL, 10 mL) and H_2O (30 mL) was performed. Removal of solvent under vacuum yielded a white solid which was analyzed by ^1H NMR and ^{11}B NMR spectroscopy.

Small scale trial 2:

To a MeOH (3 mL) solution of **6** (0.05 g, 0.13 mmol) was added a MeOH (1 mL) solution of NaBH₄ (0.01 g, 0.26 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 20 h. Removal of solvent under vacuum yielded a white solid, which was dissolved in toluene before undergoing gravity filtration. Removal of solvent under vacuum once again yielded a white solid. ¹H NMR (CDCl₃) δ: 7.64 (d, ³J = 8.6 Hz, 2H, Ar), 6.86 (ov m, 3H, Ar), 6.62 (d, ³J = 8.6 Hz, 2H, Ar), 4.29 (d, ³J = 5.4 Hz, 2H, ArCH₂N), 4.18 (d, ³J = 5.4 Hz, 1H, HN), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 1.32 (s, 12H, Bpin); ¹¹B NMR (CDCl₃) δ: 29 (br).

Small scale trial 3:

To a MeOH (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.23 mmol) was added a MeOH (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.23 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 72 h, before an excess of NaBH₄ was added. The reaction was allowed to proceed for an additional 24 h. Removal of solvent under vacuum yielded a white solid, which was analyzed by ¹H NMR spectroscopy.

Small scale trial 4:

To a MeOH (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.23 mmol) was added a MeOH (3 mL) solution of 4-aminophenylboronic acid pinacol ester (0.05 g, 0.23 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days, before an excess of NaBH₄ was added. The reaction was allowed to proceed for an additional 24

h. Removal of solvent under vacuum yielded a white solid, which was analyzed by ^1H NMR spectroscopy.

Small scale trial 5:

To a toluene (1 mL) solution of **6** (0.04 g, 0.09 mmol) was added a toluene (1 mL) solution of HBcat (0.03 g, 0.21 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a clear oil, and an extraction using CH_2Cl_2 (5 mL) and H_2O (5 mL) was performed. Removal of solvent under vacuum once again yielded a yellow oil. The structure of **10** was elucidated from ^1H NMR and ^{11}B NMR spectroscopy.

Large scale trial 1:

To a stirring MeOH (5 mL) solution of **6** (0.21 g, 0.58 mmol) was added NaBH_4 (0.04 g, 1.15 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 24 h. Removal of solvent under vacuum yielded a white solid, which was dissolved in toluene before undergoing gravity filtration. Removal of solvent under vacuum once again yielded a white solid, which was analyzed by ^1H NMR spectroscopy.

Large scale trial 2:

To a stirring MeOH (10 mL) solution of **6** (0.21 mg, 0.56 mmol) was added NaBH_4 (0.04 g, 1.12 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 24 h. Removal of solvent under vacuum yielded a white solid, which was dissolved in toluene before undergoing gravity filtration. Removal of solvent under vacuum once again yielded a white solid, which was analyzed by ^1H NMR spectroscopy.

Large scale trial 3:

To a stirring MeOH (5 mL) solution of **6** (0.21 g, 0.57 mmol) was added an excess of NaBH₄. The contents were stirred for 24 h, and an extraction using CH₂Cl₂ (3 x 10 mL) and H₂O (30 mL) was performed. Removal of solvent under vacuum yielded a white solid. Yield: 0.16 g (76%); mp: 173-175°C; FT-IR (ATR): 3370 (m), 2980 (w), 2839 (w), 1604 (s), 1515 (m), 1483 (w), 1463 (m), 1356 (s), 1328 (m), 1313 (m), 1266 (s), 1231(s), 1183 (m), 1139 (s), 1093 (m), 1024 (s), 963 (m), 859 (m), 832 (m), 817 (m), 768 (m), 738 (m), 673 (m), 657 (s), 634 (w), 599 (w); ¹H NMR (CDCl₃) δ: 7.64 (d, ³J = 8.6 Hz, 2H, Ar), 6.91-6.84 (ov m, 3H, Ar), 6.64 (d, ³J = 8.6 Hz, 2H, Ar), 4.29 (s, 2H, ArCH₂N), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 1.32 (s, 12H, Bpin); ¹¹B NMR (CDCl₃) δ: 30 (br).

Large scale trial 4:

To a stirring MeOH (5 mL) solution of **6** (0.27 g, 0.73 mmol) was added an excess of NaBH₄. The contents were stirred for 24 h, and an extraction using CH₂Cl₂ (2 x 10 mL) and H₂O (10 mL) was performed. Removal of solvent under vacuum yielded a white solid. The structure of **10** was elucidated from ¹H and ¹¹B NMR spectroscopy. Yield: 0.17 g (63%).

Large scale trial 5:

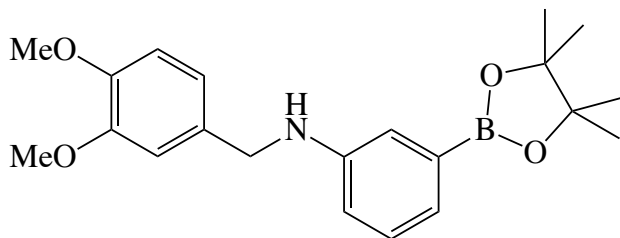
To a stirring toluene (5 mL) solution of **6** (0.63 g, 1.71 mmol) was added a toluene (2 mL) solution HBcat (0.41 g, 3.42 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH₂Cl₂ (2 x 20 mL) and H₂O (20 mL) was performed. Recrystallization from hot hexanes (50 mL) followed by

removal of solvent under vacuum yielded a white solid. The structure of **10** was elucidated from ^1H and ^{11}B NMR spectroscopy.

Large scale trial 6:

To a stirring toluene (5 mL) solution of **6** (0.63 g, 1.71 mmol) was added a toluene (2 mL) solution HBcat (0.41 g, 3.42 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH_2Cl_2 (2 x 20 mL) and H_2O (20 mL) was performed. Recrystallization from hot hexanes (50 mL) followed by removal of solvent under vacuum yielded a white solid. Yield: 0.37 g (59%), ^1H NMR (CDCl_3) δ : 7.64 (d, $^3J = 8.6$ Hz, 2H, Ar), 6.91-6.84 (ov m, 3H, Ar), 6.64 (d, $^3J = 8.6$ Hz, 2H, Ar), 4.29 (s, 2H, Ar CH_2N), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 1.32 (s, 12H, Bpin); ^{11}B NMR (CDCl_3) δ : 30 (br).

II: Reduction of 7



Small scale trial 1:

To a stirring MeOH (2 mL) solution of **7** (0.05 g, 0.13 mmol) was added NaBH_4 (0.01 g, 0.26 mmol). The contents were stirred for 18 h. Removal of solvent under vacuum yielded a clear oil, which was analyzed by ^1H NMR and ^{11}B NMR spectroscopy.

Small scale trial 2:

To a stirring MeOH (3 mL) solution of **7** (0.05 g, 0.13 mmol) was added NaBH₄ (0.01 g, 0.26 mmol). The contents were stirred for 20 h and an extraction using CH₂Cl₂ (30 mL, 10 mL) and H₂O (30 mL) was performed. Removal of solvent under vacuum yielded a white solid, which was analyzed by ¹H NMR and ¹¹B NMR spectroscopy.

Small scale trial 3:

To a sample of NaBH₄ (0.01 g, 0.26 mmol) was added a MeOH (3 mL) solution of **7** (0.05 g, 0.13 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 20 h. Removal of solvent under vacuum yielded a white solid, which was dissolved in toluene (3 mL) before undergoing gravity filtration. Removal of solvent under vacuum once again yielded a clear oil, which was analyzed by ¹H NMR and ¹¹B NMR spectroscopy.

Small scale trial 4:

To a MeOH (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.23 mmol) was added a MeOH (3 mL) solution of 3-aminophenylboronic acid pinacol ester (0.05 g, 0.23 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 72 h, before an excess of NaBH₄ was added. The reaction was allowed to proceed for an additional 24 h. Removal of solvent under vacuum yielded a clear oil, which was analyzed by ¹H NMR spectroscopy.

Small scale trial 5:

To a MeOH (3 mL) solution of 3,4-dimethoxybenzaldehyde (0.04 g, 0.23 mmol) was added a MeOH (3 mL) solution of 3-aminophenylboronic acid pinacol ester (0.05 g, 0.23 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 7 days, before an excess of NaBH₄ was added. The reaction was allowed to proceed for an additional 24 h. Removal of solvent under vacuum yielded a clear oil, which was analyzed by ¹H NMR spectroscopy.

Small scale trial 6:

To a MeOH (3 mL) solution of **7** (0.05 g, 0.14 mmol) was added NaBH₄ (0.01 g, 0.28 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 18 h. Removal of solvent under vacuum yielded a white solid, which was analyzed by ¹H NMR and ¹¹B NMR spectroscopy.

Small scale trial 7:

To a MeOH (3 mL) solution of **7** (0.05 g, 0.14 mmol) was added NaBH₄ (0.01 g, 0.28 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves and aliquots were dried after 10 min and 1 h yielding white solids, which were analyzed by ¹H NMR spectroscopy.

