12-20-2009

Synthesis of Amphibian Alkaloids and Synthesis and Affinity of Novel Cannabinoid Receptor Ligands

April R. Noble

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Synthesis of Amphibian Alkaloids

and

Synthesis and Affinity of Novel Cannabinoid Receptor Ligands

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
Chemistry

by

April Rennee Noble

B.S. Xavier University of Louisiana, 2004

December 2009
To my family and friends for all their love and support

Father: Oswell Noble Jr.

Mother: Joyce Noble

Husband: Patrick Brooks Jr.
Acknowledgements

I would like to express my appreciation and gratitude to my research advisor, Professor Mark L. Trudell for his support, encouragement and guidance throughout my studies and research. I would also like to thank my committee members, Professor Richard Cole, Professor Branko Jursic, Professor Edwin D. Stevens, and Professor Guijun Wang. I would like to acknowledge Dr. Edwin D. Stevens and Steven Fournet for the X-ray crystal structures, Dr. Richard Cole, Nazim Boutaghou, and Syeda Quadri for the Mass Spectometry data, and Corinne Gibb and Dr. Simin Liu for all the help with the NMR.

Additionally, I wish to thank Dr. Sari Izenwasser of the University of Miami Miller School of Medicine for the biological data provided in this dissertation.

I wish to express my appreciation to my group members: Dr. Lei Miao, Dr. Hong Shu, Dr. Murali Reddy, Xiaobo Gu, Andrea Forsyth, and Abha Verma and friends for all their support and help throughout my time at the University of New Orleans.

The National Institute of Drug Abuse and the University of New Orleans are gratefully acknowledged for financial support of this work.
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ABSTRACT

Amphibian alkaloids are attractive targets for synthesis due to their biological activity. An important class of amphibian alkaloids is the 2,5-disubstituted pyrrolidine-based family of compounds. There are many synthetic approaches for the preparation of the trans-2,5-disubstituted pyrrolidines, but methods for the construction of the cis-2,5-pyrrolidines are limited. Therefore, it was desired to develop an enantioselective approach for the preparation of cis-2,5-disubsituted pyrrolidines. (+)-Tropin-2-one derived from cocaine was used as starting material to exploit the inherent stereochemistry for construction of the cis-pyrrolidine ring. This permitted the unequivocal assignment of the absolute configuration of the target pyrrolidine. The structurally simple pyrrolidine alkaloid, 225H, was selected as a target to develop a general synthetic approach. The enantioselective synthesis of 225H was achieved in nine steps and good overall yield.

The search for potent cannabinoid receptor partial agonist ligands as potential marijuana addiction therapeutic agents has led to an investigation of the synthesis of diaryl ether hybrid analogues of BAY 59-3074. A series of 2-(3-alkyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitriles, 3-(2-cyano-3-(trifluoromethyl)phenoxy)phenylalkanoates, and (3-(benzyloxy)phenoxy)-6-(trifluoromethyl)benzonitriles were synthesized and evaluated in vitro for CB1 affinity. The olivetol diaryl ether analogue was the most potent ligand of the alkyl series, but the diaryl ester analogues exhibited modest affinity for CB1 receptors. The most potent compound of the series was the 2-(3-(benzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile.
Keywords: amphibian alkaloids, enantioselective synthesis, pyrrolidine, cannabinoid receptor, marijuana.
CHAPTER 1

General Strategies for the Construction of Enatiopure Pyrrolidine based Alkaloids. Total Synthesis of (+)-Pyrrolidine 225H

1.1. Abstract

Amphibian alkaloids are attractive targets for synthesis due to their biological activity. An important class of amphibian alkaloids is the 2,5-disubstituted pyrrolidine-based family of compounds. There are many synthetic approaches for the preparation of the trans-2,5-disubstituted pyrrolidines, but methods for the construction of the cis-2,5-pyrrolidines are limited. Therefore, it was desired to develop an enantioselective approach for the preparation of cis-2,5-disubstituted pyrrolidines. (+)-Tropin-2-one derived from cocaine was used as starting material to exploit the inherent stereochemistry for construction of the cis-pyrrolidine ring. This permitted the unequivocal assignment of the absolute configuration of the target pyrrolidine. The structurally simple pyrrolidine alkaloid, 225H, was selected as a target to develop a general synthetic approach. The enantioselective synthesis of 225H was achieved in nine steps and good overall yield.
1.2. Introduction

1.2.1. Amphibians

There are eight genera of the family Dendrobatid: *Dendrobates*, *Phyllobates*, *Epidobates*, *Aromobates*, *Minyobates*, *Manophryne*, *Nephelobates*, and *Colosthetus*. Members of the genus *Dendrobates* are also known as the poison dart or poison arrow frog, which were named by John Daly and Bernard Witkop. The poison dart frog is native to southern central and northern South America. These amphibians are brightly colored, which is an adaptation for these animals. There are a variety of amphibian species that have glandular secretions on the skin, which aid in the control of microorganism growth, drying of the skin, and the discouragement of predators. The poison dart frogs do not have a mechanism to deliver the poison, but the tissues of these animals are toxic in which these toxins can vary in molecular weight and are complex in their organic nature. Some of the Dendrobatid frogs secrete an extremely toxic poison, Batrachotoxin. However, the only frogs that produce the super deadly batrachotoxin are the frogs of genus *Phyllobates*, in which the *Phyllobates terribilis* is the most toxic. The most common use of this toxin is by the Indians of western Colombia for poisoning blowgun darts for use in hunting. Poison darts are prepared by accumulating the poison from the frog’s skin and dipping the dart tips in the toxin, preserving its destructive power for up to a year.
1.2.2. Pyrrolidine Amphibian Alkaloids

A variety of cyclic alkaloids have been characterized from amphibian skin, mainly from neotropical dendrobatid frogs. The dendrobatid frog does not produce the alkaloid itself, but the frog gathers the alkaloid through its diet. Ants are a major prey for these frogs, particularly frogs of genus Dendrobates. However, when alkaloid-dusted fruit flies were fed to dendrobatid frogs the pyrrolidines accumulated poorly into the skin. This suggest that the mechanism by which amphibians accumulate these alkaloids is complex and not well understood. The pyrrolidines of interest are rare and minimal in quantity in the dendrobatid frog skin extracts. The α,α´-disubstituted pyrrolidines are well-known venom constituents in myrmicine ants of the genus Monomorium. The 2,5-disubstituted pyrrolidines of the myrmicine ants serve as repellants for other ants and have insecticidal activity. The 2,5-disubstituted pyrrolidines of these ant venoms and frog skin extracts have become attractive synthetic targets.

Figure 1.1: Amphibian alkaloid structures that contain cis-pyrrolidine subunit

The cis-2,5-disubstituted pyrrolidine ring system is the foundation of several classes of amphibian alkaloids and exhibits wide-ranging biological activities (Figure 1.1). The 2,5-disubstituted pyrrolidine is also a pertinent alkaloid of non-competitive blockers of the nicotinic
acetylcholine receptor in addition to other monocyclic and bicyclic alkaloids (Figure 1.1). However, the stereochemistry and absolute configurations have not been determined for many of these alkaloids. As yet, the structure of only one pyrrolidine 197B isolated from a dendrobatid frog has been firmly established.\(^4\)

**Figure 1.2:** Structure of (+)- and (-)-197B

![Structure of (+)- and (-)-197B](image)

In addition, 197B is the only pyrrolidine that occurs as a major alkaloid, but was determined to be the *trans*-isomer in ant venom. Both the *cis*-225H and *trans*-225H have been synthesized, in racemic form, the *trans*-225H is more common in ants and led to the development of various synthetic routes to obtain this structure, while the *cis*-225H has received little attention.\(^5\)

**Figure 1.3:** Structure of *cis* and *trans*-225H

![Structure of *cis* and *trans*-225H](image)

Due to the limited sources and non-practical methods for obtaining the *cis*-225H, a general enantioselective synthetic route was desired for the preparation of natural and non-
natural pyrrolidine alkaloids in order to obtain structural, stereochemical and biological activity data.

1.2.3. **Nicotinic Acetylcholine Receptors (nAChRs)**

The nicotinic acetylcholine receptor has become the target in understanding various health consequences involved in smoking and its mechanisms of action. Nicotinic acetylcholine receptors are cholinergic receptors that form ionotropic receptors. Similar to other types of ion channels the opening of the nAChR ion channel is triggered by the binding of acetylcholine. Acetylcholine is formed from choline and formed by enzymatic reaction with coenzyme A. This neurotransmitter plays a role in memory and is involved in Alzheimer’s Disease. Nicotinic receptor ion channels are also opened by nicotine. These nicotinic receptors are the most studied ionotropic receptors and are present throughout the tissues in the body. Nicotinic receptors are made up of five subunits around the central pore. The acetylcholine binding site is on the outside of the α subunit near the N terminus. As stated earlier amphibian alkaloids engage as noncompetitive blockers of nicotinic acetylcholine receptor ion channels. These amphibian alkaloids block channel conductance and accelerate desensitization or inactivation of the nicotinic acetylcholine receptor channel.

1.2.4. **Therapeutic Targets**

These pyrrolidines are attractive targets in the development of therapeutics that are aimed at disease states and disorders mediated by nicotinic acetylcholine receptor ion channels. The
therapeutic targets of interest include Parkinson’s disease, Alzheimer’s disease, acute and chronic pain, Tourette’s syndrome, anxiety disorders, depression, and smoking cessation. Likewise, subtype selective regulation of neurotransmitter release creates the possibility to develop selective nAChR agents that would target specific neurotransmitters or systems involved in neurological and psychiatric disease. \(^5\)

Over the past several years, a variety of research groups have focused on the development of selective nicotinic agonists. Nicotinic agonists could be useful in the treatment of a variety of neurological disorders including Alzheimer's disease, Parkinson's disease and chronic pain. Epibatidine (4) is a nicotinic agonist isolated from the skin of an Ecuadorian frog *Epipedobates tricolor* that displays potent analgesic properties and is 200 more times potent than morphine.\(^1,9\)

**Figure 1.4: Nicotinic Agonists**

![Nicotinic Agonists](image)

SIB-1508 (altinicline) 5 is another nicotinic agonist with potential utility in the treatment of Parkinson's disease.\(^9,10\)
1.2.4.1. Alzheimer’s Disease

Alzheimer’s disease is the sixth-leading cause of death in the United States.\textsuperscript{11} According to the Alzheimer’s Association, there are approximately 5.3 million people living with this disease.\textsuperscript{11} There are a variety of possible causes of Alzheimer’s Disease such as the stress stemming from catastrophic life events. It is the most common form of dementia and is also a degenerative and fatal brain disorder without a cure. Alzheimer’s disease accounts for the highest percentage of dementia cases. Dementia describes the loss of any recent memory and/or other intellectual abilities. The symptoms of Alzheimer’s disease includes loss of intellectual ability, impaired thinking, trouble defining words and concepts, language disturbances (aphasia), motor activity difficulty (apraxia), failure in object recognition despite intact sensory and/or motor brain functions (agnosia), and personality alteration and/or trait accentuation prior to illness (premorbid traits).\textsuperscript{7,12-14}

There are four identifiable phases of Alzheimer’s Disease: onset, loss, disability and victim apathetic.\textsuperscript{7} With the onset of Alzheimer’s Disease, an individual may avoid what is unfamiliar and prefer familiar faces and places. In addition, an individual may experience less drive, slower reaction time, and difficulty in learning new things.\textsuperscript{7} The second phase is the experience of more loses of familiarity. An individual may be unable to execute familiar tasks and have difficulty with common concepts.\textsuperscript{7} During this phase, an individual may start to require supervision. The third phase is disability in which an individual may start getting disoriented. At this point, recognition of familiar people and/or places and the track of time and place become unrecognizable. The final phase is victim apathetic. During this final phase, an individual is now unable to find their way around familiar space and may begin wandering to
find what seems to be familiar. Nonetheless, the individual may now need aid with daily life as memory loss begins to be gradual. There are warning signs such as problems remembering particular things and events and/or a slowed thinking process. These are linked to major changes in the way the mind operates, which is not a normal process in aging and could in fact be signaling that the brain cells are failing.

The brain has over 100 billion nerve cells in which each nerve cell communicates with many other nerve cells to form networks to carry out particular functions. Some of these nerve cells have certain functions involved in thought, sight, hearing, learning and memory. However, in Alzheimer’s disease, there are huge numbers of brain cells that die, which are consistent with a failing brain. There are three characteristics of brain changes or a failing brain: neurofibrillary tangles, neuritic plaques, and granulovacular degeneration. The neurofibrillary tangles are an accumulation of abnormal fibers (twisted tau fibers) concentrated in the cell’s cytoplasm. These tangles occur densely in the hippocampus, which is the “seat of emotions” and the location of recent and/or short term memory. Neuritic plaques build up between the nerve cells and contain beta-amyloid deposits. Even though it is possible to develop these plaques and tangles as one ages an Alzheimer’s brain will develop them more severely. Granulovacular degeneration occurs in the interior of the cell in which the cell fills with vacuoles consisting of fluid and granular material. Increases in granulovacular degeneration decreases mental function. Two abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells.