Small scale trial 8:

To a toluene (2 mL) solution of **7** (0.05 g, 0.15 mmol) was added a toluene (1 mL) solution of HBpin (0.04 g, 0.29 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h.

Removal of solvent under vacuum yielded a clear oil, which was analyzed by ^1H NMR spectroscopy.

Small scale trial 9:

To a toluene (2 mL) solution of **7** (0.05 g, 0.15 mmol) was added a toluene (1 mL) solution of HBpin (0.04 g, 0.29 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a clear oil, which was dissolved in H_2O (3 mL). Removal of solvent under vacuum once again yielded a clear oil, which was analyzed by ^1H NMR and ^{11}B NMR spectroscopy.

Small scale trial 10:

To a toluene (1 mL) solution of **7** (0.04 g, 0.11 mmol) was added a toluene (1 mL) solution of HBcat (0.03 g, 0.23 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a clear oil, and an extraction using CH_2Cl_2 (5 mL) and H_2O (5 mL) was performed. Removal of solvent under vacuum once again yielded a yellow oil, which was analyzed by ^1H NMR and ^{11}B NMR spectroscopy.

Large scale trial 1:

To a stirring MeOH (5 mL) solution of **7** (0.20 g, 0.54 mmol) was added NaBH_4 (0.04 g, 1.09 mmol). The reaction was allowed to proceed under inert atmosphere with 3Å molecular sieves for 20 h. Removal of solvent under vacuum yielded a white solid, which was dissolved in toluene before undergoing gravity filtration. Removal of solvent under vacuum once again yielded a clear oil, which was analyzed by ^1H NMR spectroscopy.

Large scale trial 2:

To a stirring toluene (5 mL) solution of **7** (0.20 g, 0.54 mmol) was added a toluene (1 mL) solution of HBcat (0.13 g, 1.08 mmol). The contents were stirred for 18 h, and an extraction using CH₂Cl₂ (2 x 10 mL) and H₂O (10 mL) was performed. Removal of solvent under vacuum yielded a clear oil. The structure of **11** was elucidated from ¹H and ¹¹B NMR spectroscopy. Yield: 0.16 g (77%).

Large scale trial 3:

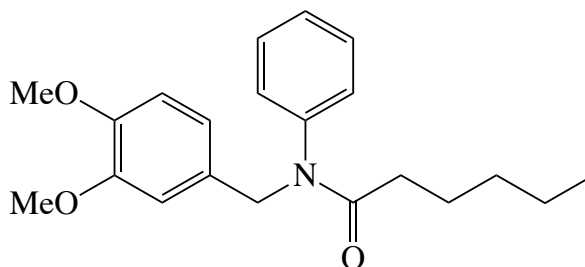
To a stirring toluene (5 mL) solution of **7** (0.69 g, 1.88 mmol) was added a toluene (2 mL) solution HBcat (0.45 g, 3.75 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH₂Cl₂ (2 x 20 mL) and H₂O (20 mL) was performed. Recrystallization from hot hexanes (25 mL) followed by removal of solvent under vacuum yielded a white solid. The structure of **11** was elucidated from ¹H and ¹¹B NMR spectroscopy.

Large scale trial 4:

To a stirring toluene (5 mL) solution of **7** (0.74 g, 2.00 mmol) was added a toluene (2 mL) solution HBcat (0.48 g, 4.00 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. Removal of solvent under vacuum yielded a white solid, and an extraction using CH₂Cl₂ (2 x 20 mL) and H₂O (20 mL) was performed. Recrystallization from hot hexanes (15 mL) followed by removal of solvent under vacuum yielded a white solid. Yield: 0.49 g (66 %); ¹H NMR (CDCl₃) δ: 7.20-7.14 (ov m, 3H, Ar), 6.89-6.75 (ov m, 4H, Ar), 4.27 (s, 2H, ArCH₂N), 3.87 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 1.34 (s, 12H, Bpin); ¹¹B NMR (CDCl₃) δ: 30 (br).

4.4 Amidation

12: Amidation of **9** with hexanoyl chloride



Small scale trial 1:

To a stirring toluene (2 mL) solution of **9** (0.05 g, 0.21 mmol) and triethylamine (0.03 g, 0.24 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.03 g, 0.21 mmol). The reaction was allowed to proceed under inert atmosphere for 3 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum, yielding a clear oil which was analyzed by ^1H NMR spectroscopy.

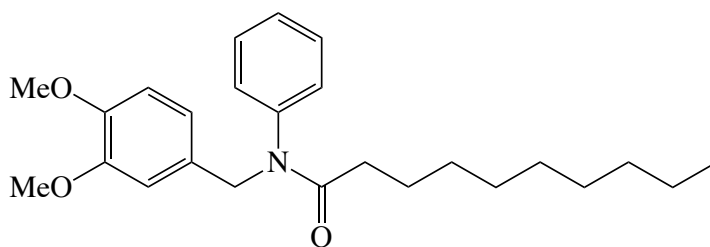
Small scale trial 2:

To a stirring toluene (2 mL) solution of **9** (0.05 g, 0.21 mmol) and triethylamine (0.02 g, 0.23 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.03 g, 0.21 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum, yielding a clear oil. Yield: 0.06 g (87%); ^1H NMR (CDCl_3) δ : 7.34-7.26 (ov m, 3H, Ar), 6.94-6.90 (ov m, 2H, Ar), 6.76-6.60 (ov m, 3H, Ar), 4.79 (s, 2H, ArCH_2N), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.02 (t, $^3J = 7.6$ Hz, 2H, COCH_2), 1.57 (quint, $^3J = 7.6$ Hz, 2H, COCH_2CH_2), 1.24-1.14 (ov m, 4H, $\text{CO}(\text{CH}_2)_2(\text{CH}_2)_2$), 0.80 (t, $^3J = 6.8$ Hz, 3H, $\text{CO}(\text{CH}_2)_4\text{CH}_3$).

Large scale trial 1:

To a stirring toluene (15 mL) solution of **9** (0.80 g, 3.28 mmol) and triethylamine (0.37 g, 3.66 mmol) was added a toluene (5 mL) solution of hexanoyl chloride (0.44 g, 3.28 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum, yielding a yellow oil. Yield: 0.98 g (87%); FT-IR (ATR): 2930 (m), 2870 (w), 1651 (s), 1593 (s), 1513 (s), 1495 (s), 1463 (m), 1452 (m), 1396 (s), 1356 (w), 1258 (s), 1236 (s), 1156 (s), 1139 (s), 1073 (w), 1027 (s), 859 (w), 811 (m), 765 (m), 742 (w), 700 (s), 655 (m), 595 (w); ^1H NMR (CDCl_3) δ : 7.35-7.26 (ov m, 3H, Ar), 6.96-6.91 (ov m, 2H, Ar), 6.77-6.62 (ov m, 3H, Ar), 4.80 (s, 2H, ArCH_2N), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.04 (t, $^3J = 7.6$ Hz, 2H, COCH_2), 1.86 (br s, 1H, NH), 1.58 (quint, $^3J = 7.6$ Hz, 2H, COCH_2CH_2), 1.26-1.13 (ov m, 4H, $\text{CO}(\text{CH}_2)_2(\text{CH}_2)_2$), 0.81 (t, $^3J = 6.6$ Hz, 3H, $\text{CO}(\text{CH}_2)_4\text{CH}_3$); ^{13}C $\{^1\text{H}\}$ NMR (CDCl_3) δ : 173.0 (C=O), 148.7 (Ar), 148.2 (Ar), 142.4 (Ar), 130.3 (Ar), 129.4 (Ar), 128.5 (Ar), 127.8 (Ar), 121.3 (Ar), 112.0 (Ar), 110.6 (Ar), 55.8 (OCH_3), 52.6 (ArCH_2N), 34.3 (CH_2), 31.4 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

13: Amidation of 9 with decanoyl chloride



Small scale trial 1:

To a stirring toluene (1 mL) solution of **9** (0.03 g, 0.10 mmol) and triethylamine (0.01 g, 0.07 mmol) was added a toluene (1 mL) solution of decanoyl chloride (0.01 g, 0.07 mmol). The reaction was allowed to proceed under inert atmosphere for 18 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a white oil, which was analyzed by ¹H NMR spectroscopy.

Large scale trial 1:

To a stirring toluene (6 mL) solution of **9** (0.50 g, 2.05 mmol) and triethylamine (0.23 g, 2.27 mmol) was added a toluene (1 mL) solution of decanoyl chloride (0.39 g, 2.05 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil, which was analyzed by ¹H NMR spectroscopy.

Large scale trial 2:

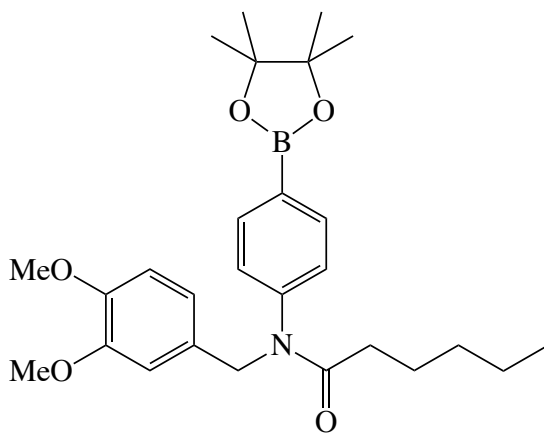
To a stirring toluene (4 mL) solution of **9** (0.14 g, 0.58 mmol) and triethylamine (0.07 g, 0.65 mmol) was added a toluene (2 mL) solution of decanoyl chloride (0.11 g, 0.59 mmol). The reaction was allowed to proceed under inert atmosphere for 48 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. FT-IR (ATR): 3364 (w), 2923 (m), 2853 (w), 1652 (s), 1594 (m), 1514 (s), 1495 (m), 1463 (m), 1395 (m), 1355 (s), 1260 (s), 1235 (s), 1155 (m), 1139 (s), 1074 (w), 1027 (s) 859 (w), 810 (w), 766 (m), 731 (m), 699 (s), 654 (m), 597 (w); ¹H NMR (CDCl₃) δ: 7.33-7.21 (ov m, 3H, Ar), 6.96-6.91 (ov m, 2H, Ar), 6.78-6.66 (ov m, 3H, Ar), 4.81 (s, 2H, ArCH₂N), 3.84 (s, 3H, OCH₃),

3.79 (s, 3H, OCH₃), 2.04 (t, ³J = 7.4 Hz, COCH₂), 1.57 (quint, ³J = 7.4 Hz, COCH₂CH₂), 1.19 (br s, 12H, (CH₂)_n), 0.85 (t, ³J = 6.7 Hz, 3H, CH₂CH₃); ¹³C{¹H} NMR (CDCl₃) δ: 173.0 (C=O), 148.7 (Ar), 148.2 (Ar), 142.4 (Ar), 130.3 (Ar), 129.4 (Ar), 128.5 (Ar), 127.8 (Ar), 121.3 (Ar), 112.0 (Ar), 110.6 (Ar), 55.8 (OCH₃), 53.6 (ArCH₂N), 34.4 (CH₂), 31.8 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 25.6 (CH₂), 22.6 (CH₂), 14.1 (CH₃).

Large scale trial 3:

To a stirring toluene (5 mL) solution of **9** (0.28 g, 1.14 mmol) and triethylamine (0.13 g, 1.25 mmol) was added a toluene (1 mL) solution of decanoyl chloride (0.22 g, 1.14 mmol). The reaction was allowed to proceed under inert atmosphere for 48 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil.

14: Amidation of 10 with hexanoyl chloride



Small scale trial 1:

To a stirring toluene (1.5 mL) solution of **10** (0.03 g, 0.07 mmol) and triethylamine (0.01 g, 0.07 mmol) was added a toluene (0.5 mL) solution of hexanoyl chloride (0.01 g, 0.07 mmol). The

reaction was allowed to proceed under inert atmosphere for 20 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. ^1H NMR (CDCl_3) δ : 7.75 (d, $^3J = 8.0$ Hz, 2H, Ar), 6.96 (d, $^3J = 8.2$ Hz, 2H, Ar), 6.80-6.58 (ov m, 3H, Ar), 4.80 (s, 2H, Ar CH_2N), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.03 (t, $^3J = 7.8$ Hz, 2H, COCH_2), 1.57 (quint, $^3J = 7.8$ Hz, 2H, COCH_2CH_2), 1.34 (s, 12H, Bpin), 1.23-1.11 (ov m, 4H, $\text{CO}(\text{CH}_2)_2(\text{CH}_2)_2$), 0.81 (t, $^3J = 7.0$ Hz, 3H, $\text{CO}(\text{CH}_2)_4\text{CH}_3$).

Large scale trial 1:

To a stirring toluene (6 mL) solution of **10** (0.11 g, 0.31 mmol) and triethylamine (0.03 g, 0.34 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.04 g, 0.31 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **14** was elucidated from ^1H and ^{11}B NMR spectroscopy.

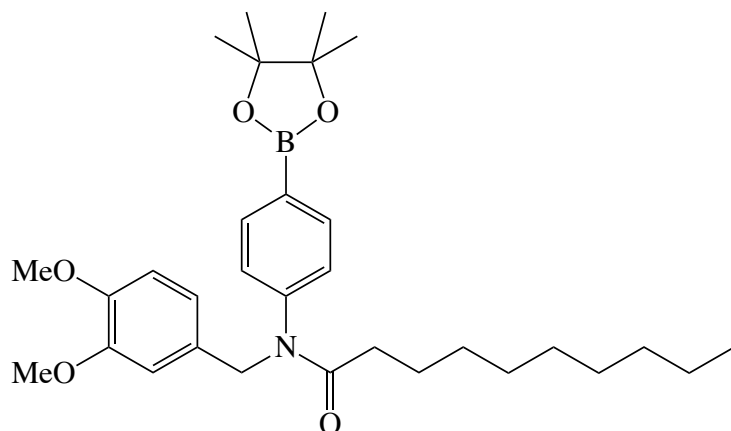
Large scale trial 2:

To a stirring toluene (5 mL) solution of **10** (0.11 g, 0.60 mmol) and triethylamine (0.07 g, 0.65 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.08 g, 0.60 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **14** was elucidated from ^1H and ^{11}B NMR spectroscopy.

Large scale trial 3:

To a stirring toluene (2 mL) solution of **10** (0.22 g, 0.31 mmol) and triethylamine (0.03 g, 0.34 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.04 g, 0.31 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. FT-IR (ATR): 2231 (m), 1655 (m), 1603 (s), 1562 (w), 1514 (m), 1464 (m), 1396 (m), 1359 (s), 1321 (m), 1259 (s), 1237 (m), 1217 (m), 1140 (s), 1090 (s), 1028 (m), 1015 (m), 962 (m), 857 (m), 826 (w), 766 (w), 741 (w), 720 (w), 661 (s), 579 (w); ^1H NMR (CDCl_3) δ : 7.75 (d, $^3J = 8.0$ Hz, 2H, Ar), 6.96 (d, $^3J = 8.0$ Hz, 2H, Ar), 6.80-6.58 (ov m, 3H, Ar), 4.80 (s, 2H, ArCH_2N), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.03 (t, $^3J = 7.8$ Hz, 2H, COCH_2), 1.57 (quint, $^3J = 7.8$ Hz, 2H, COCH_2CH_2), 1.34 (s, 12H, Bpin), 1.23-1.11 (ov m, 4H, $\text{CO}(\text{CH}_2)_2(\text{CH}_2)_2$), 0.81 (t, $^3J = 7.0$ Hz, 3H, $\text{CO}(\text{CH}_2)_4\text{CH}_3$); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 172.8 (C=O), 148.7 (Ar), 148.2 (Ar), 145.0 (Ar), 135.9 (Ar), 130.2 (Ar), 127.8 (Ar), 121.3 (Ar), 112.0 (Ar), 110.6 (Ar), 84.1 ($\text{C}(\text{CH}_3)_2$), 55.8 (OCH_3), 52.6 (ArCH_2N), 34.4 (CH_2), 31.4 (CH_2), 25.3 (CH_3), 24.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3); ^{11}B NMR (CDCl_3) δ : 29 (br).

15: Amidation of 10 with decanoyl chloride



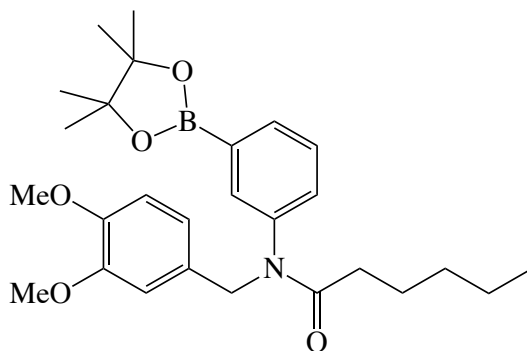
Small scale trial 1:

To a stirring toluene (1.5 mL) solution of **10** (0.04 g, 0.11 mmol) and triethylamine (0.01 g, 0.12 mmol) was added a toluene (0.5 mL) solution of decanoyl chloride (0.02 g, 0.11 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **15** was elucidated from ^1H and ^{11}B NMR spectroscopy.