As stated earlier, there are no effective treatments available for Alzheimer’s Disease. The treatments that are available are based on treating certain symptoms of the disease such as cognitive, behavioral and psychiatric symptoms. The memory, language and other thought
processes are cognitive symptoms. The way an individual may feel or acts are both behavioral and psychiatric symptoms. There are a host of medications for treatment of the cognitive, behavioral and psychiatric symptoms involved in Alzheimer’s Disease. The cognitive symptoms can be treated with different chemicals involved in carrying messages between the brain’s nerve cells.\textsuperscript{11-13} For example, cholinesterase inhibitors prevent the breakdown of acetylcholine which supports the communication among nerve cells by keeping the acetylcholine levels high. Examples of cholinesterase inhibitors that are commonly prescribed are Donepezil, Rivastigmine, and Galantamine. The behavioral and psychiatric symptoms are treated with antidepressants (Prozac and Zoloft), antipsychotics (clozapine and Abilify), and anxiolytics (Ativan).\textsuperscript{11-13}

1.2.4.2. Parkinson’s Disease

Both men and women equally are affected by Parkinson’s disease. According to the National Parkinson Foundation, 60,000 new cases are diagnosed a year joining the 1.5 million Americans currently living with Parkinson’s disease.\textsuperscript{15} Parkinson’s Disease is a gradual and chronic neurodegenerative disease of the central nervous system that impairs speech, motor skills and a host of other functions. It occurs when neurons in the substantia nigra of the brain die or become impaired.\textsuperscript{16} The cells in the substantia nigra produce dopamine, which aids in coordination of muscles and movement.\textsuperscript{17} However, when a significant amount of the dopamine-producing cells are impaired, the symptoms of Parkinson's disease can appear. The movement disorders seen in Parkinson’s disease are due to the loss of dopamine production in the brain. The symptoms and/or key signs are characterized the stiffness of muscles (rigidity),
slowness and poverty of movement (bradykinesia), balance difficulty, and involuntary shaking movements (tremor). Other signs of Parkinson’s disease include altered facial expressions, posture, irregular handwriting, and shuffled walk.

In the past, the causation of the onset of Parkinson’s disease was unknown. However, it is believed to be caused by genetic abnormalities, toxins, or head trauma. There is no diagnosis to detect Parkinson’s disease as well as no treatment available to slow or stop the progression of Parkinson’s disease. Nonetheless, there are medications available to ease the symptoms. The symptoms of Parkinson’s disease are caused by a lack of dopamine. Therefore, the medications used attempt to mimic dopamine to aid in the improvement of the common symptoms associated with Parkinson’s disease.

Treatments for Parkinson’s disease are approached by exploring neuroprotective and dopamine-releasing properties of the nicotinic acetylcholine receptor. There are a variety of commonly prescribed medications for the treatment of Parkinson’s disease. Levodopa (L-dopa) is modified by brain enzymes to produce dopamine to aid in the reduction of symptoms and remains the most effective treatment for many Parkinsonian symptoms. L-dopa is combined with an enzyme inhibitor to prevent the breakdown by blood enzymes. Other treatments include dopamine agonists, which do not have to be modified by brain enzymes, but are likely to cause other side effects than L-dopa. These dopamine agonists include amantadine, anticholinergic medications, and selegiline, which alter the movement control center in the brain without stimulating the dopamine receptors. Amandtadine was initially studied as an antiviral medication, but was found to reduce symptoms of fatigue, tremor, and bradykinesia better used for early symptomatic stages. Anticholinergic medications reduce tremor or rigidity, but are used in elderly patients or those with cognitive problems. Selegiline inhibits monoamine
oxidase B, which breaks down dopamine and may aid in the improvement of Parkinson’s Disease, but there is no firm evidence to support this claim to date.\textsuperscript{15-19}

1.2.4.3. Smoking Cessation

The nicotinic acetylcholine receptor has become the target in understanding various health consequences involved in smoking and its mechanisms of action. Nicotine (3) is an addictive drug and accounts for more deaths than cocaine and other hard drugs. The combination of nicotine (3) and other components are carcinogenic and can lead to a host of cancers.\textsuperscript{20} Approximately 10\% of US lung cancers are attributable to radon, which is recognized as the second leading cause of lung cancer. Tobacco smoke in combination with radon exposure has a synergistic effect.\textsuperscript{20}

Nicotine (3) stimulates acetylcholine receptors and increases the activity of dopaminergic neurons of the mesolimbic system.\textsuperscript{21} When acetylcholine (Ach) is released by an acetylcholinergic terminal button, the receptors open briefly and permit calcium ions to enter. The calcium ions stimulate neurotransmitter release. The enzyme AChE destroys Ach and the receptors close again or enter a desensitized state during which they bind with but not react to AChE.\textsuperscript{21} Therefore, while smoking a persons’ nicotine level rises slowly in the brain and stays steady for a prolonged period because it isn’t destroyed by AChE. The nicotinic receptors are activated but sustained at low levels and converts many of the nicotinic receptors to a densensitized state.\textsuperscript{21} Conceivably, nicotine (3) has dual effects of activation and densensitization.
Cessation of smoking after long term use causes withdrawal symptoms, including anxiety, restlessness, insomnia and inability to concentrate. These symptoms increase the likelihood of relapse but don’t explain why the addiction occurs. The root of withdrawal symptoms is the lack of nicotine (3). Therefore, nicotine replacement is a form of treatment which is considered to alleviate withdrawal symptoms leading to a higher success rate of cessation. Addiction can be considered the repetitive administration of drugs to produce positive reinforcement. Desensitization and tolerance development is a result of repetitive exposure due to adaptive changes in the organism.

Nicotine (3) is the main active ingredient in tobacco. It is an alkaloid named from Nicotiana tabacum and is a cholinergic agonist that mimics the action of acetylcholine. Lobeline (6) is an alkaloid that is found in Indian tobacco that aids in drug addiction and is currently in the pilot phase III clinical trials. Lobeline (6) acts as a mixed agonist-antagonist at the nicotinic acetylcholine receptor.

**Figure 1.5:** Smoking Cessation Aid
1.3. Previous Synthetic Routes

A survey of the literature revealed that the most successful approach for the synthesis of cis-2,5-disubstituted pyrrolidines is to employ amino acids as starting materials. There are many advantages to starting with a natural amino acid due to the versatility of the starting material. Compounds of this nature are commercially available, and inexpensive. An example of a synthesis using glutamic acid as a starting material proceeds through a β-enaminoester intermediate is shown in Scheme 1.1.

Scheme 1.1: Enamine reduction to obtain cis-pyrrolidine

The Moloney group performed enamine reduction and subsequent regioselective and diastereoselective alkylations to construct cis-2,5-disubstituted pyrrolidines.\textsuperscript{5,23} The starting material for the synthesis is pyroglutamic acid and the lactam carbonyl is manipulated through the Eschenmoser contraction by the condensation of a lactam with an α-bromoester. The enaminone products from the Eschenmoser contraction are highly substrate and reagent dependent and for β-enamino (mono) esters cis-stereocontrol can be achieved with catalytic
hydrogenation.\textsuperscript{5,23} Benzoylation of the amine 8 nitrogen gave a separable mixture of \textit{cis} and \textit{trans} products, but there is the possibility of equilibration during acetylation, which may complicate future pyrrolidine synthesis. Therefore, the compound was of limited synthetic utility.

The Carretero group performed catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides with vinyl sulfones to construct \textit{cis}-2,5-pyrrolidines.\textsuperscript{24}

\textbf{Scheme 1.2:} Catalytic Enantioselection to obtain \textit{cis}-pyrrolidines

The outlined procedure uses metal catalyzed asymmetric 1,3-cycloaddition to form the \textit{cis}-pyrrolidine. The use of the Cu\textsuperscript{I}-Taniaphos catalyst system was the most enantioselective. Other catalyst systems included Zn(II), Ag(I), Cu(I), Cu(II) complexes with chiral N,N-, P,P-, P,N-, P,S- bidendate ligands.\textsuperscript{24-23} Vinyl sulfones were employed due to the highly electron deficient nature of the carbon-carbon double bond (Figure 1.6).
The electronic character at the aryl moieties was evaluated. The aryl vinyl sulfones (e.g., 14a) didn’t give enantioselectivity enhancement, but the thiophenyl vinyl sulfone 14b showed similar asymmetric induction and the 2-pyridyl sulfone 14c didn’t give an enhancement of enantioselectivity whereas the N,N-dimethylamino 14d gave no reaction. The dipole components were also evaluated and electron rich arenes, electron poor arenes, and ortho, meta, para substitutions were employed. The reactions produced good yields and were exo-stereoselective, but the bulkier imines were less enantioselective. Therefore, this procedure is limited to substrates that produce the desired enantioselectivity.

The initial approach to the synthesis of racemic pyrrolidines was based on the reductive amination of 1,4-diketones widely used by Jones et al. as shown in Scheme 1.3.
**Scheme 1.3:** Reductive amination of 1,4-diketones

The 1,4-diketone was prepared from alcohol 15 by buffered pyridinium chlorochromate oxidation to give the unstable enone 16. Enone 16 was manipulated through the Stetter reaction when treated with the appropriate aldehyde, triethylamine, and a thiazolium salt catalyst. The condensation of enone 16 and the aldehyde gave the 1,4-diketone 17. Treatment of the 1,4-diketone 17 with ammonium acetate, NaBH₃CN and KOH followed by subsequent reduction with sodium borohydride of the pyrroline produced a 1:1 ratio of the cis to trans pyrrolidines 1 and 18, respectively. The *trans*-pyrrolidine 225H has been isolated from both the *Solenopsis molesta* and *Solenopsis texanas* ants and more recently the *cis*-isomer has been detected in trace amounts in the amphibian skin extracts. Even though, the physical and spectral properties of the pyrrolidine 225H were identical to the authentic sample, the compound still has not been fully characterized nor has the absolute configuration been determined. An enantiopure total synthesis would allow correlation of the configuration with the specific optical rotation.

The Trudell group has synthesized two enantiopure *cis*-2,5-pyrrolidine building blocks prepared from cocaine 19 (Scheme 1.4). Cocaine degradation to (+)-2-tropinone (20) is a one-
pot three-step synthesis. Typically performed on a 35g scale this process yields 10g of the optically pure chiral building block, 2-tropinone (20).²⁷ Through the degradation of cocaine, the inherent stereochemistry of C1 and C5 is exploited.

**Scheme 1.4:** Chiral building blocks

(+)-2-Tropinone (20) was identified as the initial chiral building block for the preparation of enantiopure cis-2,5-pyrrolidine 225H.²⁷ This building block was the target for the complete synthetic procedure due to its availability and the ease in preparation. Confiscated grade (-)-cocaine•HCl 19 was degraded to (+)-2-tropinone (20) in an overall yield of 80% (Scheme 1.5).
Scheme 1.5: Synthesis of (+)-2-tropinone

The degradation of cocaine 19 furnished (-)-anhydroecgonine 22. The carboxylic acid was suspended in dichloromethane and treated with diphenylphosphoryl azide and DMAP to afford the acyl azide 23. The acyl azide 23 was then refluxed in 1 N hydrochloric acid to afford 2-tropinone (20) via a Curtius rearrangement. In Scheme 1.6, the 2-tropinone (20) was demethylated and protected as the Cbz-carbamate 24 by refluxing in a solution of Cbz-Cl and toluene. Protection of the nitrogen is needed to reduce basicity and for protection from oxidation during the ozonolysis in the subsequent step. 27
The Cbz protected 2-tropinone 24 was converted into the methyl enol ether 25 using trimethyl orthoformate catalyzed by p-toluenesulfonic acid. The double bond of the methyl enol ether 25 was cleaved by ozone at -78 ºC and subsequent reductive workup with triphenylphosphine furnished the enantiopure cis-2,5-disubstituted pyrrolidine 26.27

1.4. Retrosynthetic Approach and Synthetic Strategy

The retrosynthetic approach utilizing the (+)-2-tropinone (20) chiral building block for the preparation of enantiopure cis-2,5-disubstituted pyrrolidine is outlined in Scheme 1.7. The synthesis was envisaged to start from confiscated grade (-)-cocaine•HCl 19. The first approach to the target amphibian alkaloid 225H will utilize similar chemistry as that employed in the synthesis of (-)-monomorine.27b The synthesis will employ the deprotection of the 2,5-disubstituted pyrrolidine 31 to afford the amphibian alkaloid 225H (32).
**Scheme 1.7:** Retrosynthetic approach via (+)-2-tropinone

The aldehyde moiety of 29 will be protected as the acetal to afford 30. The ester moiety of 29 will undergo reduction followed by concomitant Wittig olefination and hydrogenation to afford the five carbon unit necessary for the C2 side chain 32. The acetal 30 will be hydrolyzed followed by concomitant Wittig olefination and subjected to hydrogenation to afford 31. Oxidative cleavage and subsequent reductive workup of the methyl enol ether 28 yields the enantiopure cis-2,5-disubstituted pyrrolidine 29. The ethyl carbamate 26 will be converted into the methyl enol ether 28. Cocaine 19 undergoes degradation followed by N-demethylation and protection as the ethyl carbamate to afford ethyl carbamate 2-tropinone 27.

The retrosynthetic approach utilizing the R-(−)-anhydroecognine methyl ester 21 chiral building block for the preparation of enantiopure cis-2,5-disubstituted pyrrolidine is outlined in Scheme 1.8.
**Scheme 1.8:** Retrosynthetic approach via R-(-)-anhydroecgonine methyl ester

The synthesis was envisaged to start from confiscated grade (-)-cocaine•HCl 19. The chiral building block, anhydroecgonine derivative 33, will be explored as an intermediate in approaching amphibian alkaloid (+)-225H (32) as shown in Scheme 1.8. The synthesis will employ the deprotection of the 2,5-disubstituted pyrrolidine 31 to afford the amphibian alkaloid 225H (32). The α-ketoester moiety of 34 will undergo reduction, oxidative cleavage followed by Wittig olefination to furnish the n-pentyl side chain in 32. Concomitant hydrolysis of the acetal moiety of 32 followed by Wittig olefination and hydrogenation will furnish the ethyl carbamate protected methyl ester 31. Oxidative cleavage and subsequent reductive workup of 33 followed by selective protection of the aldehyde as an acetal furnished the enantiopure cis-2,5-disubstituted pyrrolidine 34. The synthesis will employ the preparation of anhydroecgonine methyl ester 21 from cocaine 19 followed by N-demethylation and protection as the ethyl carbamate to furnish 33.
1.5. Results and Discussion

1.5.1. Synthesis of Chiral Building Blocks

The synthetic approach for the preparation of (+)-2-tropinone (20) is outlined in Scheme 1.5. The degradation of cocaine 19 furnished (-)-anhydroecgonine (22) in 93% yield. The carboxylic acid was suspended in dichloromethane and treated with diphenylphosphoryl azide and DMAP to afford the acyl azide 23. The acyl azide 23 was refluxed in 1 N hydrochloric acid to afford 2-tropinone (20) via a Curtius rearrangement in 33% yield. In Scheme 1.9, the 2-tropinone (20) was demethylated and protected as the ethyl carbamate 27 by refluxing in a solution of ethyl chloroformate and toluene in 57% yield. The protected 2-tropinone 27 was converted into the methyl enol ether 28 using trimethyl orthoformate catalyzed by p-toluenesulfonic acid with a yield of 89% (Scheme 1.9).

Scheme 1.9: Synthesis of carbamate protected cis-2,5-pyrrolidine disubstituted pyrrolidine
Cleavage of the carbon-carbon double bond of methyl enol ether 28 by ozone at -78 ºC and subsequent reductive workup with triphenylphosphine should furnish the enantiopure cis-2,5-disubstituted pyrrolidine 29. The methyl enol ether 28 was hydrolyzed due to the presence of water and was recovered as the ketone 27. A more versatile enol ether was desired for the convenient tropane intermediate necessary for the synthesis of our desired pyrrolidine, 225H. In addition to the unstable methyl enol ether 28, Scheme 1.9 consisted of six steps to yield the disubstituted pyrrolidine 29. Therefore, a stable enol ether intermediate and a more direct approach to the cis-pyrrolidine was desired for the cis-2,5-disubstituted pyrrolidine.

For the development of a more direct conversion of cocaine into a cis-2,5-pyrrolidine derivative, ozonolysis of anhydroecgonine methyl ester 21 was investigated. As illustrated in Scheme 1.10, confiscated grade (-)-cocaine•HCl 19 was refluxed in 0.8N hydrochloric acid to afford the ecognine 35 in 99% yield.²⁸

**Scheme 1.10: Synthesis of R-(−)-anhydroecgonine methyl ester**

Subsequent dehydration with phosphorus oxychloride and concomitant esterification using methanol afforded the methyl ester 21 in 85% yield.
1.5.2. Initial Studies Directed toward (+)-225H

In Scheme 1.11, the nitrogen atom of the methyl ester 21 was demethylated and protected as an ethyl carbamate 33 with a yield of 99%.

Scheme 1.11: Initial Studies Directed Toward (+)-225H

The carbon-carbon double bond of 33 was cleaved by ozonolysis at -78 °C with a subsequent reductive workup with triphenylphosphine to afford the tricarbonyl compound 36 with a yield of 66% with a specific rotation of $[\alpha]_D^{25} = +25.7$ (c = 1.0, EtOAc). Selective protection of the
aldehyde moiety in 36 was achieved by using trimethyl orthoformate catalyzed by cerium (III) chloride heptahydrate. This afforded acetal 34 in a 79% yield with a specific rotation of $[\alpha]_D^{25} = +0.98$ (c = 1.0, EtOAc). The α-ketoester moiety in 34 underwent reduction with sodium borohydride and concomitant oxidative cleavage with sodium periodate to furnish the aldehyde 37 in a 69% yield. However, the aldehyde proved to be labile toward epimerization in which purification by chromatography led to a mixture of diastereomers. Even though epimerization occurred the synthesis was continued to establish the methodology for olefination. The C2-n-pentyl side chain was constructed by Wittig olefination of aldehyde 37. The acetal moiety in 37 was hydrolyzed to furnish the aldehyde 38 with a 58% yield. The C5 side chain was constructed using the same Wittig olefination synthesis to furnish the diene 39 in 40% yield. This led to a sufficiently complex mixture of products due to epimerization at C2. Hydrogenation of the olefinic side chains would reduce the complexity of the molecule to furnish a pyrrolidine 31. Finally, deprotection of the ethyl carbamate 31 with 33% HBr in AcOH should afford the cis-pyrrolidine 225H (31). Further investigation revealed that the α-ketoester was also unstable and sensitive to epimerization. Subsequent preparation of 36 and 34 gave inconsistent optical rotations.

1.5.3. Retrosynthetic Approach to (+)-225H

Due to epimerization of 36 and 34 a different synthetic approach was developed for the synthesis of (+)-225H utilizing the (+)-2-tropinone (20) approach via a silyl enol ether intermediate (Scheme 1.12) and the Wittig olefination methodology.
Scheme 1.12: Retrosynthetic approach via silyl enol ether

The chiral building block, (+)-2-tropinone (20), was revisited in order to revise the procedure for the cis-2,5 disubstituted pyrrolidine building block. The instability of the methyl enol ether 28 was envisaged to be avoided by preparation of the silyl enol ether 40.\(^{29}\) The retrosynthetic approach for the preparation of enantiopure cis-2,5-disubstituted pyrrolidine is outlined in Scheme 1.12. The strategy was to employ the deprotection of the 2,5-disubstituted pyrrolidine 31 to afford the amphibian alkaloid 225H (32). The C5-n-pentyl side chain of 32 would be constructed by a Wittig olefination sequence followed by hydrogenation of the olefinic side chain to furnish the pyrrolidine 31. The ester moiety of 41 would undergo reduction to aldehyde 42. The construction of the C2-n-hexyl side chain of 32 would utilize the same Wittig olefination sequence and olefinic side chain hydrogenation procedures to afford 41. Oxidative cleavage and subsequent reductive workup of 40 followed by diazomethane would furnish 29.
The ethyl carbamate 27 would be converted into the silyl enol ether 40. Cocaine 19 undergoes degradation followed by N-demethylation and protection as the ethyl carbamate to afford ethyl carbamate 2-tropinone 27.

1.5.4. Synthesis of (+)-225H

The ethyl carbamate protected 2-tropinone 27 was converted into the silyl enol ether 40 using sodium hydride and tert-butyl dimethyl silyl chloride at 0 ºC in 93% yield (scheme 1.13) with a specific rotation of \([\alpha]_D^{25} = -49.6\) (c = 0.6, MeOH).29

Scheme 1.13: Synthesis of silyl enol ether

The double bond of the silyl enol ether 40 was cleaved by ozone at -78 ºC and concomitant reductive workup with triphenylphosphine. Then the reaction mixture was treated with CH₂N₂ to furnish the enantiopure cis-2,5-disubstituted pyrrolidine 29 in 33% yield over 3 steps with a specific rotation of \([\alpha]_D = +4.57\) (c = 0.2, MeOH) (Scheme 1.14).27b,29
Scheme 14: Synthesis of (+)-225H

To avoid epimerization at C2 the n-hexyl side chain of 32 was constructed by a Wittig olefination sequence to afford the alkene 43 in 35% yield followed by hydrogenation of the olefinic side chain to greatly reduce the molecular complexity to furnish the pyrrolidine 41 in 60% yield with a specific rotation of $[\alpha]_{D}^{25} = -12.0$ (c = 0.6, EtOAc). The reduction of the ester 41 with DIBAL-H gave the aldehyde 42 in 91% yield. Construction of the C5 n-pentyl side chain utilized the same Wittig olefination sequence to afford the alkene 44 in 47% yield. The olefinic side chain of 44 underwent hydrogenation to furnish pyrrolidine 31 in 64% yield with a specific rotation of $[\alpha]_{D}^{25} = +9.26$ (c = 0.6, EtOAc). Finally, deprotection of the ethyl carbamate with 33% HBr in AcOH afforded the cis-pyrrolidine 225H (32) in 84% yield with a specific rotation of $[\alpha]_{D}^{25} = +15.6$ (c = 0.4, EtOAc).
In summary, we have developed the first enantioselective synthetic route that exploits the natural stereochemistry inherent to cocaine for the synthesis of enantiopure cis-2,5-pyrrolidine based alkaloids. Both (+)-2-tropinone (20) and R-(-)-anydroecgonine methyl ester (21), derived from cocaine, were readily converted into the cis-2,5-pyrrolidine building blocks 29 and 36, respectively. The enantiopure building blocks were ideally suited for the construction of more complex alkaloids due to the asymmetry of the appendages and the orthogonal reactivity of the functional groups. The utility of (+)-2-tropinone (20) as a chiral building block was demonstrated by the 9-step synthesis of (+)-cis-pyrrolidine 225H (32). This approach will be effective for providing other natural and non-natural derivative for structure-activity studies and will be the subject of future investigations.

1.6. Conclusion

The development of the first enantioselective synthetic route to cis-2,5-pyrrolidine based alkaloids exploiting the natural stereochemistry inherent to cocaine has been developed. The desired cis-2,5-pyrrolidine was prepared from the (-)-cocaine desired intermediate, (+)-2-tropinone (20), in 9-steps. The enantiopure building block, (+)-2-tropinone (20) is well-suited for the construction of more complex alkaloids due to the asymmetry of the appendages and the orthogonal reactivity of the functional groups. This approach will be effective for providing pyrrolidine ring systems for the synthesis of other natural and non-natural derivatives for future investigations and structure-activity studies.
1.7. Experimental Section

General Methods

All chemicals were purchased from Aldrich Chemical Company unless otherwise noted. Anhydrous toluene, tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and methanol (MeOH) were purchased from Mallinckrodt Baker, Inc and were used under nitrogen without any further purification. Thin layer chromatography (TLC) 20 x 20 cm glass plates precoated with 250 µm silica gel were purchased from Sorbent Technologies and used to monitor reactions via visualization with short-wave UV light, iodine, potassium permanganate, phosphomolybdic acid (PMA), 2,4-dinitrophenyl hydrazine or Dragendorff’s reagent. Chromatography is in reference to flash column chromatography on silica gel (Silica Gel 60, 230-400 mesh). High-pressure hydrogenations were carried out on a Parr apparatus. Proton and carbon NMR were recorded on a Varian-Gemini 400 and 500 MHz nuclear magnetic resonance spectrometer, respectively at ambient temperature in deuterated chloroform from Cambridge Isotope Laboratories, Inc. $^1$H NMR chemical shifts are reported in δ values (ppm) with tetramethylsilane (TMS), employed as the internal standard. $^{13}$C NMR chemical shifts are reported in δ values (ppm) with chloroform-D (CDCl$_3$, 77.0 ppm), employed as the internal standard. Optical rotations were measure on Autopol III autopolarimeter at the sodium D line (2 mL samples cell). Elemental analyses were obtained from Atlantic Microlabs, Inc.
8-Methyl-8-azabicyclo[3.2.1]octan-2-one (20)\textsuperscript{27}

Confiscated (-)-cocaine hydrochloride 19 (34.0 g, 100 mmol) in concentrated hydrochloric acid (276 mL) was refluxed for 24 h. The reaction mixture was allowed to come to room temperature, diluted with deionized water (255 mL) and extracted with Et\textsubscript{2}O (2 x 127 mL) to remove the benzoic acid. The aqueous layer was evaporated until dryness under the vacuum. The solid was further dried under vacuum with an oil bath at 100°C for 24 h. This afforded crude (-)-anhydroecgonine (19.2 g, 94%) without further purification was used in the next step.

To the finely powder acid (5.16 g, 25.3 mmol) from the previous crude step were added Na\textsubscript{2}CO\textsubscript{3} (7.62 g, 72 mmol) and DMAP (91.5 mg, 0.75 mmol), and the flask was sealed under nitrogen. To the flask dried CH\textsubscript{2}Cl\textsubscript{2} (110 mL) was added followed by the addition of diphenylphosphorylazide (DPPA) (7.77 mL, 0.036 mmol). The reaction mixture was stirred vigorously for 48 h. The solvent was removed under vacuum. The resulting residue is dissolved in deionized H\textsubscript{2}O (32 mL). A solution of 1N HCl (181 mL) was carefully added to the solution and the mixture was heated to reflux in oil bath at 120 °C until CO\textsubscript{2} and N\textsubscript{2} evolution ceased (~35 mins.). The aqueous HCl was removed under vacuum and the residue was made basic (~PH = 9.5-10) with saturated Na\textsubscript{2}CO\textsubscript{3}. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 150 mL). The organic layers were combined and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under vacuum. The resulting liquid was purified using the Kugelrohr (vacuum bulb to bulb distillation). This afforded 19 (1.11 g, 31%, 3 steps) as a colorless liquid. \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \( \delta \)
1.58-1.72 (m, 3H), 2.06-2.18 (m, 4H), 2.20-2.28 (m, 1H), 2.34 (s, 3H), 3.15-3.25 (m, 2H).

2-Oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (27)\(^\text{30}\)

To a solution of 20 (0.643 g, 4.62 mmol), and K\(_2\)CO\(_3\) (382 mg, 2.31 mmol) in toluene (8 mL) was added ethyl chloroformate (2.20 mL, 23.1 mmol). The reaction mixture was heated to reflux for 24 h. The solvent was removed under vacuum and the resulting residue was dissolved in deionized H\(_2\)O (9 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 9 mL). The organic layers were combined and dried over Na\(_2\)SO\(_4\). The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO\(_2\), 3:7 CH\(_2\)Cl\(_2\)/hexane) to yield 26 (0.514 g, 80%) as a pale yellow oil. [\(\alpha\)]\(^{20}\)\(_D\) -15.4 (c 0.4, MeOH). \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.23 (t, J = 6.8 Hz, 3H), 1.78-1.84 (m, 3H), 2.17-2.22 (m, 3H), 2.35-2.45 (m, 2H), 4.10-4.14 (m, 2H), 4.40 (s, 1H), 4.47 (s, 1H). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 14.6, 30.6(2), 32.5(2), 52.8, 61.5, 64.1, 154.3, 205.7. Anal. Calcd. for C\(_{10}\)H\(_{15}\)NO\(_3\): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.90; H, 7.67; N, 7.10.
R-(-)-anhydroecgonine methyl ester (21)

A solution of confiscated grade(-)-cocaine hydrochloride 19 (15.0 g, 44.4 mmol) in 0.8 N hydrochloric acid (200 mL) was heated to reflux for 24 h. The solution was cooled to room temperature, and extracted with Et$_2$O (200 mL). The aqueous layer was evaporated under vacuum to dryness. The solid was further dried under the vacuum at 100 ºC for 24 h. This afforded crude ecgnine 35 which without further purification was used in the next step.