Large scale trial 1:

To a stirring toluene (6 mL) solution of **10** (0.20 g, 0.55 mmol) and triethylamine (0.01 g, 0.60 mmol) was added a toluene (1 mL) solution of decanoyl chloride (0.10 g, 0.55 mmol). The reaction was allowed to proceed under inert atmosphere for 48 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. Yield: 0.22 g (76%); FT-IR (ATR): 2923 (m), 2853 (w), 1641 (s), 1603 (s), 1564 (w), 1509 (m), 1461 (w), 1413 (w), 1389 (m), 1360 (s), 1326 (m), 1256 (m), 1225 (m), 1185 (w), 1141 (s), 1117 (m), 1032 (m), 1018 (m), 962 (w), 920 (w), 855 (s), 827 (m), 765 (w), 678 (w), 659 (s), 602 (w); ^1H NMR (CDCl_3) δ : 7.75 (d, $^3J = 8.2$ Hz, 2H, Ar), 6.96 (d, $^3J = 8.2$ Hz, 2H, Ar), 6.80-6.58 (ov m, 3H, Ar), 4.80 (s, 2H, ArCH_2N), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.03 (t, $^3J = 7.0$ Hz, 2H, COCH_2), 1.57 (quint, $^3J = 7.0$ Hz, 2H, COCH_2CH_2), 1.34 (s, 12H, Bpin), 1.18 (br s, 12H, $(\text{CH}_2)_n$), 0.85 (t, $^3J = 6.2$ Hz, 3H, CH_2CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ : 172.8 (C=O), 148.7 (Ar), 148.2 (Ar), 145.1 (Ar), 135.9 (Ar), 130.3 (Ar), 127.8 (Ar), 121.3 (Ar), 112.0 (Ar), 110.5 (Ar), 84.1 ($\text{C}(\text{CH}_3)_2$), 55.8 (OCH_3), 52.5 (ArCH_2N), 34.4 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.6 (CH_2), 24.9 (CH_3), 22.6 (CH_2), 14.1 (CH_3); ^{11}B NMR (CDCl_3) δ : 30 (br).

16: Amidation of 11 with hexanoyl chloride



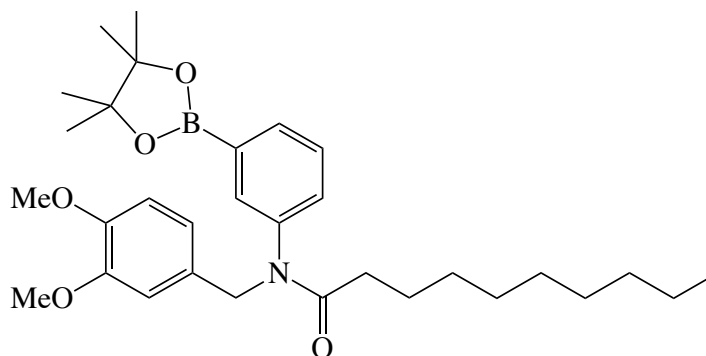
Small scale trial 1:

To a stirring toluene (2 mL) solution of **11** (0.15 g, 0.42 mmol) and triethylamine (0.05 g, 0.43 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.06 g, 0.57 mmol). The reaction was allowed to proceed under inert atmosphere for 24 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **16** was elucidated from ^1H and ^{11}B NMR spectroscopy, though further purification is required.

Large scale trial 1:

To a stirring toluene (5 mL) solution of **11** (0.22 g, 0.59 mmol) and triethylamine (0.07 g, 0.64 mmol) was added a toluene (1 mL) solution of hexanoyl chloride (0.08 g, 0.59 mmol). The reaction was allowed to proceed under inert atmosphere for 48 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **16** was elucidated from ^1H NMR spectroscopy, though further purification is required.

17: Amidation of 11 with decanoyl chloride



Large scale trial 1:

To a stirring toluene (5 mL) solution of **11** (0.20 g, 0.54 mmol) and triethylamine (0.06 g, 0.59 mmol) was added a toluene (1 mL) solution of decanoyl chloride (0.10 g, 0.54 mmol). The reaction was allowed to proceed under inert atmosphere for 48 h. A white precipitate was collected by suction filtration, and the solvent was removed from the filtrate under vacuum yielding a yellow oil. The structure of **17** was elucidated from ^1H NMR spectroscopy, though further purification is required.

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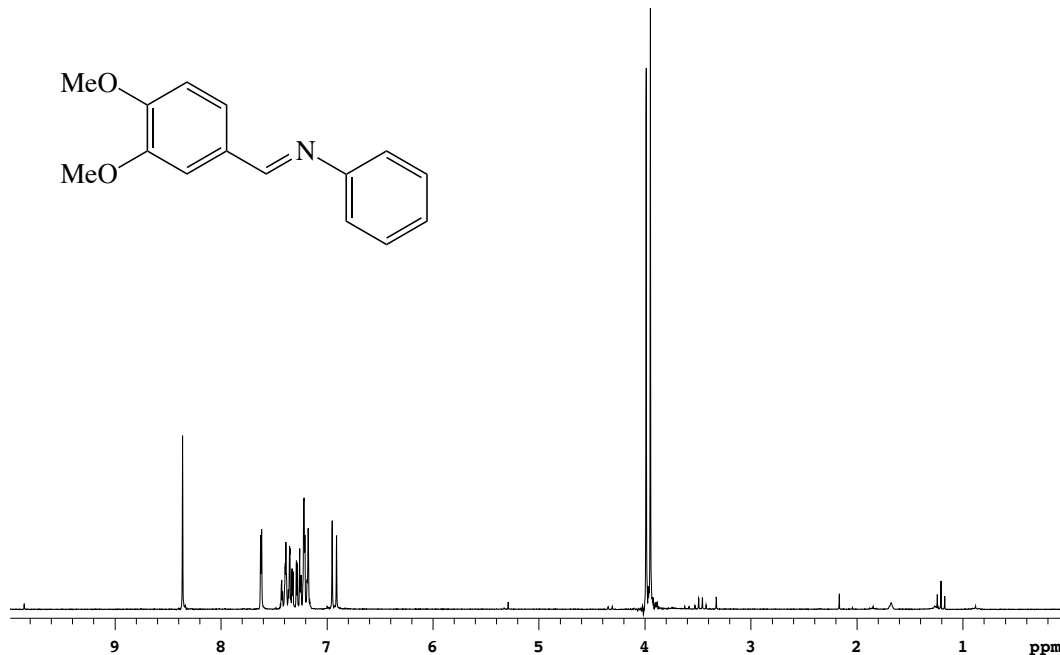
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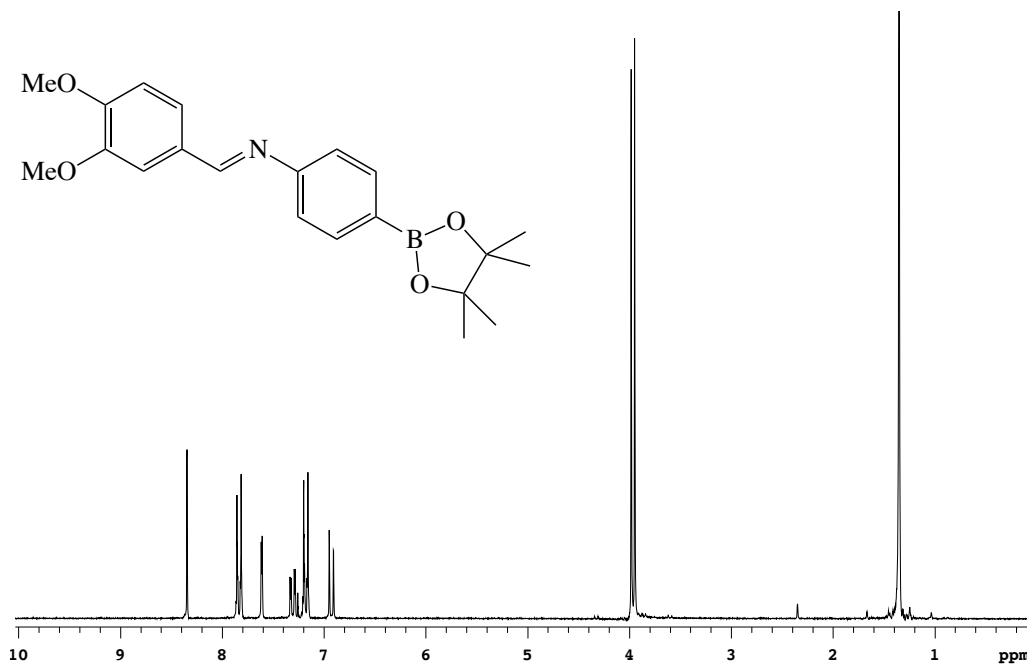
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Appendices