To the finely powdered solid 35, POCl$_3$ (60 mL) was added and the mixture was heated to reflux for 2.5 hours. Excess POCl$_3$ was removed under reduced pressure and the residue was chilled in a dry ice-acetone bath. Methanol (60 mL) was added to the residue and the mixture was brought back to room temperature by swirling. Methanol was removed under reduced pressure. The residue was dissolved in H$_2$O (100 mL) and heated with a saturated ammonium hydroxide solution with NaCl. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 100 mL). The organic layers were combined and dried over K$_2$CO$_3$, filtered and concentrated to dryness. The residue was purified by flash chromatography (SiO$_2$, 5% MeOH in EtOAc) to afford 20 (5.80 g, 85% yield) as a pale yellow oil. $^1$HNMR (400 MHz, CDCl$_3$) δ 1.36-1.41 (m, 1H), 1.69-1.76 (m, 2H), 2.00-2.07 (m, 3H), 2.23 (s, 3H), 2.50 (d, $J$ = 19.6 Hz, 1H), 3.12 (t, $J$ = 5.2 Hz, 1H), 3.64-3.68 (m, 3H), 6.70 (s, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ 29.2, 30.7, 33.5, 35.2, 50.5, 56.0, 57.6, 133.1, 134.9, 165.4.
**N-Ethoxycarbonyl-2-methoxycarbonyl-8-azabicyclo[3.2.1]oct-2-ene (33)**

To a stirred solution of R-(-)-anhydroecgonine methyl ester 21 (6.1 g, 34 mmol), and K₂CO₃ (4.65 g) in toluene (130 mL) under nitrogen, ethyl chloroformate (32 mL, 337 mmol) was added. The solution was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in H₂O (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The organic layers were combined, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue is purified by flash chromatography (SiO₂, 1:4 EtOAc/hexane) to afford 33 (6.16 g, 99%) as a pale yellow oil. [α]ₐ²⁵ -82.0 (c 1.0, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 1.11-1.17 (m, 3H), 1.52 (s, 1H), 1.81-2.09 (m, 4H), 2.76 (s, 1H), 3.62-3.67 (m, 3H), 3.99-4.07 (m, 2H), 4.30 (s, 1H), 4.78 (s, H), 6.66 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 14.6, 30.2, 34.3, 34.8, 51.4, 51.7, 52.9, 61.0, 136.2, 136.7, 154.2, 165.4. Anal. Calcd. for C₁₂H₁₇NO₄: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.24; H, 7.16; N, 5.85.

**Ozone was bubbled through a solution of 33 (4.47 g, 18.7 mmol) in CH₂Cl₂ (40 mL) at -78 ºC until a slight blue color persisted. The mixture was flushed with nitrogen for 10 minutes. Then Ph₃P (9.80 g, 37.4 mmol) was added to the solution and the mixture stirred overnight. The solvent was evaporated to dryness under reduced pressure.**
and the residue was purified by flash column chromatography (SiO₂, EtOAc/hexane, 1:1) to afford 36 (5.15 g, 66%) as an oil. \([\alpha]_D^{25} +25.7 \ (c \ 1.0, \ EtOAc)\). \(^1\)HNMR (400 MHz, CDCl₃) δ 0.95-1.09 (m, 3H), 1.47-1.56 (m, 1H), 1.76-1.88 (m, 1H), 2.04-2.21 (m, 1H), 2.38-2.51 (m, 1H), 2.81-3.00 (m, 1H), 3.71 (s, 3H), 3.86-3.93 (m, 2H), 4.17-4.23 (m, 1H), 4.77-4.86 (m, 1H), 9.60 (s, 1H). \(^1^3\)C NMR (400 MHz, CDCl₃) δ 14.2, 27.2, 31.2, 48.2, 53.0, 61.6, 61.9, 63.1, 154.2, 160.8, 192.11, 200.6. Anal. Calcd. for C₁₂H₁₇NO₆·1 1/2 H₂O: C, 49.06; H, 6.69; N, 4.77. Found: C, 49.27; H, 6.30; N, 4.80.

\[
\text{H}_2\text{CO} \leftarrow \text{OCH}_3
\]

**\((2S,5R)\)-Ethyl 2-(2,2-dimethoxyethyl)-5-(2-methoxy-2-oxoacetyl)pyrrolidine-1-carboxylate (34)**

To a solution of aldehyde 36 (2.52 g, 9.29 mmol) and CeCl₃·7H₂O (3.60 g, 9.66 mmol) in CH₃OH (50 mL), HC(OCH₃)₃ (10 mL, 82.2 mmol) was added. The reaction was stirred for 30 minutes at room temperature then quenched with saturated NaHCO₃ (10 mL). The reaction mixture was extracted with EtOAc (2 x 40 mL), washed with brine and dried over Na₂SO₄. The solvent was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (SiO₂, 1:1 EtOAc/hexane) to afford 34 (2.0 g, 69% yield) as an oil. \([\alpha]_D^{25} +0.98 \ (c \ 1.0, \ EtOAc)\). \(^1\)HNMR (400 MHz, CDCl₃) δ 0.90-1.05 (m, 3H), 1.39 (s, 1H), 1.60 (s, 1H), 1.70-1.80 (m, 3H), 1.91-2.08 (m, 2H), 3.04 (s, 6H), 3.61 (s, 2H), 3.78-3.84 (m, 3H), 4.67 (d, \(J = 31.6 \ Hz, \ 1H\)). \(^1^3\)C NMR (400 MHz, CDCl₃) δ 13.8, 20.4, 22.0, 36.5, 51.0, 53.3, 55.3, 54.6, 59.8, 62.8, 102.1, 154.6, 161.0, 200.2.
(2S,5R)-Ethyl 2-(2,2-dimethoxyethyl-5-formylpyrrolidine-1-carboxylate (37)

CH$_3$OH (6 mL) was added dropwise to a solution of acetal 34 (2.0 g, 6.4 mmol) and NaBH$_4$ (600 mg, 16 mmol) in THF (60 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes and then cooled to 0 ºC. (CH$_3$)$_2$CO (4 mL), H$_2$O (30 mL) and Et$_2$O (50 mL) were added to the reaction mixture at 0 ºC and stirred for 15 minutes. NaIO$_4$ (4.0 g, 19 mmol) was added to the reaction mixture at 0 ºC and stirred for 1 h and at room temperature for 20 minutes. The reaction was quenched with brine (80 mL), extracted with EtOAc (2 x 40 mL), dried over Na$_2$SO$_4$ and evaporated to dryness. This afforded a crude oil 37 (0.90 g, 69 % yield) which without further purification was used in the next step. $^1$HNMR (400 MHz, CDCl$_3$) δ 1.12-1.24 (m, 3H), 1.53-2.13 (m, 6H), 2.14-3.40 (m, 6H), 3.99-4.43 (m, 5H), 9.39 (s, 1H).

(2S,5R)-Ethyl 2-(2-oxoethyl)-5-(pent-1-enyl)pyrrolidine-1-carboxylate (38)

The aldehyde 37 was dissolved in toluene (20 mL) and added to a previously prepared solution of (n-butyl) triphenylphosphonium bromide and t-BuOK in toluene (57 mL) and stirred for 1.5 h. The reaction mixture was stirred at room temperature for 8 h. EtOAc (80 mL) and a solution of Na$_2$S$_2$O$_3$ (38 mL) was added to quench the reaction.
The reaction mixture was extracted with EtOAc (2 x 80 mL), washed with brine, dried over Na$_2$SO$_4$ and evaporated to dryness. The residue was dissolved in acetone (10 mL) and $p$-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added to the solution and stirred for 1 h. The solvent was evaporated and the residue was dissolved in CH$_2$Cl$_2$ (mL), washed with saturated NaHCO$_3$ solution, dried over Na$_2$SO$_4$ and evaporated to dryness under vacuum. The residue was purified by flash chromatography (SiO$_2$, 2:3 EtOAc/hexane) to afford 38 (0.93 g, 58% yield).

(2S,5R)-Ethyl 2-(hex-2-enyl)-5-(pent-1-enyl)pyrrolidine-1-carboxylate (39)

The aldehyde 38 (37.5 mg, 0.148 mmol) was dissolved in THF (2 mL) and added to a previously prepared solution on (n-butyl) triphenylphosphonium bromide and nBuLi (0.15 mL, 0.37 mmol) in THF (3 mL) that was stirred at room temperature for 1.5 h. The combined reaction mixture was stirred at room temperature overnight. EtOAc (10 mL) and Na$_2$S$_2$O$_3$ solution (5 mL) was added to the reaction mixture and extracted with EtOAc (2 x 10 mL), washed with brine, dried over Na$_2$SO$_4$ and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 1:4 EtOAc/hexane) to afford 39 (0.12 g, 40% yield). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.90 (t, $J$ = 2.4 Hz, 6H), 1.17-1.48 (m, 8H), 1.54-1.74 (m, 2H), 1.82-2.04 (m, 7H), 2.55 (s, 1H), 3.86 (s, 1H), 4.06-4.12 (m, 2H), 5.27-5.48 (m, 4H). $^{13}$C NMR (400 MHz, CDCl$_3$) 13.9, 14.3(2), 23.5(2), 31.6, 34.9(2), 39.2, 55.7, 60.9, 58.9, 125.9, 128.7, 130.7, 139.0, 155.7. MS (ESI) $m/z$ 293.4 (M).
(1R,5R)-Ethyl 2-(tert-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (40)²⁰

NaH (70 mg, 0.58 mmol) was suspended in dry THF (4 mL) under nitrogen at 0°C with ice-NaCl bath. A solution of compound 27 (115 mg, 3 mmol) in dry THF (1 mL) was added dropwise and continued stirring at 0 °C for 2 h. Then TBSCl (1.0 M in THF, 1.2 mL, 1.2 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to continue stirring overnight. At 0 °C, H₂O (5 mL) was added slowly. The solution was extracted with Et₂O (3 x 10 mL). The organic portions were combined, dried over MgSO₄ and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, hexane gradient, CH₂Cl₂) to afford 40 (169 mg, 93% yield) as a colorless oil. [α]₀⁺²⁵ -49.6 (c 0.6, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 0.14-0.17 (m, 6H), 0.93 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H), 1.56-1.76 (m, 4H), 1.98-2.13 (m, 3H), 4.09-4.17 (m, 2H), 4.34 (s, 1H), 4.49 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) -4.10(2), 14.9, 25.8, 26.1(3), 29.4, 31.4, 34.4, 52.2, 57.5, 61.1, 97.35, 154.7. MS (ESI) m/z 312.3 (M + 1). Anal. Calcd. for C₁₆H₂₉NO₃Si: C, 61.69; H, 9.38; N, 4.50. Found: C, 61.86; H, 9.61; N, 4.38.
(2R,5S)-1-Ethyl 2-methyl 5-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (29)

Ozone was bubbled through a solution of the TBS enol 40 (4.62 g, 14.8 mmol) in 40 mL CH₂Cl₂ at -78 ºC until a slight blue color persisted. The mixture was flushed with nitrogen for 10 minutes. Then Ph₃P (4.28 g, 16.3 mmol) was added to the solution and the mixture stirred overnight. The solvent was evaporated to dryness. The residue was triturated with 2N HCl (20 mL) and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure to afford an oil that was used directly in the next step without further purification.

To a stirred solution of the crude oil in Et₂O (25 mL) at 0 ºC, CH₂N₂ was passed through the solution until a yellow color persisted. Nitrogen was then passed through the reaction mixture for 30 minutes. The cold bath was removed and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexane gradient, Et₂O, hexane) to afford 29 (1.19 g, 33%) a colorless oil. \([\alpha]_{D}^{25} +4.57 (c 0.2, \text{MeOH})\). \(^1\)HNMR (400 MHz, CDCl₃) δ 1.18-1.27 (m, 3H), 1.70 (d, \(J = 5.2\) Hz, 1H), 1.97-2.01 (m, 2H), 2.16-2.28 (m, 2H), 2.55-2.72 (m, 1H), 3.74 (s, 3H), 4.08-4.43 (m, 4H). \(^{13}\)C NMR (400 MHz, CDCl₃) δ 14.8, 29.2, 30.5, 48.7, 54.1, 59.7, 60.1, 61.7, 173.6, 201.2. MS (ESI) \(m/z\) 266.2 (M + Na). Anal. Calcd. for C₁₁H₁₇NO₅·1/4 H₂O: C, 53.32; H, 7.12; N, 5.65. Found: C, 53.00; H, 7.19; N, 5.32.
(2R,5S)-1-Ethyl 2-methyl 5-(hex-2-enyl)pyrrolidine-1,2-dicarboxylate (43)

CH$_3$CH$_2$CH$_2$CH$_2$PPh$_3$Br (5 g, 12 mmol) was suspended in dry THF (40 mL) under nitrogen at room temperature. t-BuOK (1.0 M in THF, 11.3 mL, 11.3 mmol) was added dropwise to the solution and stirred for 2 h. The aldehyde 29 (1.2 g, 4.9 mmol) was dissolved in THF (5 mL) and added dropwise to the reaction mixture. The combined reaction mixture was stirred for 8 h, then EtOAc (20 mL) and Na$_2$S$_2$O$_3$ solution (10 mL) was added. The reaction mixture was extracted with EtOAc (2 x 20 mL), washed with brine, dried over Na$_2$SO$_4$ and evaporated to dryness. The residue was purified by flash column chromatography (SiO$_2$, hexane ) to afford 43 (485 mg, 35%) an oil. $^1$HNMR (400 MHz, CDCl$_3$) δ 0.91 (t, $J = 24.4$ Hz, 3H), 1.77-1.47 (m, 7H), 1.68-1.78 (m, 1H), 1.88-2.21 (m, 5H), 2.45-2.73 (m, 1H), 3.74 (s, 3H), 3.93-4.37 (m, 3H), 5.16-5.61 (m, 2H).

(2R,5R)-1-Ethyl 2-methyl 5-hexyllpyrrolidine-1,2-dicarboxylate (41)

A solution of 43 (485 mg, 1.7 mmol), 10% Pd/C (108 mg) in EtOH (20 mL) was hydrogenated using a hydrogen balloon for 2 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO$_2$, hexane) to afford 41 (292 mg, 60%) an oil. [α]$_D^{25}$ -12.0 (c 0.6, EtOAc). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.85 (t, $J = 5.2$ Hz,
3H), 1.12-1.42 (m, 11H), 1.64-2.19 (m, 6H), 3.69 (s, 3H), 3.91-4.32 (m, 4H). \(^{13}\)CNMR (400 MHz, CDCl\(_3\)) \(\delta\) 14.3, 14.8, 22.8, 26.6(2), 28.4, 29.4, 29.6, 32.0, 52.4, 59.6, 61.3, 61.4, 156.3, 173.5. MS (ESI) \(m/z\) 286.4 (M + 1), 308.5 (M + Na). Anal. Calcd. for C\(_{15}\)H\(_{27}\)NO\(_4\): C, 63.13; H, 9.54; N, 4.91. Found: C, 63.64; H, 9.92; N, 4.74.

\[
\text{CO}_2\text{Et}
\]

(2R,5R)-Ethyl 2-formyl-5-hexylpyrrolidine-1-carboxylate (42)

Ester 41 (180 mg, 0.63 mmol) was dissolved in toluene (3 mL) under nitrogen at -78 °C. DIBAL-H (1.0 M in toluene, 0.69 mL, 0.69 mmol) was added dropwise over 45 minutes. The reaction mixture was allowed to continue stirring at -78 °C for 15 minutes and then the cold bath is removed. Et\(_2\)O (10 mL), H\(_2\)O (4 mL) and 15% NaOH (6 mL) were added. The mixture was extracted with Et\(_2\)O (2 x 20 mL) and the combined organic layers were dried over MgSO\(_4\) evaporated to dryness. The residue was purified by flash chromatography (SiO\(_2\), hexane) to afford 42 (146 mg, 91%) an oil. \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.87 (t, \(J = 6.0\) Hz, 3H), 1.13-1.45 (m, 14H), 1.53-2.23 (m, 3H), 3.68-3.74 (m, 1H), 3.91-4.35 (m, 3H), 9.58 (s, 1H).

\[
\text{CO}_2\text{Et}
\]

(2R,5R)-ethyl 2-hexyl-5-(pent-1-enyl)pyrrolidine-1-carboxylate (44)

CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)PPh\(_3\)Br (570 mg, 1.4 mmol) was suspended in dry THF (20 mL) under nitrogen at room temperature. \(t\)-BuOK (1.0 M in THF, 1.3 mL, 1.3 mmol) was
added dropwise to the solution and stirred for 2 h. The aldehyde 42 (150 mg, 0.57 mmol) was dissolved in THF (5 mL) and added dropwise to the reaction mixture. The combined reaction mixture was stirred for 8 h, then EtOAc (10 mL) and Na₂S₂O₃ solution (5 mL) was added. The reaction mixture was extracted with EtOAc (2 x 10 mL), washed with brine, dried over Na₂SO₄ and evaporated to dryness. The residue was purified by flash column chromatography (SiO₂, hexane) to afford 44 (79.6 mg, 47%) an oil.

(2R,5S)-ethyl 2-hexyl-5-pentylpyrrolidine-1-carboxylate (31)

A solution of 44 (80 mg, 0.27 mmol), 10% Pd/C (31 mg) in EtOH (10 mL) was hydrogenated using a hydrogen balloon for 2 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO₂, hexane) to afford 44 (51.6 mg, 64%) an oil. [α]D²⁵ +9.26 (c 0.6, EtOAc). ¹HNMR (400 MHz, CDCl₃) δ 0.88 (t, J = 7.2 Hz, 6H), 1.18-1.47 (m, 19H), 1.58-2.26 (m, 6H), 3.58-4.34 (m, 4H). ¹³CNMR (400 MHz, CDCl₃) δ 14.2(2), 14.9, 22.8(2), 26.2, 26.5, 29.6(3), 32.0(2), 35.9(2), 60.7, 160.4. MS (ESI) m/z 298.6 (M + 1). Anal. Calcd for C₁₈H₃₅NO₂:  C, 72.68; H, 11.86; N, 4.71. Found: C, 72.52; H, 11.76; N, 4.69.
(2R, 5S)-2-hexyl-5-pentylpyrrolidine

A solution of 44 (25 mg, 0.10 mmol) in 33% HBr/AcOH (2 mL) was stirred at rt under nitrogen for 48 h. EtOAc (20 mL) and sat. NaHCO₃ solution was added to the mixture until the solution was basic. The mixture was extracted with EtOAc (2 x 10 mL), washed with brine, dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO₂, EtOAc/MeOH/Et₃N, 40:2:1). The purified oil was dissolved in CH₂Cl₂ (5 mL) and washed with sat. NaHCO₃ solution (5 mL) and the solvent was evaporated to dryness under reduced pressure to afford 32 (16 mg, 84%) a light yellow oil. [α]D²⁵ +15.6 (c 0.4, MeOH). ¹HNMR (400 MHz, CDCl₃) δ 0.89-0.86 (m, 6H), 1.21-1.40 (m, 19H), 1.42-1.53 (m, 2H), 1.76-1.90 (m, 2H), 2.89-2.98 (m, 2H). ¹³CNMR (400 MHz, CDCl₃) δ 14.0, 14.1, 22.6(2), 27.0, 27.2, 29.3(2), 30.2, 31.7(2), 35.1(2), 59.6(2). MALDI-TOF-MS 226.3390 [M⁺ + H]. Anal. Calcd. for C₁₅H₃₁N: C, 79.92; H, 13.86; N, 6.21. Found: C, 72.52; H, 11.76; N, 4.69.

1.8. References


CHAPTER 2

Synthesis of Diaryl Ether Analogues of BAY 59-3074 as Potential Therapeutics for Marijuana Abuse

2.1. Abstract

The search for potent cannabinoid receptor partial agonist as potential marijuana addiction therapeutic agents has led to an investigation of the synthesis of diaryl ether hybrid analogues of BAY 59-3074. A series of 2-(3-alkyl-5-hydroxyphenoxy)-6-(trifluoromethyl) benzonitriles, 3-(2-cyano-3-(trifluoromethyl)phenoxy) phenylalkanoates, and (3-(benzyloxy)phenoxy)-6-(trifluoromethyl) benzonitriles were synthesized and evaluated in vitro for CB1 affinity. The olivetol diaryl ether analogue was the most potent ligand of the alkyl series, but the diaryl ester analogues exhibited modest affinity for CB1 receptors. The most potent compound of the series was the 2-(3-(benzyloxy)phenoxy)-6-(trifluoromethyl) benzonitrile.
2.2. Introduction

2.2.1. Drug Addiction

Cannabis (marijuana) is one of the most commonly abused recreational drugs self-administered by smoking. Cannabis related disorders are becoming a major public health issue. In 2006, 25% of Americans age 12 and over abused marijuana at least once prior to the year of being surveyed.¹ According to the NIDA, a study showed that 10.9% of 8th graders, 23.9% of 10th graders, and 32.4% of 12th graders had abused marijuana at least once in the year prior to being surveyed.²

Cannabis has been used by various civilizations as a therapeutic agent with advances as an analgesic, nausea, appetite stimulation and a host of other medical applications.³-⁵ Historical evidence suggests that Emperor Shen Nung 3000 B.C. was the first to recognize that cannabis had potential medicinal properties, which was used as an analgesic.⁶ In India, the effects of smoking cannabis were associated with faith and were used as anesthetics and aphrodisiacs.⁷ Cannabis is obtained from the Indian hemp Cannabis Sativa L. and contains a variety of natural cannabinoids.⁸

Cannabinoids are terpenophenolic compounds with a structural relationship similar to (-)-trans-Δ⁹-tetrahydrocannabinol (Δ⁹-THC) ¹ or compounds with the ability to bind to cannabinoid receptors. To date, at least 66 cannabinoids have been isolated from the cannabis plant.⁹ The most prevalent natural cannabinoids that have been studied extensively are THC ¹, cannabidiol (CBD) (²), and cannabinol (CBN) (³) (Figure 2.1).
THC 1 is the major psychoactive constituent of marijuana. This psychoactive constituent has high lipid solubility and low water solubility. THC 1 has analgetic and neuroprotective properties with equal affinity for the two subtypes of the cannabinoid receptor, and produces the “high” associated with the binding to the CB receptor in the brain.

In 1963, the structure and stereochemistry of cannabidiol (2) and THC 1 were first determined, but cannabinoids were first discovered in the 1940’s with the structure identification of CBD 2 and CBN 3. Unlike THC 1, cannabidol (2) is not psychoactive and possess medical benefits such as relieving convulsion, inflammation, anxiety and nausea. It is an allosteric antagonist at the brain cannabinoid receptor that alters psychoactive effects of THC 1 and is selective for central nervous system (CNS) cannabinoid receptor subtype (CB1 subtype) over receptor subtypes found in the immune system (CB1 subtype). Cannabinol (3) is the main product in the degradation of THC 1 and is found to be mildly psychoactive and has the same affinity at CB2 as cannabidol (2).

Currently, there are no effective treatments for marijuana abuse. Due to marijuana dependence being a major public health issue the development of new
medications for treatment of marijuana abuse is essential. The physiological and behavioral effects of cannabinoids have been studied extensively and suggest that a cannabinoid antagonist could be useful as treatment for marijuana abuse.\textsuperscript{12-14} There is an urgency for the development of pharmacotherapies to treat marijuana addiction while understanding the mechanism of marijuana action on the central nervous system (CNS).

2.2.2 Cannabis, Addiction and the Cannabinoid Hypothesis

Some drugs of abuse have reinforcing effects, which can lead to abuse and/or addiction. Addictive drugs have reinforcing effects which include activation of the reinforcement mechanism which causes the release of dopamine (4) in the nucleus accumbens.\textsuperscript{15}

**Figure 2.2:** Structure of dopamine

![Structure of dopamine](image)

The abusive burden surrounding marijuana is produced by those reinforcing properties, which lead to repeated marijuana use.\textsuperscript{13} Addiction is thought to be caused by unpleasant physiological effects upon discontinued use of an abused substance in which tolerance can develop. It is believed that tolerance is produced to compensate for the intoxicated condition of the body.\textsuperscript{15} The abused drug acts to disturb the homeostatic mechanisms in
the brain in which these mechanisms produce effects opposite to the drug of abuse by compensating for the disturbance.\textsuperscript{15} Cannabis has both psychoactive and physiological effects. These effects include short term physical and neurological effects such as increased heart rate, lowered blood pressure, short term memory, and psychomotor impairments.\textsuperscript{13,15}

Drug seeking behaviors are mediated by the release of dopamine (\textsuperscript{4}). The more dopamine that is present allows for the increased activation of dopamine receptors (Figure 2.3).\textsuperscript{15}

**THC Binding to THC Receptors**

![THC Binding to THC Receptors](image)

*Figure 2.3. THC binds to the THC receptors (magenta) on the neighboring terminal, which sends a signal to the dopamine terminal to release more dopamine.\textsuperscript{16}*

With the increased dopamine present there is an increase in the cAMP production inside the post synaptic cell, which alters the normal activity of neurons.\textsuperscript{16} Besides drugs of
abuse, stress and other salient stimuli mediate dopamine release. Therefore, dopamine release does not suggest that drugs of abuse are activating the natural reward system. Drug addiction can not only be linked to the activation of the reward system mediated by the dopamine in the nucleus accumbens. With this in mind, dopamine’s role in the CNS can not be taken too lightly.

According to the proposed “Cannabinoid Hypothesis”, the endocannabinoid physiological system control system (EPCS) has a potential role in the regulation of the rewarding effects of abused drugs through the neurobiological mechanisms. Drug addiction is mediated by a variety of neurotransmitters in the brain circuit. The cannabinoid receptors are abundantly present in the brain. These receptors use retrograde signaling, which is associated with the inhibition of transmission at the synapse by neurotransmitter suppression. Due to this abundant presence in the brain retrograde signaling of these cannabinoids are limitless and may explain the behavioral effects associated with cannabis. The retrograde messengers inhibit a host of transmitters such as dopamine, serotonin, GABA, and acetylcholine. The endocannabinoid transmission plays a significant role in the dependence/withdrawal to abused substances and drug seeking behavior through mediation of motivation.