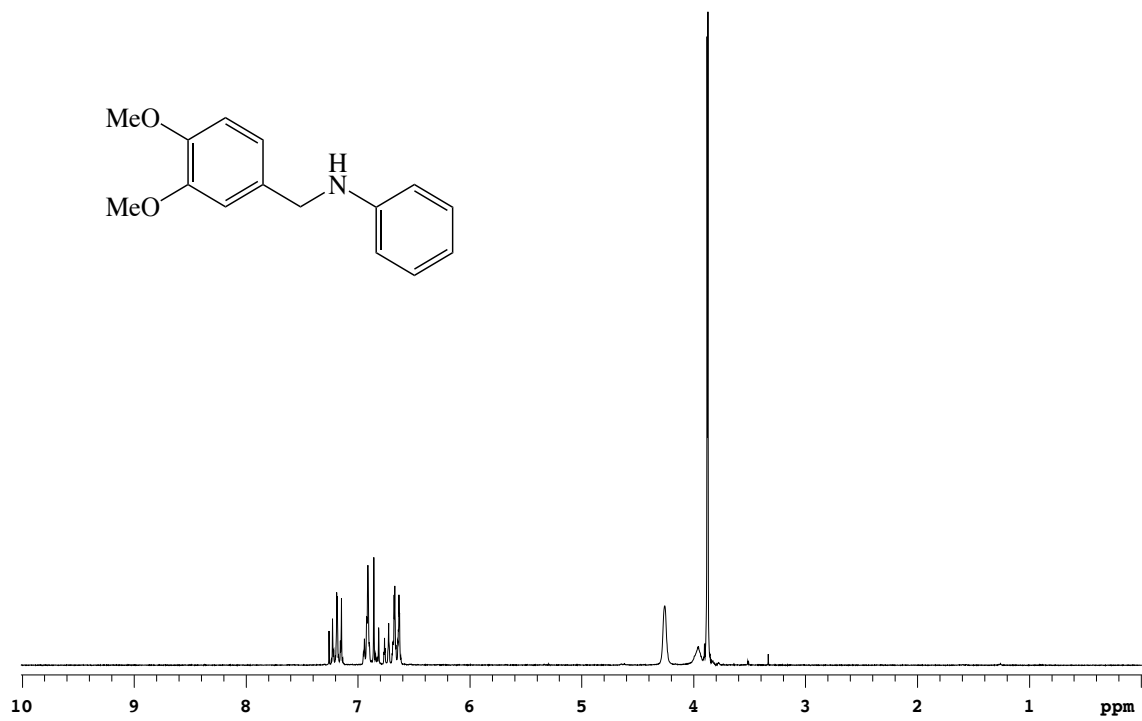
A. Select NMR Spectra



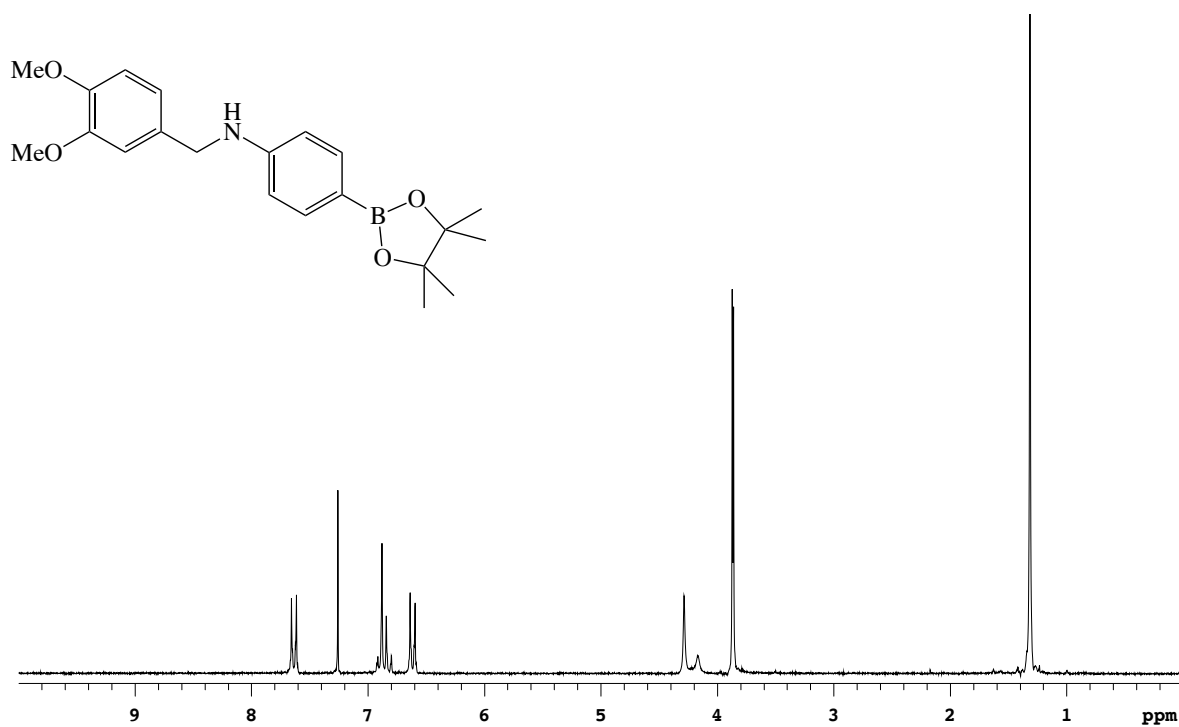
Spectrum 1: ¹H NMR (200 MHz, CDCl₃) **5**



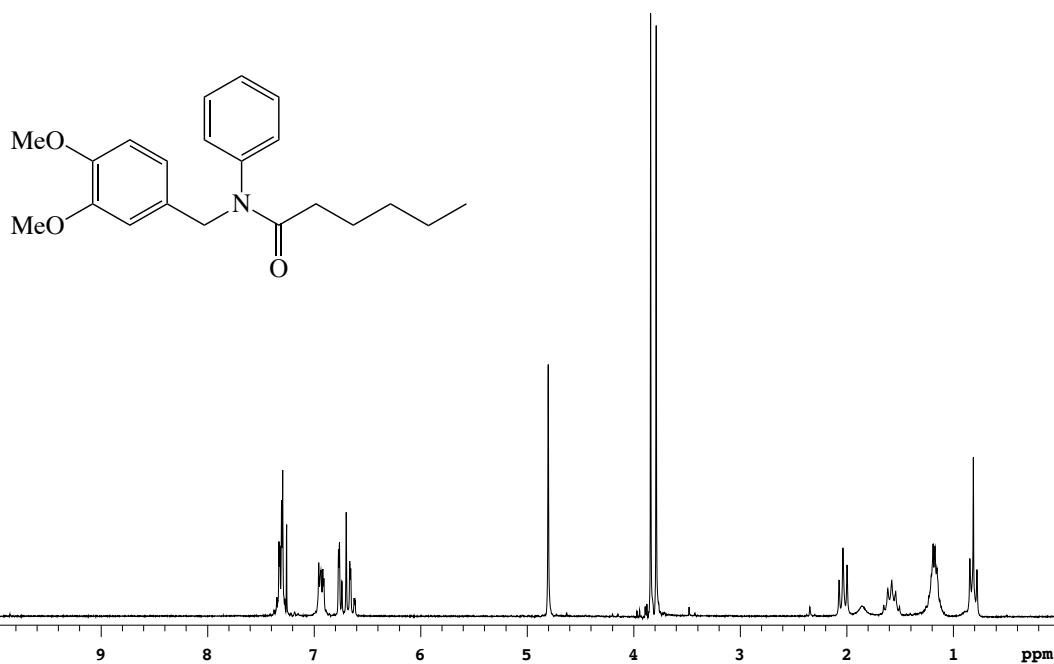
Spectrum 2: ¹H NMR (200 MHz, CDCl₃) **6**



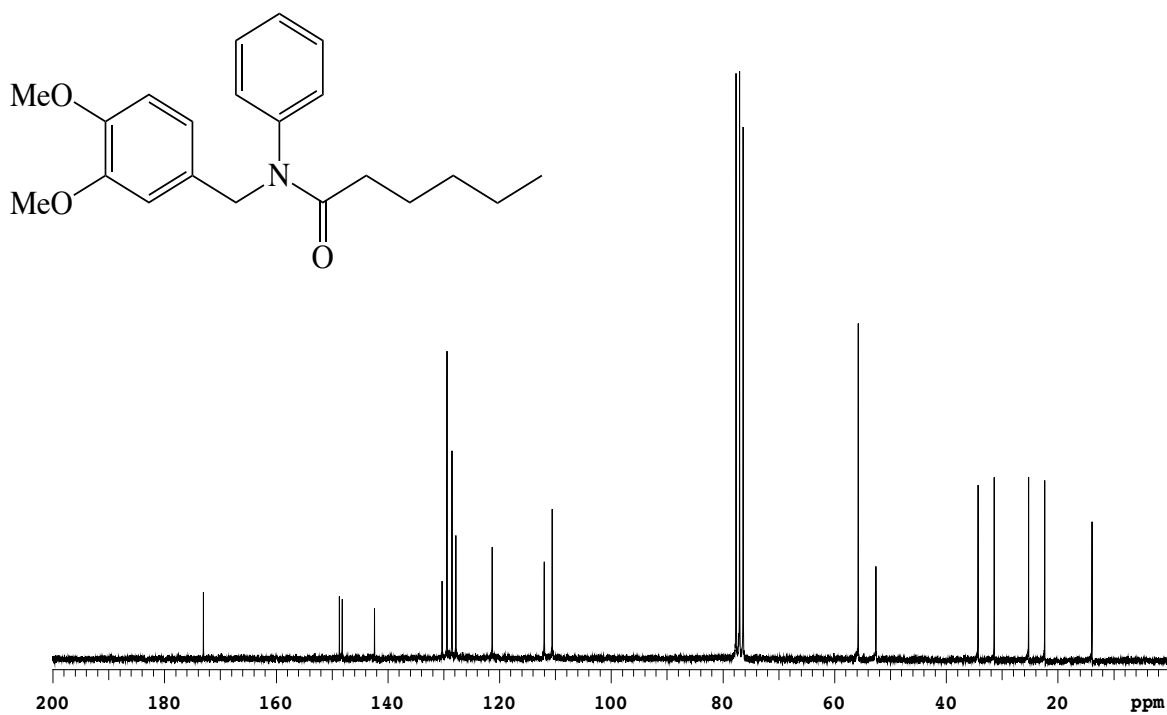
Spectrum 3: ¹H NMR (200 MHz, CDCl₃) **9**