Molecular and neurobiological studies on the basis of the physiological and neurobehavioral effects of marijuana and cannabinoids have lagged behind other natural addictive drugs such as cocaine, opium and tobacco. The CB1 receptor has gained interest due to its presence within the CNS and association with the brain-reward circuits of the mesocorticollimbic dopamine systems which are located in the substantia nigra and ventral tegmental. Many drugs of abuse elevate dopamine levels and the ability of
these CB1 receptor antagonist or inverse agonists to attenuate these elevations has suggested their potential application as pharmacotherapies for treating drug abuse disorders.\textsuperscript{12,14} Therefore, the administration of a drug that blocks the CB1 receptors abolishes the high produced by smoking marijuana.

The homeostatic disturbance in the body can be restored by cannabinoid ligands. The cannabinoid antagonist, Rimonabant, shows promise in the downregulation of drug abuse and alcoholism, and smoking cessation.\textsuperscript{15} Although the CB1 receptors have the ability to modulate effects of drug abuse, the exact mechanism of their interaction was uncertain.\textsuperscript{15} The effects of cannabinoids and marijuana use are mediated by the activation of cannabinoid receptors. There are two well characterized cannabinoids, CB1 and CB2, whose identities have been elusive due to the study plant natural product, THC\textsuperscript{1}. Due to the discovery of CB1 and CB2 investigation into endocannabinoids function has blossomed. One potential role that is of focus is the ability of CB1 receptors to modulate effects of drug abuse. In addition, medical use of cannabis can beneficially aid in the treatment of nausea and vomiting\textsuperscript{5}, hunger stimulation in chemotherapy and AIDS patients\textsuperscript{18}, glaucoma, and as an analgesic.\textsuperscript{6}
2.2.3. Cannabinoid Receptors and G Protein Coupling

Mammalian tissue has 2 types of cannabinoid receptors: CB1 and CB2. Both cannabinoid receptors are transmembrane G-protein coupled receptors.\textsuperscript{14,19} CB1 receptors are predominately found at nerve terminals and mediate inhibition of transmitter release.\textsuperscript{20} They are predominately located in the brain, adipose tissue, muscle, liver, GI tract and pancreas. CB2 receptors are present in the CNS, but in a much lower concentration than CB1 receptors.\textsuperscript{21} CB2 receptors are found in immune cells and modulate cytokine release.\textsuperscript{21} They are predominately located in the T-cells, B-cells, spleen, tonsils, and monocytes. There has been long and great debate over the physiological and behavioral effects of cannabinoids through nonspecific and specific interactions. Evidence has suggested that these receptors and G proteins are pre-coupled.

Figure 2.4: Structure of G-protein coupled receptors CB1 and CB2
These G protein-coupled receptors shown above include an extracellular N-terminal domain, 7 transmembrane helices with intervening loops that extend both intra- and extracellularly, and a cytoplasmic C-terminal domain.\textsuperscript{22} The G protein-coupled receptors (GPCRs), also known as seven-transmembrane domain receptors (7TM receptors), sense molecules outside the cell and activate inside signal transduction pathways.

The G protein-coupled receptors are involved in many diseases, and are also the target of around half of all modern medicinal drugs.\textsuperscript{23} Some examples of their physiological roles include behavioral, mood and immune system regulation. There are two principal signal transduction pathways involving the G-protein coupled receptors: the cAMP signal pathway and the phosphatidylinositol signal pathway.\textsuperscript{24}

The G-proteins are bound to receptors in an inactive state. Ligands or signal mediators can activate these G protein-coupled receptor by creating a conformational change in the receptor. Upon ligand recognition, there is a conformational change in the receptor and the G-protein is activated. Once activation occurs the G-protein can detach from the receptor and either activate another G-protein by exchanging its bound guanosine diphosphate (GDP) for a guanosine triphosphate (GTP) or return back to its inactive state. It is believed that a receptor molecule exists in a conformational equilibrium between active and inactive biophysical states.\textsuperscript{25}

The binding of ligands to the receptor may shift the equilibrium toward the active receptor states.\textsuperscript{26} There are two types of ligands that exist: agonists and or antagonists. Agonist are a class of ligands that favor the active states.\textsuperscript{29} Within the agonist ligands there are low efficacy agonist deemed partial agonists. Among antagonists there are both antagonist and ligands that exhibit inverse agonist pharmacological profiles. Inverse
agonists favor the inactive states. How exactly the active and inactive states differ has yet to be determined. To date, the characterization of these receptors have relied upon ligand receptor interactions.

2.2.3.1. CB1 Receptor Ligands

There are five main chemical classes of cannabinoids: natural cannabinoids, synthetic cannabinoids, eicosanoids, 1,5-diarylpypyrazoles, and aminooindoles. Natural “classical” cannabinoids are dibenzopyran derivatives. Synthetic “nonclassical” cannabinoids are bicyclic and tricyclic analogues of Δ9-THC 1. However, eicosanoids “endocannabinoids” have a completely different structure. The four classes of cannabinoid ligands that represent the essential characteristics of CB1 receptor agonist include classical cannabinoid, Δ9-THC 1; nonclassical cannabinoid, CP 55,940 (5); aminooindole WIN 55,2112-2 (6) and the endogenous cannabinoid, anandamide (7).

Figure 2.5: Structure of CB1 Receptor Agonists
CB1 receptor agonists are responsible for cAMP production inhibition\textsuperscript{32}, calcium influx inhibition\textsuperscript{33}, potassium channel activation\textsuperscript{34}, MAP Kinase pathway activation\textsuperscript{35}, and an increase in intracellular dopamine levels in the brain\textsuperscript{12,14,36-39}.

In rat brain tissue, there was the discovery of a high affinity and pharmacologically distinct class of cannabinoid receptors\textsuperscript{19a}. This discovery led the search for a variety of natural endogenous ligands in the brain that have the ability to bind to this cannabinoid receptor. These endocannabinoids are produced within the body and can activate cannabinoid receptors. Upon the identification of the two cannabinoid receptors, the endogenous ligands anandamide (7) and 2-arachidonyl glycerol ether (2-AG) (8) were isolated.

\bf{Figure 2.6: Structure of Endogenous Ligand}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

Anandamide (7) has a similar potency as THC 1 at the CB1 receptor and acts as a partial agonist. However, 2-AG 8 has the ability to bind to both the CB1 and CB2 receptors and act as a full agonist at both and has a higher concentration in the brain than anandamide (7).\textsuperscript{40-41} Anandamide (7) and 2-AG 8 are the most extensively studied endogenous cannabinoids, but in order to understand the endocannabinoids system synthetic ligands were necessary.
Synthetic cannabinoids are useful in the determination of structure-activity relationships (SAR) of the endocannabinoid system. There was a need to find new synthetic cannabinoids with an increase in therapeutic activity and limited adverse side effects. However, the question remained if cannabinoid compounds could be used in pain suppression. In the 1980’s, Pfizer focused on these novel analgesic compounds. Early attempts at cannabinoid based analgesics and antiemetics led to the development of levonantradol (9) (Figure 2.7).

**Figure 2.7: Structure of Levonantradol**

![Structure of Levonantradol](image)

This cannabinoid compound was more potent than THC 1, easier to administer, but had too many side effects. From these early studies, CP55-940 (5), a synthetic analog of Δ⁹-THC 1 was created and lead to the important discovery of CB1 receptor in 1988. CP 55,940 (5) mimics the effects of THC 1 and is a full agonist at both CB1 and CB2 receptors. This synthetic analog allowed for radioligand binding assays that were not possible for Δ⁹-THC 1 due to the lipophilicity, which led to non-specific binding during in vitro experiments. The development of this analog led to further advancement in the cannabinoid field and also pushed for the need of selective agonists and antagonists for CB1 and CB2 receptors. SR141716A 10 (figure 2.8) commonly referred to as
Rimonabant was the first potent and selective antagonist (inverse agonist) of CB1 receptors.

**Figure 2.8:** Structure of SR 141716A

![Structure of SR 141716A](image)

Rimonabant 10 was developed as an anti-obesity drug used for blockade of CB1 receptor that cause “munchies” among marijuana users.\textsuperscript{12-14}

The aminoalkylindole derivative, WIN-55212-2 (6) is also a potent cannabinoid receptor agonist. This potent agonist has both analgesic\textsuperscript{43} and neuropathic\textsuperscript{44} properties and anti-inflammatory.\textsuperscript{45} WIN-55212-2 (6) is a full agonist at the CB1 receptor with a higher affinity than THC 1 for the CB1 receptor.\textsuperscript{46} The *in vitro* SARs of WIN-55212-2 (6) led to the development of new agonists. Nabilone 11 (Figure 2.9) is a synthetic analogue of $\Delta^9$-THC 1 and is licensed for medical use.
Nabilone (11) mimics THC 1 and is used therapeutically as an analgesic and antiemetic. This compound is not considered a narcotic by the World Health Organization (WHO) because it lacks the euphoric and recreational potential. In 1985, the U.S. Food and Drug Administration (FDA) approved nabilone (11) for treating chemotherapy-induced nausea and vomiting\(^5\), anorexia and as an appetite stimulant for AIDS patients.\(^{18}\)

Due to the extensive work on cannabinoids there is an increased interest in creating more medically, beneficial synthetic cannabinoids. Cannabinoid SAR data has indicated that the side chain and the phenolic hydroxyl groups are pertinent in CB1 receptor recognition. Synthetic cannabinoids can target one or both receptors and can act or block, which allows more therapeutic options than medical marijuana.

### 2.2.4. Binding Affinity and Inhibition Constant

Neurotransmitters, inhibitors, activators, and substrates are considered ligands. The cellular response is obtained by the ligand acting as a signal molecule to a target protein by an intermolecular force like ionic bonds, hydrogen bonds, and Van der Waals forces.\(^{47}\) Ligands have the ability to bind and form complexes with molecules to initiate a cellular
response that alters the chemical conformation of the receptor protein. A receptor is considered an agonist when a ligand binds to it and alters the function creating a response. The alteration of the receptor is characterized by the amount of the physiological response and the concentration of the agonist required to activate the physiological response. If an agonist can maximally stimulate the receptor it is considered a full agonist, but if an agonist can only partially activate the physiological response it is considered a partial agonist. However, if the physiological response is not activated by binding of the ligand to the receptor it is then deemed an antagonist.

The binding affinity is defined as the interaction between ligand and its binding sites (strength of binding). Generally, if a ligand has a high affinity the intermolecular force is greater, and has longer time at the receptor compared to low affinity. In addition, a high binding affinity implies a low concentration of a ligand to maximally occupy a receptor and trigger a physiological response. On the other hand, a low binding affinity implies a high concentration of ligand to maximally occupied and the maximum physiological response to the ligand is achieved. Binding affinities are determined using a radiolabeled ligand, which are radioisotope labeled compounds and are used in vivo studies as tracers in positron emission tomography (PET) studies and for in vitro binding studies.

Binding assays are done by using a radioligand usually an agonist in a low concentration either at or below the dissociation constant, $K_d$. The binding specificity is determined in the presence of the range of the concentration competing non-radio labelled compound usually an antagonist to measure the potency through binding.
competition at the radio labelled ligand. $K_d$ is the dissociation constant of the radioligand for a particular receptor.

The inhibition constant, $K_i$, or the half maximal inhibitory constant, $IC_{50}$, qualitatively indicates the potency for drug binding. $IC_{50}$ represents the concentration to produce half of the maximal inhibition. It measures the amount of drug that is necessary to inhibit biochemical pathways by half. For drug candidates, $K_i$ is the measurement of the effectiveness of a compound to inhibit certain biochemical pathways. The $IC_{50}$ is converted to $K_i$ by using the Cheng-Prusoff equation.\(^{48}\)

$$K_i = \frac{IC_{50}}{[S]} \frac{1}{K_m}$$  \[1\]

$[S]$ is the substrate concentration and $K_m$ is the substrate’s affinity for an enzyme. The $K_i$ or $IC_{50}$ values display the binding affinity that the ligand binds to the receptor. Experimental values of the $IC_{50}$ are variable based on radioligand concentration whereas $K_i$ is an absolute value.

2.2.5. Ligand Design Strategy

CB1 antagonists have been shown to block the effects of THC 1 and are also devoid of abuse liability. However, current antagonists exhibit inverse agonist activity eliciting the opposite response to an agonist. Thus making CB1 antagonist unsuitable for drug addiction treatment due to the potential side effects that include nausea, decreased
food intake and body weight, increased nociceptive sensitivity, and increased anxiety and depression, which is associated with Rimonabant (53). An alternative to this approach is the development of partial agonist as therapy. Partial agonist stimulate dopamine, raise basal dopamine levels without euphoric effects and the abuse liability is diminished due to a weaker efficacy. The development of a useful cannabinoid partial agonist has application for the treatment of cannabinoid and/or psychostimulant addiction. The compounds CB25 (12), and BAY59-3074 (13) exhibit low efficacy agonist profiles both in vitro and in vivo as compared to THC 1.

**Figure 2.10:** Cannabinoid partial agonist

These compounds are less potent than full agonist CP 55,940 (5) and WIN 55212-2 (6) by stimulation of $[^{35}S]$ GTPγS binding. Our strategy will focus on the synthesis and development of new cannabinoid partial agonist ligands with less efficacy than THC 1 based upon the structures of the lead compounds CB25 (12) and BAY 59-3074 (13) that are envisaged to exploit the favorable properties of each molecule. CB25 (12) exhibits a high affinity ($K_i = 5$ nM) at the CB receptors. However, CB25 (12) is very hydrophobic (ClogP = 6.2) and is unlikely to be a viable drug candidate. It is desired to improve the hydrophilicity (ClogP < 5) while taking advantage of the high potency of
CB25 (12) by replacing the amide side chain with an aryl moiety similar to ring-A of BAY 59-3074 (13).

![Chemical structure of CB25 and BAY 59-3074](image)

BAY 59-3074 (13) exhibits modest affinity ($K_i = 55 \text{ nM}$)\textsuperscript{56} and displays good lipophilicity (ClogP = 4.77)\textsuperscript{55} compared to CB25 (12) and its analogues are more likely to be viable drug candidates. We want to synthesize these novel BAY 59-3074-CB25 hybrid analogues and characterize the binding affinity at the cannabinoid receptors in which the in vitro data will suggest potential for potent receptor affinity.

The ligand design strategy will utilize SARs for a series of lead compounds that will optimize potency and hydrophilicity. The diaryl ether derivative will serve as a template for SAR studies of novel partial agonist.

**Figure 2.11:** Diaryl Ether Derivative Template

![Diagram of the diaryl ether derivative template](image)

Structural modifications will include modifications of the two side chains, $R_1$ and $R_2$. Studies will provide SAR data to identify potent classes of CB receptor ligands. These
diaryl ether derivatives of BAY 59-3074 are the first class of compounds that will be prepared based on the basic scaffold since no SAR data for has been collected for BAY 59-3074 (13) at the CB receptors. The diaryl ether core will be derived from commercially available activated aryl fluoride and a 3-benzyloxyphenol. Microwave assisted uncatalyzed coupling reactions will be utilized to generate the diaryl ether scaffold in high yield. Debenzylation under hydrogenolysis conditions will provide the diaryl ether phenol. The sulfonate ester will be achieved by using phase transfer catalysis to afford BAY 59-3074.

2.3. Results and Discussion

2.3.1. Synthesis of 5-Alkylbenzene-1,3-diols

Commercially available diols included resorcinol, orcinol and olivetol. The propyl and hexyl alkylresorcinols were also available through Japanese suppliers, but were too expensive (> $100 for milligram quantities). Therefore, the alkylresorcinols were synthesized using an approach developed by the Makriyannis group. The initial approach involved the Grignard reaction between 3,5-dimethoxybenzaldehyde (14) and the appropriate alkylmagnesium halide to obtain the corresponding alcohol 15 (Scheme 2.1).
Scheme 2.1: Synthesis of 5-Alkylbenzene-1,3-diols\textsuperscript{59}

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{RMgX}} \text{HO-R} \\
\text{MeO} \text{OMe} & \xrightarrow{\text{THF, -78°C}} \text{MeO} \text{OMe} \\
\text{BBr}_3, \text{CH}_2\text{Cl}_2 & \xrightarrow{-78°C \rightarrow \text{RT}} \text{HO} \text{OH}
\end{align*}
\]

\(R = \text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)

The alcohol 15 was then deoxygenated under catalytic hydrogenolysis using 10\%Pd/C and a hydrogen balloon in glacial acetic acid at 60 \(^\circ\text{C}\) to furnish the resorcinol dimethyl ether 16. The dimethyl ether groups of 16 were deprotected with BBr\(_3\) at -78 \(^\circ\text{C}\) to give the desired 5-alkylbenzene-1,3-diol 17. This procedure was employed to synthesize the propyl, butyl, and hexyl benzene-1,3-diols in 99\%, 88\%, and 99\% yield, respectively.

The 5-ethylbenzene-1,3-diol 19 was synthesized using a procedure from the Linusson group (Scheme 2.2).\textsuperscript{60} The carbonyl of 3,5-dihydroxyacetophenone (18) was reduced under catalytic hydrogenation (1 atm) conditions with 10\%Pd/C in 4\% HCl at room temperature to furnish the ethylresorcinol 19 in 72\% yield.

Scheme 16: Synthesis of 5-ethylbenzene-1,3-diol\textsuperscript{60}
2.3.2. Synthesis of BAY 59-3074 and Alkyl Analogues

A variety of natural products and biologically interesting compounds contain a diaryl ether motif.\textsuperscript{57} Diaryl ethers have been synthesized by coupling phenols to electron deficient aryl halides through $S_N$\textsubscript{Ar}-based addition reactions with microwave irradiation within 5-10 minutes.\textsuperscript{57} The synthesis of the diaryl ether scaffold is outlined in Scheme 2.3. The appropriate benzoxyphenol 21 was synthesized by the monobenzylation of the desired resorcinol derivative 20 using NaH and benzyl bromide (BnBr) at room temperature. The diaryl scaffold was synthesized from commercially available 2-fluoro-6-(trifluoromethyl) benzonitrile and the appropriate alkylbenzoxoxyphenol 21 through microwave assisted uncatalyzed coupling reactions following the approach taken by the Wang group.\textsuperscript{57} Debenzylation of the benzoxyphenol 22 was established under hydrogenolysis conditions with 10% Pd/C in EtOH at 45 °C to provide the diaryl ether phenol 23.
**Scheme 2.3:** Synthesis of BAY 59-3074 Alkyl Analogues

The binding affinities of the 2-(3-hydroxy-5-alkylphenoxy)-6-(trifluoromethyl)benzonitriles summarized in Table 2.1, were determined by the ability of the compounds to displace bound radiolabeled ligands binding in rat brain tissue. The binding affinities of the novel BAY 59-3074 alkyl analogues were determined at the cannabinoid receptor (CB1) by inhibition of \[^3H\]SR141716A since it is selective for the CB1 receptor. Even though CB2 receptors may be present in the brain their concentration is minimal compared to the CB1 receptors. Our focus is the development of CNS compounds so it was deemed unnecessary to determine the CB2 affinities at this time.
Table 2.1: *In Vitro* binding data at CB1 and $[^3]$H$SR141716A inhibition

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Cmpd.</th>
<th>Code #</th>
<th>X</th>
<th>Y</th>
<th>ClogP$^a$</th>
<th>$[^3]$H$SR141716A (CB1) $K_i$ (nM)$^b$</th>
<th>CB1$^c$ (10 µM)</th>
<th>CB1$^c$ (100 µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23b</td>
<td>ARN 156</td>
<td>OH</td>
<td>CH$_3$</td>
<td>4.39</td>
<td>23,055±3217</td>
<td>16</td>
<td>30</td>
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<tr>
<td>23c</td>
<td>ARN 167</td>
<td>OH</td>
<td>CH$_2$CH$_3$</td>
<td>4.92</td>
<td></td>
<td>21</td>
<td>37</td>
</tr>
<tr>
<td>23d</td>
<td>ARN 180</td>
<td>OH</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>5.45</td>
<td></td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>23e</td>
<td>ARN 191</td>
<td>OH</td>
<td>CH$_2$(CH$_2$)$_2$CH$_3$</td>
<td>5.98</td>
<td></td>
<td>35</td>
<td>94</td>
</tr>
<tr>
<td>23f</td>
<td>ARN 158</td>
<td>OH</td>
<td>CH$_2$(CH$_2$)$_3$CH$_3$</td>
<td>6.50</td>
<td>293±107</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>23g</td>
<td>ARN 190</td>
<td>OH</td>
<td>CH$_2$(CH$_2$)$_4$CH$_3$</td>
<td>7.03</td>
<td>TBA</td>
<td>TBA</td>
<td>TBA</td>
</tr>
<tr>
<td>13</td>
<td>BAY 59-3074</td>
<td>H</td>
<td>SO$_2$(CH$_2$)$_3$CF$_3$</td>
<td>4.77</td>
<td>55$^d$</td>
<td>61</td>
<td>65</td>
</tr>
</tbody>
</table>

$^a$The ClogP values were calculated using CS ChemDraw Ultra 10.0. $^b$All the values are mean ± SEM of three experiments. $^c$Binding affinities at CB1 receptor measured as % inhibition. $^d$See reference 56.

It was desired to improve hydrophilicity (ClogP < 5) in order to maximize blood brain barrier permeability according to Lipinski’s rules.$^{61}$ However, as the alkyl chain increased in length the hydrophilicity decreased and the lipophilicity increased. The most potent of the alkyl series was the olivetol derivative 23f. In general, the alkyl series were less potent than BAY 59-3074 ($K_i = 55$ nM)$^{56}$. The alkyl series 23e-23g (ClogP = 4.39 - 6.55)$^{55}$ was more lipophilic compared to the BAY 59-3074 (ClogP = 4.77)$^{55}$, but 23b was an improvement in the hydrophilicity. Even though 23b showed an improvement in
hydrophilicity its potency was extremely low in comparison to 23f. Therefore, it was
desired to synthesize the BAY 59-3074 for comparison and a series of esters to determine
if the electron density can enhance the inhibition of the BAY 59-3074 analogues at the
CB1 receptors.

The diaryl ether phenol 23a undergoes phase transfer catalysis with 4,4,4-
Trifluoro-butane-1-sulfonyl chloride, 45% NaOH and tetrabutylammonium bromide at
0°C to afford BAY 59-3074 (13) in 40% yield (Scheme 2.4).62

**Scheme 2.4:** Synthesis of BAY 59-3074

The binding affinity for the sulphonate ester 13 is presented in Table 2.1. The BAY 59-
3074 has modest binding affinity ($K_i = 55$ nM)56 and a greater affinity compared to the
alkyl series reported in Table 2.1. Therefore, the syntheses of the ester analogues were
attractive targets.
2.3.3. Synthesis of BAY 59-3074 Ester Analogues

The same phase transfer catalysis utilized for BAY 59-3074 was employed to synthesize the diaryl ether ester analogues (Scheme 2.5).

**Scheme 2.5:** Synthesis of Diaryl Ether Esters Analogues

The diaryl ether phenol 23a undergoes phase transfer catalysis with the appropriate acid halide, 45% NaOH and tetrabutylammonium bromide at 0 °C to afford the desired diaryl ether ester analogue 24.
Table 2.2: [³H]SR141716A uptake inhibition at CB1

Upon evaluation of the ester series, there was significant improvement of the hydrophilicity 24a-24e (ClogP 3.92 – 6.02)\(^5\) compared to the alkyl series 23b-23g (ClogP 4.39 – 7.03)\(^5\). The alkyl chain in the ester series increased in length the hydrophilicity decreased and the lipophilicity increased. The butyl ester, 68d, exhibited modest percent inhibition at the CB1 receptor in comparison to the other synthesized esters. By comparing the affinities of 24d and 24e there is a significant difference derived from the addition of a single carbon atom. This difference suggests that there is a size maximum in the ester moiety. Therefore, it was desired to compare the synthesized compounds that exhibited modest to high percent inhibition at the CB1 receptor. In
addition to comparing the synthesized compounds, we choose to include 22a and 23a intermediates to observe the percent inhibition to focus on potential lead compounds.

2.3.4. Evaluation of BAY 59-3074 Analogues

These novel BAY 59-3074-CB25 hybrid analogues were synthesized and the binding affinity at the cannabinoid receptors was determined (Table 2.3).

Table 2.3: Comparison of $[^3]$H]SR141716A uptake inhibition at CB1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Code #</th>
<th>ClogP$^a$</th>
<th>CB1$^c$ (10µM)</th>
<th>CB1$^c$ (100µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>BAY 59-3074</td>
<td>4.77</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>22a</td>
<td>AS 109</td>
<td>6.24</td>
<td>49</td>
<td>56</td>
</tr>
<tr>
<td>23a</td>
<td>ARN 142</td>
<td>3.89</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>23f</td>
<td>ARN 158</td>
<td>6.50</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>24d</td>
<td>ARN 202</td>
<td>5.49</td>
<td>25</td>
<td>49</td>
</tr>
</tbody>
</table>

$^a$The clogP values were calculated using CS ChemDraw Ultra 10.0. $^b$All the values are mean ± SEM of three experiments. $^c$Binding affinities at CB1 receptor measured as % inhibition.
Table 2.3 serves as a survey of each class of analogues and the most potent ligand of the series. Although our focus lies in developing a compound with improved hydrophilicity, the benzyl ether intermediate 22a showed some promise. In evaluating the compounds, 22a was deemed the most potent with inhibition values greater than the alkyl and ester analogues of each series. However, the potency is less than that of the BAY 59-3074. Improvement was made upon the hydrophilicity with the ester analogue series, but the potency was lower than 13. Future SAR studies will focus on using the benzyl ether 22a as a lead compound for the development of novel CB1 ligands.

2.3.5. Synthesis of BAY 59-3074 Benzyl Ether Analogues

Using the benzyl ether 22a as a lead compound a variety of benzyl analogues with electron withdrawing and donating groups were synthesized (Scheme 2.6). The binding affinity at CB receptors is currently under investigation and will be reported in due course.
Scheme 2.6: Synthesis of BAY 59-3074-CB25 hybrid benzyl analogues

2.4. Conclusion

A series of BAY 59-3074 analogues were synthesized to obtain a new class of CB1 receptor ligands. A series of alkyl ligands 23b-23g, ester ligands 24a-24e, and the benzyl ether intermediate 22a were synthesized and evaluated. The alkyl series produced the olivetol derivative 23f as a potential lead compound suggesting that an alkyl chain of 5 carbons can lead to a potent CB1 ligand. Within the ester series, there was improvement of the hydrophilicity 24a-24e compared to the alkyl series 23b-23g. The valeryl ester derivative 24d showed modest affinity at the CB1 receptors. Comparison of 24d and 24e gave insight into the chain length that can be applied to modifying these potential lead compounds. The significant decrease in affinity led to the formulation that there is a size limitation for the ester series. The benzyl ether intermediate 22a exhibited
the highest affinity over both the alkyl and ester series. Future SAR studies will focus on
the benzyl ether 22a as a lead compound for the development of novel CB1 ligands.