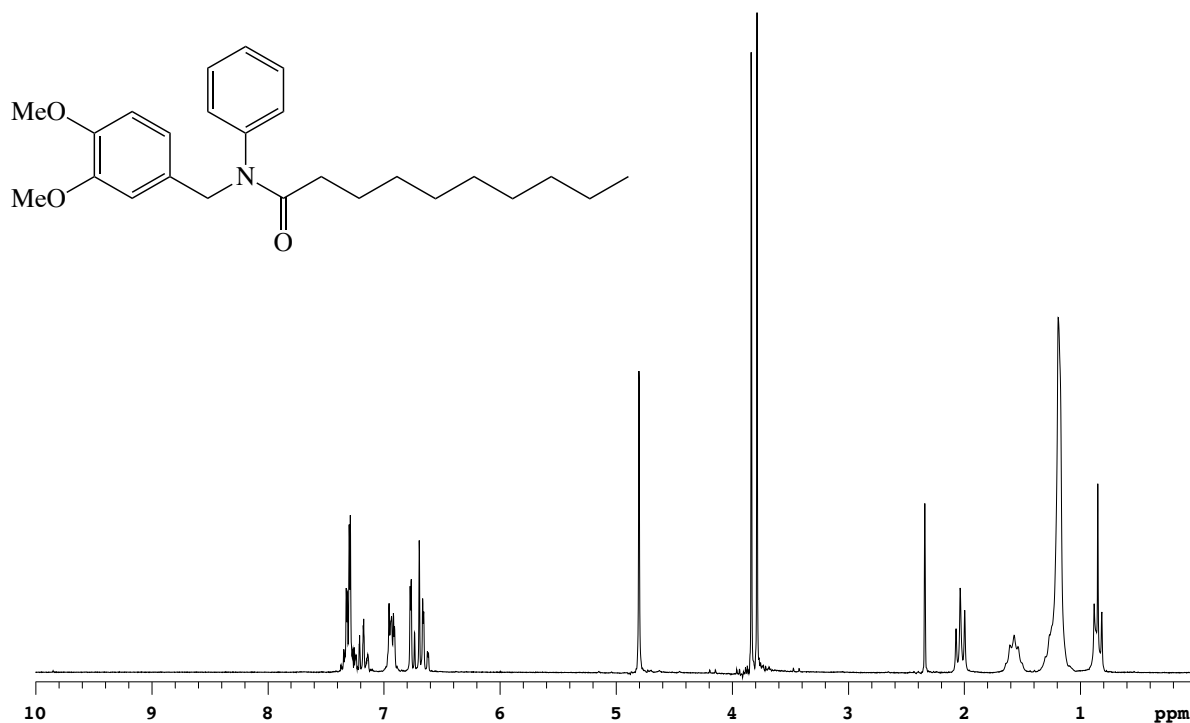
Spectrum 4: ¹H NMR (200 MHz, CDCl₃) **10**



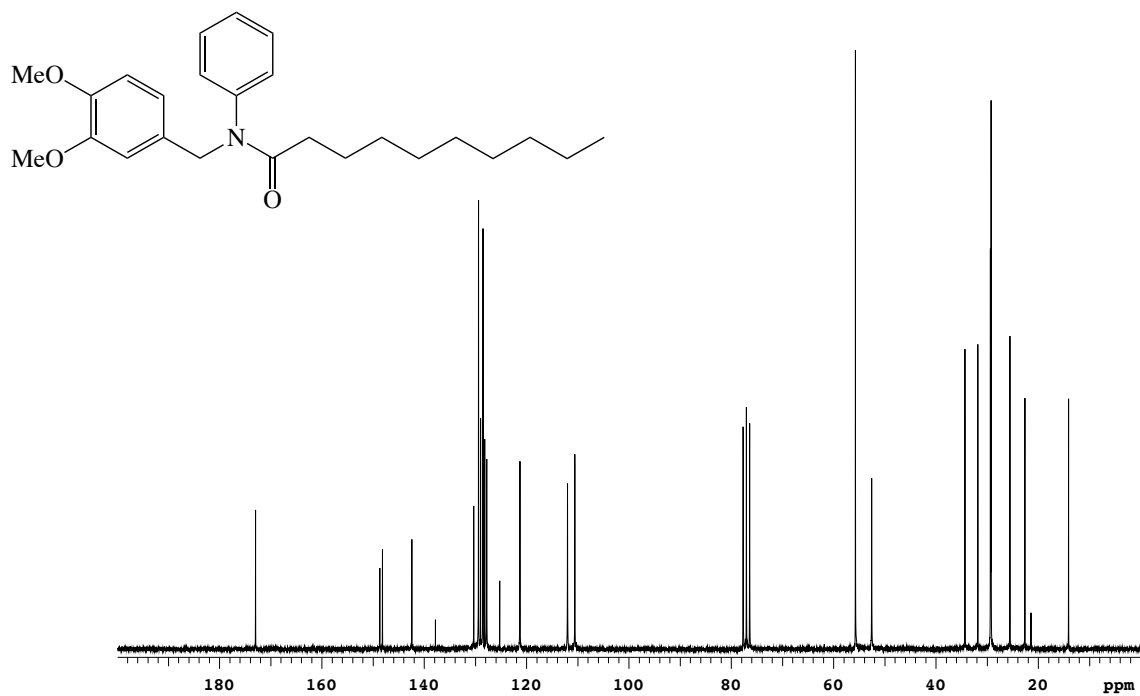
Spectrum 5: ¹H NMR (200 MHz, CDCl₃) **12**



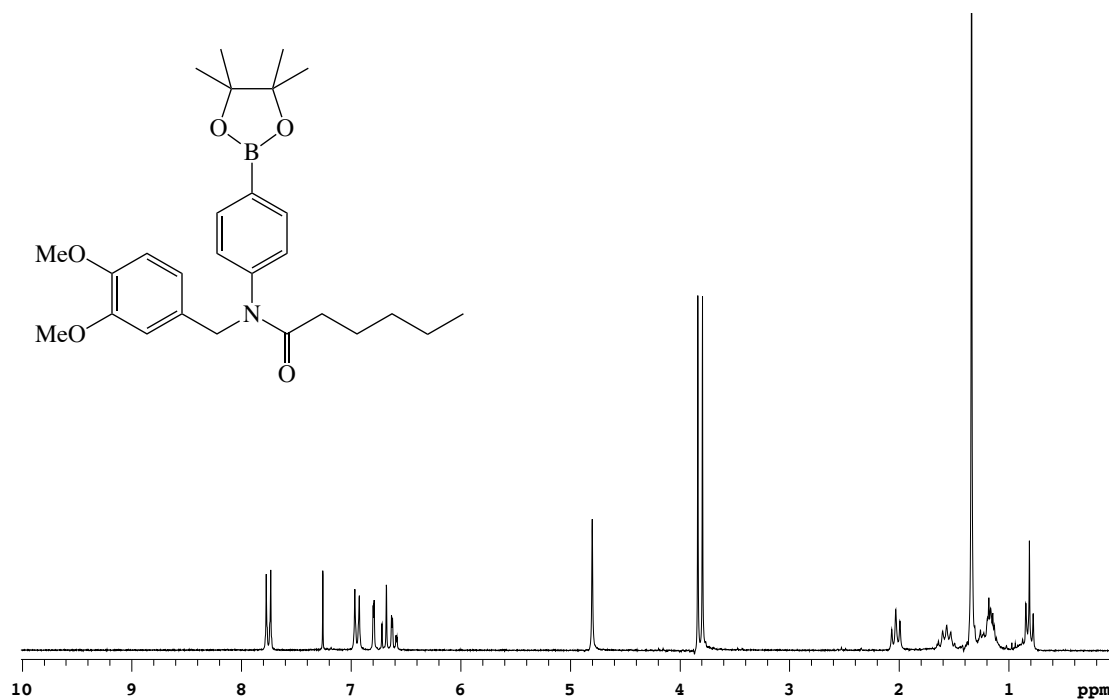
Spectrum 6: ¹³C{¹H} NMR (50.3 MHz, CDCl₃) **12**



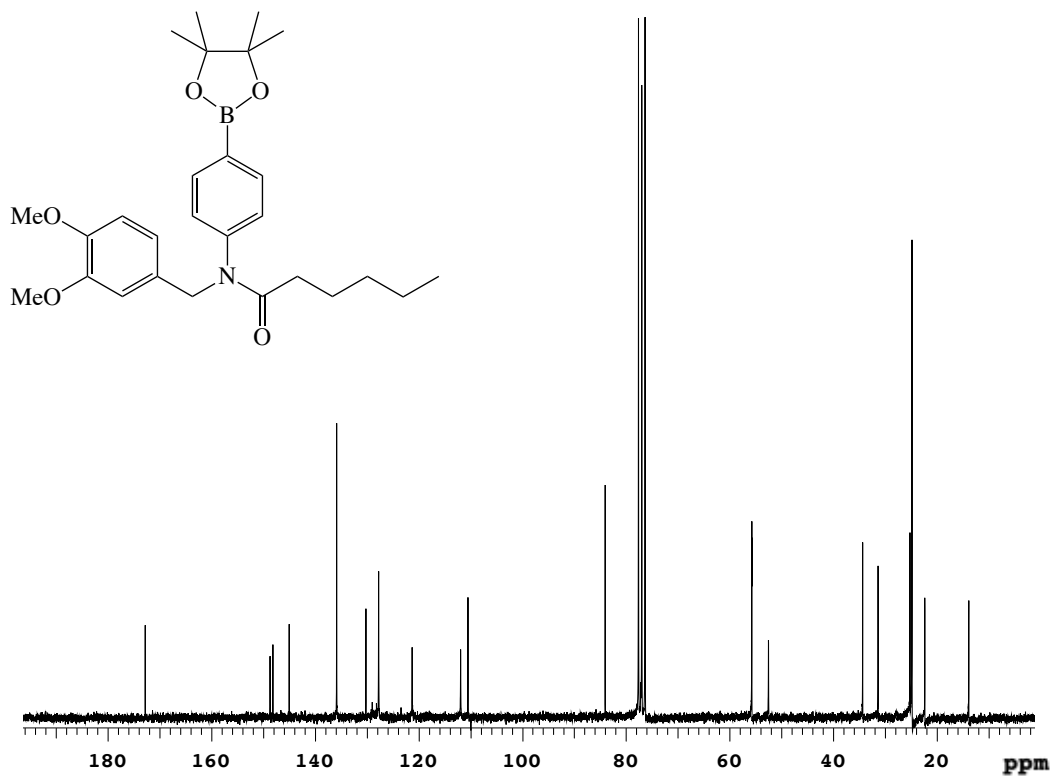
Spectrum 7: ¹H NMR (200 MHz, CDCl₃) **13**



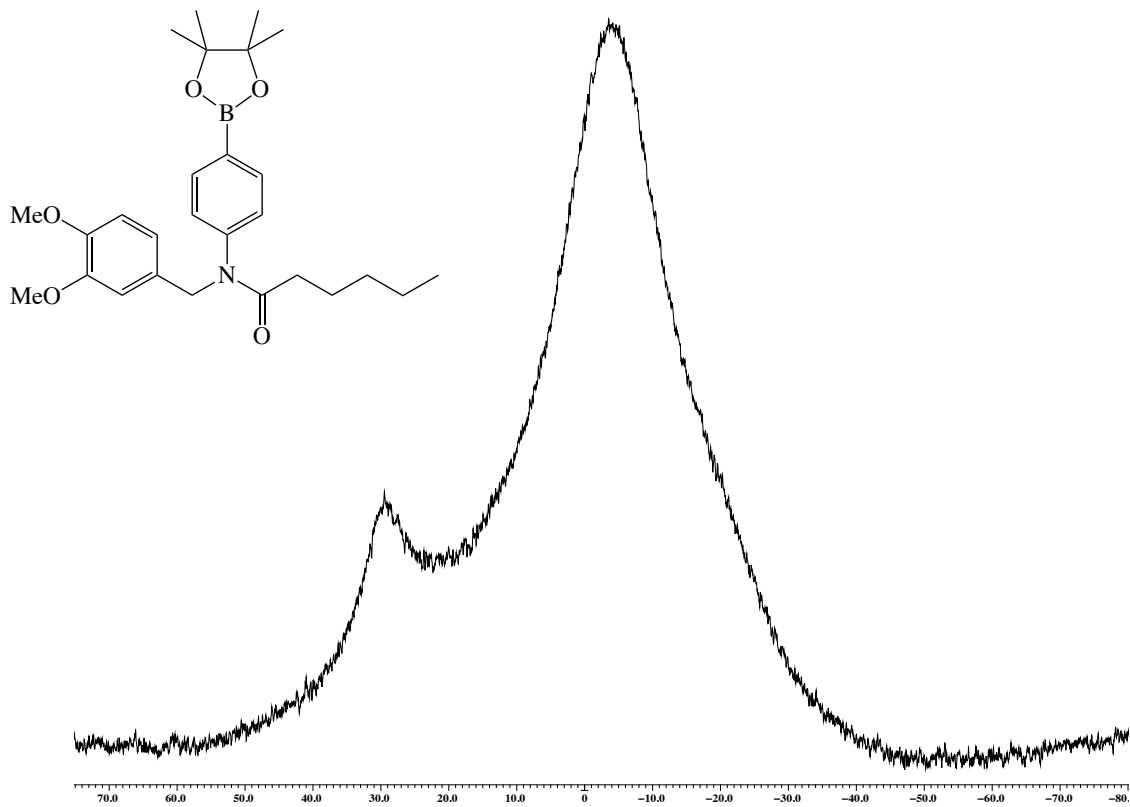
Spectrum 8: ¹³C {¹H} NMR (50.3 MHz, CDCl₃) **13**



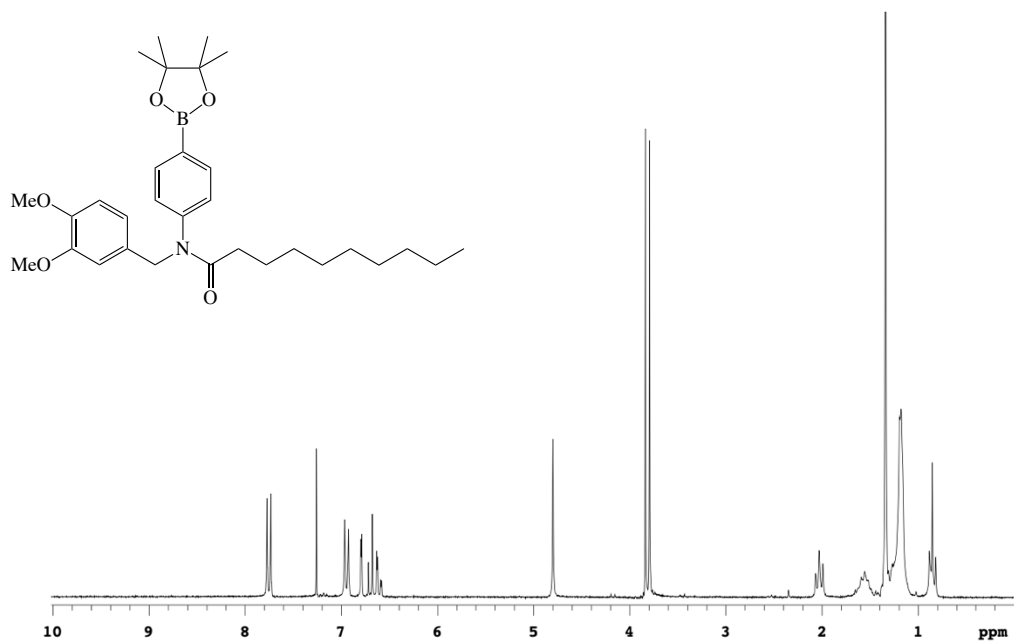
Spectrum 9: $^1\text{H NMR}$ (200 MHz, CDCl_3) **14**



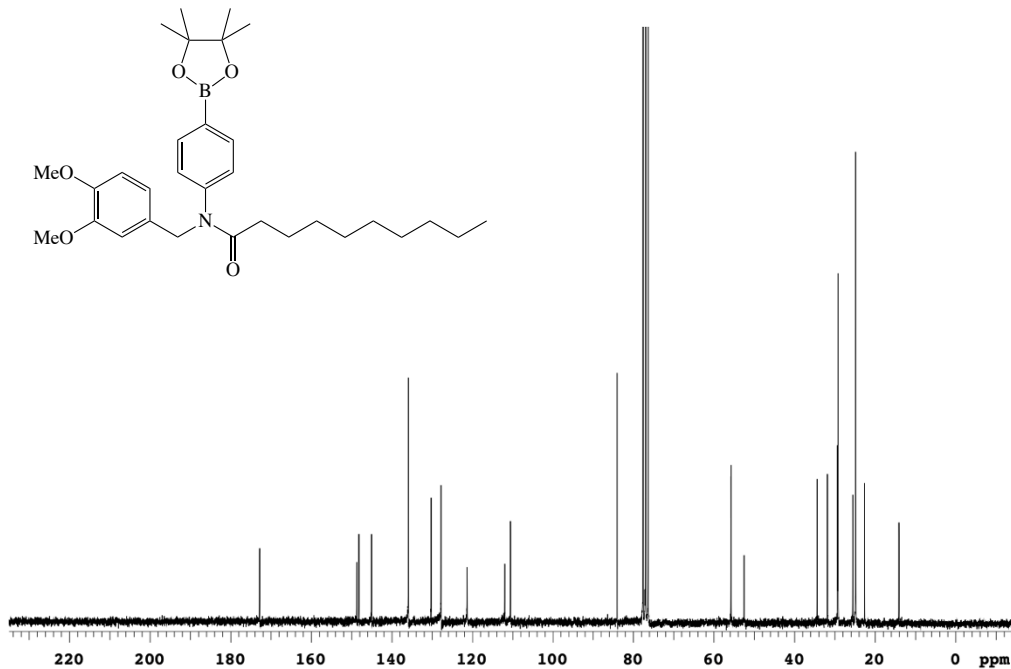
Spectrum 10: $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CDCl_3) **14**



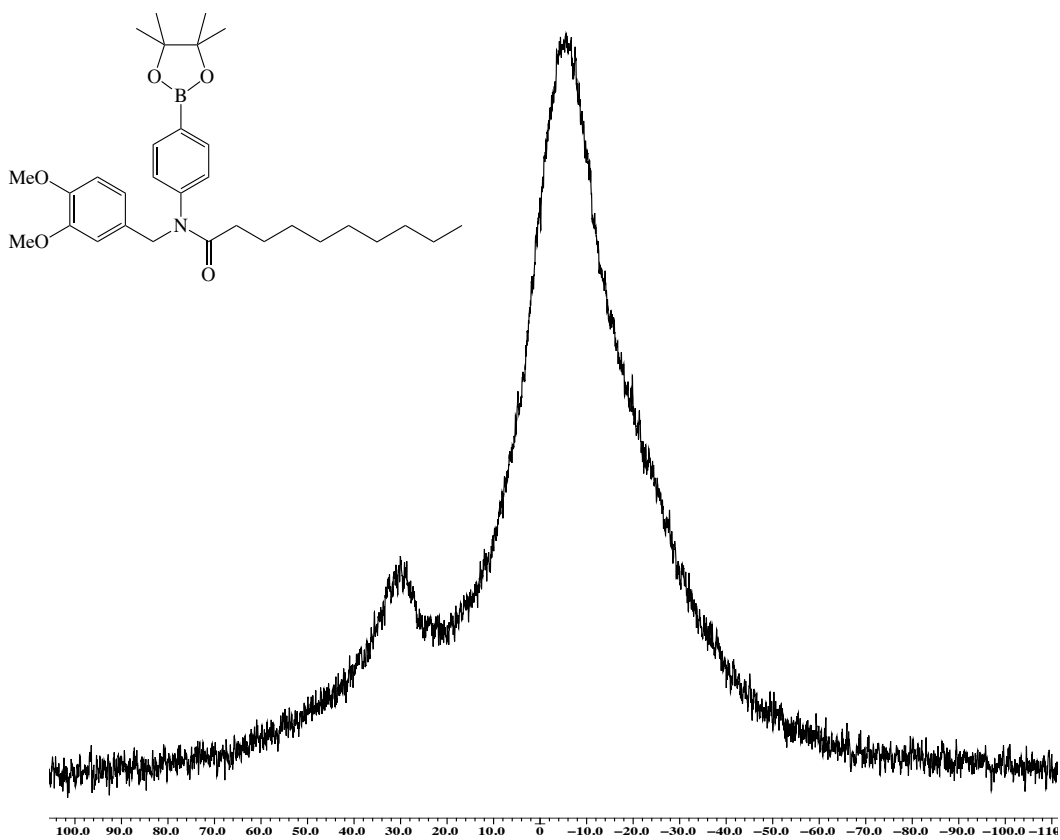
Spectrum 11: ^{11}B NMR (128 MHz, CDCl_3) **14**



Spectrum 12: ^1H NMR (200 MHz, CDCl_3) **15**



Spectrum 13: $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, CDCl_3) **15**



Spectrum 14: ^{11}B NMR (128 MHz, CDCl_3) **15**

B. Curriculum Vitae

Maxim F. Landry

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124 Erinvale Dr.
Moncton, NB
E1A 6T4

Education

Mount Allison University, Class of 2019, Sackville NB
Bachelor of Science in Chemistry with Honours

Research Experience

Organic and inorganic synthesis and characterization October 2016 - April 2019

- Conducted experimental research under the supervision of Dr. Stephen Westcott.
- Synthesized novel Schiff base compounds and their analogous amino alcohols from salicylaldehyde derivatives and sulfachloropyridazine.
- Synthesized novel boron-containing capsaicin derivatives as potential anti-cancer agents.

Experimental Techniques

NMR, FT-IR (ATR), GC/MS, GC/FID, HPLC, UV/Vis, FAAS

- Trained in experimental procedure and data analysis.

Synthetic techniques

- Experienced in carrying out microscale reactions and microwave reactions, as well as working under inert atmosphere (MBRAUN Glovebox). Comfortable working with Schlenk lines and using distillation techniques.

Conference Abstracts and Presentations

‘Hot Peppers and Boron: Analogues of Capsaicin as Potential Anti-Cancer Agents’ **M. F. Landry**, C. M. Vogels, S. A. Westcott. 10th annual NBHRF New Brunswick Health Research Conference, Fredericton, NB, Canada, November 2018.

‘Schiff bases, amino alcohols and boron salts derived from salicylaldehyde derivatives and sulfachloropyridazine’ M. F. Landry, M. C. Murphy, C. M. Vogels, S. A. Westcott. 43rd annual Science Atlantic/CIC Student Chemistry Conference ChemCon, Halifax, NS, Canada, June 2018.

*Underlined names indicate presenters

Employment

Teaching Assistant - Mount Allison University September 2017 - April 2019

- Assisted students with experiments carried out in first year introductory chemistry, second year organic chemistry and third year physical chemistry laboratories.

Peer Mentor - Mount Allison University September 2017 - November 2017

- Met weekly with a group of first year science students to help them develop strong work habits and study skills as a mentor for Mount Allison’s Science Success Program.

Academic Mentor - Mount Allison University August 2016 - April 2017

- Assisted students with academic matters, scheduled study sessions, and organized workshops.

Park Attendant - Magic Mountain Waterpark, Moncton NB June 2015 - August 2016

- Worked in various areas of customer service.
- Named park attendant “Rookie of the Year”. September 2015
- Promoted to “Team Captain”, a supervisory position. May 2016 - August 2016

Auto Detailer - Taylor Ford Lincoln, Moncton NB July 2013 - August 2013

- Responsible for the complete cleaning of customer vehicles.

Volunteer Experience

Best Buddies - Mount Allison University September 2016 - March 2019

- Participated in biweekly activities with teenagers and adults with intellectual and developmental disabilities.
- Served as parent coordinator. September 2017 - March 2019
- Initiated, developed, and implemented the first Best Buddies summer program at Mount Allison University. May - August 2018

S.M.I.L.E. - Mount Allison University September 2016 - March 2019

- Paired with children with various intellectual and developmental disabilities as a member of Mount Allison’s chapter of Sensory Motor Instructional Leadership Experience.

- Ronald McDonald Family Room - Moncton Hospital** August 2016 - February 2017
- Performed various chores to make guests comfortable and provided tours of the family room to new families.

Extracurricular Activities

Business of Science Workshop - Mount Allison University September 2018

- Took part in a three day workshop that primarily involved working in a group to develop a business pitch for a scientific innovation.
- Awarded 2nd place in the pitch competition by a panel of judges.

Chemistry and Biochemistry Society - Mount Allison University May 2018 - April 2019

- Vice President of Chemistry

MASSIE Conversation Partner - Mount Allison University May 2018 - August 2018

- Responsible for meeting weekly with a student from the Mount Allison Semester Studies in English program as a means of facilitating English speaking skills development.

Hiring Committee - Mount Allison University March 2018 - May 2018

- Served as a student representative on a selection committee for a tenure track position in the department of chemistry and biochemistry.

First Year Physics Representative - Mount Allison University September 2015 - April 2016

- Attended departmental meetings as a representative for first year physics students.

Physician Shadowing January 2015 - June 2015

- Shadowed physicians and other health professionals across numerous specialties at the Moncton Hospital.

Awards and Honours

Harold E. Bigelow Undergraduate Scholarship in Chemistry (\$1,325)	September 2018 - May 2019
R.A. Jodrey Scholarship (\$12,000)	September 2015 - May 2019
Dean's List	2015-2016, 2016-2017, 2017-2018
New Brunswick Health Research Foundation Studentship (\$6,592)	May 2018 - August 2018
TA of the month	March 2018, January 2019
Carnegie Independent Student Research Fund (\$7,000)	May 2017 - August 2017

References

- Dr. Stephen Westcott, Professor, Tier 1 Canada Research Chair, Mount Allison University, Sackville NB, swestcott@mta.ca
- Dr. Glen Briand, Professor, Mount Allison University, Sackville NB, gbriand@mta.ca
- Dr. Vicki Meli, Associate Professor, Mount Allison University, Sackville NB, vmeli@mta.ca