2.5. Experimental Section

General Methods

All chemicals were purchased from Aldrich Chemical Company unless otherwise
noted. Anhydrous toluene, tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and
methanol (MeOH) were purchased from Mallinckrodt Baker, Inc and were used under
nitrogen without any further purification. Thin layer chromatography (TLC) 20 x 20 cm
glass plates precoated with 250 µm silica gel were purchased from Sorbent Technologies
and used to monitor reactions via visualization with short-wave UV light, iodine,
potassium permanganate, phosphomolybdic acid (PMA), 2,4-dinitrophenyl hydrazine or
Dragendorff’s reagent. Chromatography is in reference to column chromatography on
silica gel (Silica Gel 60, 230-400 mesh). High-pressure hydrogenations were carried out
on a Parr apparatus. Proton and carbon NMR were recorded on a Varian-Gemini 300 and
400 MHz nuclear magnetic resonance spectrometer, respectively at ambient temperature
in deuterated chloroform from Cambridge Isotope Laboratories, Inc. $^1$H NMR chemical
shifts are reported in δ values (ppm) with tetramethylsilane (TMS), employed as the
internal standard. $^{13}$C NMR chemical shifts are reported in δ values (ppm) with
chloroform-D (CDCl$_3$, 77.0 ppm), employed as the internal standard. Elemental analyses
were obtained from Atlantic Microlabs, Inc.
General Method A: Preparation of Alkylresorcinols

Gringard Methodology\textsuperscript{59}

To a stirred solution of 3,5-dimethoxybenzaldehyde (14) (1 equiv.) in THF and Et\textsubscript{2}O at -78 °C under argon was added alkylmagnesium halide (1.28 equiv.) dropwise over 30 minutes. The reaction was gradually brought to room temperature and stirred for 1 h. The reaction was quenched dropwise by adding saturated aqueous NH\textsubscript{4}Cl. The reaction was then diluted with EtOAc and brine, and stirred vigorously. The reaction mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO\textsubscript{4}, and evaporated to dryness under reduced pressure.

Deoxygenation Methodology\textsuperscript{59}

To a stirred solution of the dimethoxyalcohol 15 (1 equiv.) in glacial acetic acid was added 10 % Pd/C (10 wt. %) and the resulting suspension was stirred vigorously under a hydrogen atmosphere using a hydrogen balloon overnight at 60 °C. Upon completion the reaction mixture was diluted with Et\textsubscript{2}O, brine, and water and filter through a pad of celite to remove the catalyst. The organic layer was separated, diluted with water and neutralized by the addition of NaHCO\textsubscript{3}. The aqueous layer was extracted with Et\textsubscript{2}O. The combined organic layers were washed with brine, dried over MgSO\textsubscript{4} and evaporated under reduced pressure.
**Demethylation Methodology**

To a stirred solution of 1-hexyl-3,5-dimethoxybenzene 16 (1 equiv.) in anhydrous CH₂Cl₂ at -78 °C under an argon atmosphere was added BBr₃ (2.5 equiv.) dropwise over 15 minutes. Following the addition the reaction mixture was gradually brought to room temperature and allowed to continue stirring for 4 h. The reaction mixture was quenched by the addition of MeOH and ice at 0 °C, the resulting mixture was warmed to room temperature, stirred for 40 minutes and the solvent was removed under reduced pressure. The residual oil was diluted with EtOAc and the solution was washed with saturated aqueous NaHCO₃, water and brine. The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure.

**General Method B: Preparation of 2-ethylbenzene-1,3-diol**

A solution of 3,5-dihydroxyacetophenone 18 (1 equiv.) and 10% Pd/C (50 wt. %) in 4% HCl was hydrogenated using a hydrogen balloon overnight. The reaction mixture was filtered through celite, and extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to dryness under reduced pressure.

**General Method C: Preparation of monobenzylated 1,3-diols**

The diol (1 equiv.) in DMF was added dropwise to NaH (1 equiv.) in DMF. The reaction mixture was allowed to stir for 30 minutes at room temperature. BnBr (1 equiv.) in DMF was added dropwise to the reaction mixture and allowed to stir for 2 h at room temperature. Distilled H₂O was added and the mixture was extracted with EtOAc. The
organic layers were combined, washed with 0.5 N HCl, washed with brine, dried over Na₂SO₄, and evaporated to dryness under reduced pressure.

**General Method D: Preparation of Diaryl Ethers**[^57]

2-Fluoro-6-(trifluoromethyl)benzonitrile (10 mmol), phenol 21 (10~12 mmol), and potassium carbonate (20 mmol) were added to DMSO. Using a microwave power of 300-400 W the temperature was ramped from room temperature to the boiling point of DMSO. Upon completion of the reaction, it was cooled to room temperature, put into ice water, and extracted with Et₂O. The organic layers were combined, washed with 0.5 N HCl, washed with brine, dried over Na₂SO₄, and evaporated to dryness under reduced pressure.

**General Method E: Preparation of Debenzylated Diaryl Ethers**

A solution of 2-(3-(benzyloxy)-5-alkylenoxy)-6-(trifluoromethyl)benzonitrile 22 (1 equiv.) and 10% Pd/C (50 wt. %) in EtOH (23 mL) was hydrogenated using a hydrogen balloon at 45 ºC. The reaction mixture was filtered through celite and evaporated to dryness under reduced pressure.

**General Method F: Preparation of sulphonic ester, BAY 50-3074**

Under argon, the phenol 23a (0.711 mmol) is dissolved in DCM and tetrabutylammonium iodide (0.337 mmol) and 20M NaOH were added and stirred. At 0 ºC, 4,4,4-trifluorobutane-1-sulphonyl chloride (0.809 mmol) dissolved in DCM was added. The reaction mixture was allowed to stir for 1 h after the color change at 0 ºC and

[^57]: Hyperlink reference to a specific method or source.
another 1 h at room temperature. The reaction mixture was diluted with water and extracted with DCM. The organic layers were collected, washed with brine, and dried over MgSO$_4$.

**General Method G: Preparation of Esters**

Under argon, the phenol 23a (0.53 mmol) is dissolved in DCM and tetrabutylammonium iodide (0.27 mmol) and 20M NaOH were added and stirred. At 0 ºC, the acid halide (0.63 mmol) dissolved in DCM was added. The reaction mixture was allowed to stir for 1 h after the color change at 0 ºC and for another 1 h at room temperature. The reaction mixture was diluted with water and extracted with DCM. The organic layers were collected, washed with brine, and dried over MgSO$_4$.

![Chemical structure of 1-(3,5-Dimethoxyphenyl)propan-1-ol (15a)](image)

**1-(3,5-Dimethoxyphenyl)propan-1-ol (15a)$^{59}$**

**General Method A.** No further purification to afford 8.38 g (98%) of (15a) as a pale yellow oil: R$_f$ 0.40 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 0.93 (t, $J$ = 7.6 Hz, 3H), 1.68-1.81 (m, 2H), 3.79 (s, 6H), 4.23 (t, $J$ = 6.4 Hz, 1H), 2.73 (broad s, 1, OH), 6.37 (s, 1H), 6.50 (d, $J$ = 2.0 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 10.1, 31.9, 56.0(2), 77.8, 98.4, 104.7(2), 147.7, 160.9(2).
1-Propyl-3,5-dimethoxybenzene (16a)<sup>59</sup>

**General Method A.** The residue was purified by column chromatography (SiO<sub>2</sub>, gradient of hexane, Et<sub>2</sub>O/hexane, 1:9) to afford 0.910 g (43%) of (16a) as a pale yellow oil: R<sub>f</sub> 0.78 (CH<sub>2</sub>Cl<sub>2</sub>/hexane, 3:7). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.98 (t, <i>J</i> = 7.2 Hz, 3H), 1.67 (q, <i>J</i> = 7.6 Hz, 2H), 2.56 (t, <i>J</i> = 7.2 Hz, 2H), 3.80 (s, 6H), 6.33 (t, <i>J</i> = 2.4 Hz, 1H), 6.38 (d, <i>J</i> = 2.4 Hz, 2H). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>) δ 14.1, 24.6, 38.6, 55.4(2), 97.8, 106.8(2), 145.4, 161.0(2).

5-Propylbenzene-1,3-diol (17a)<sup>59</sup>

**General Method A.** No further purification to afford 0.839 g (99%) of (17a) as an amber oil: R<sub>f</sub> 0.48 (EtOAc/hexane, 3:7). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.92 (t, <i>J</i> = 7.6 Hz, 3H), 1.60 (q, <i>J</i> = 7.2 Hz, 2H), 2.47 (t, <i>J</i> = 7.6 Hz, 2H), 4.72 (broad s, 1, OH), 6.17 (s, 1H), 6.24 (d, <i>J</i> = 1.6 Hz, 2H). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>) δ 14.0, 24.3, 38.1, 100.4, 108.3(2), 146.0, 159.2(2).
1-(3,5-Dimethoxyphenyl)butan-1-ol (15b)$^{59}$

**General Method A.** No further purification to afford 3.85 g (99%) of (15b) as pale yellow oil: $R_f$ 0.68 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 0.92 (t, $J$ = 7.2 Hz, 3H), 1.23-1.47 (m, 2H), 1.59-1.79 (m, 2H), 3.77 (s, 6H), 4.57 (t, $J$ = 6.8 Hz, 1H), 6.35 (td, $J$ = 2.0 Hz, 2.4 Hz, 1H), 6.49 (t, $J$ = 2.4 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 14.2, 19.2, 41.3, 55.5(2), 74.6, 99.5, 104.0(2), 147.9, 161.0(2).

1-Butyl-3,5-dimethoxybenzene (16b)$^{59}$

**General Method A.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, Et$_2$O/hexane, 1:9) to afford 1.383 g (39%) of (16b) as a yellow oil: $R_f$ 0.89 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 1.00 (t, $J$ = 7.2 Hz, 3H), 1.42 (sextet, $J$ = 7.6 Hz, 2H), 1.62-1.70 (m, 2H), 2.62 (t, $J$ = 7.6 Hz, 2H), 3.82 (s, 6H), 6.36 (t, $J$ = 2.4 Hz, 1H), 6.42 (d, $J$ = 2.0 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 14.2, 22.7, 33.7, 36.3, 55.3(2), 97.8, 106.7(2), 145.6, 161.0(2).
5-Butylbenzene-1,3-diol (17b)$^{59}$

**General Method A.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, Et$_2$O/hexane, 1:9) to afford 1.04 g (88%) of (17b) as an amber oil: R$_f$ 0.45 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.86 (t, $J$ = 7.6 Hz, 3H), 1.23-1.32 (m, 2H), 1.43-1.51 (m, 2H), 2.40 (t, $J$ = 7.6 Hz, 2H), 5.43 (broad s, 1, OH), 6.24 (t, $J$ = 2.0 Hz, 1H), 6.28 (d, $J$ = 2.4 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.1, 22.5, 33.4, 35.7, 100.4, 108.3(2), 146.4, 156.8(2).

1-(3,5-Dimethoxyphenyl)hexan-1-ol (15c)$^{59}$

**General Method A.** No further purification to afford 8.22 g (97%) of (15c) as a pale yellow oil: R$_f$ 0.64 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.86 (dt, $J$ = 3.6 Hz, 6.8 Hz, 3H), 1.25-1.29 (m, 5H), 1.37-1.43 (m, 1H), 1.63-1.77 (m, 2H), 3.78 (s, 6H), 4.58 (q, $J$ = 7.2 Hz, 1H), 6.35 (t, $J$ = 2.4 Hz, 1H), 6.49 (dd, $J$ = 2.4 Hz, 2.4 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.2, 22.8, 25.7, 31.9, 39.2, 55.5(2), 74.9, 99.5, 104.0(2), 147.9, 161.1(2).
1-Hexyl-3,5-dimethoxybenzene (16c)$^{59}$

**General Method A.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, Et$_2$O/hexane, 1:9) to afford 1.23 g (32%) of (60c) as a yellow oil: R$_f$ 0.38 (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.28-1.38 (m, 6H), 1.57-1.64 (m, 2H), 2.55 (t, $J$ = 7.6 Hz, 2H), 3.78 (s, 6H), 6.30 (t, $J$ = 2.4 Hz, 1H), 6.35 (d, $J$ = 2.0 Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.3, 22.9, 29.3, 31.5, 32.0, 36.6, 55.4(2), 97.8, 106.7(2), 145.6, 161.0(2).

5-Hexylbenzene-1,3-diol (17c)$^{59}$

**General Method A.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, Et$_2$O/hexane, 1:9) to afford 1.23 g (99%) of (17c) as a light brown oil: R$_f$ (EtOAc/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.88 (t, $J$ = 2.4 Hz, 3H), 1.24-1.28 (m, 6H), 1.55 (t, $J$ = 6.0 Hz, 2H), 2.47 (t, $J$ = 7.6 Hz, 2H), 5.50 (broad s, 1, OH), 6.18 (s, 1H), 6.24 (s, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.3, 22.8, 29.2, 31.2, 31.9, 36.0, 100.4, 108.2(2), 146.4, 156.9(2).
5-Ethylbenzene-1,3-diol (19)

**General Method B.** The residue was purified by column chromatography (SiO₂, gradient of hexane, EtOAc/hexane, 1:4) to afford 1.31 g (72%) of (19) as a colorless oil: Rₜ 0.16 (EtOAc/hexane, 1:4). ¹HNMR (400 MHz, CDCl₃) δ 1.19 (t, J = 7.6 Hz, 3H), 2.53 (q, J = 7.6 Hz, 2H), 5.06 (broad s, 2, OH), 6.19 (t, J = 2.4 Hz, 1H), 6.27 (d, J = 2.0 Hz, 2H). ¹³CNMR (400 MHz, CDCl₃) δ 15.4, 28.9, 100.5, 107.6(2), 135.5, 157.0(2).

3-Benzylxylophenol (21a)

**General Method C.** The residue was purified by column chromatography (SiO₂, gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 0.86 g (24%) of (21a) as an amber oil: Rₜ 0.46 (EtOAc/hexane, 1:4). ¹HNMR (400 MHz, (CD₃)₂CO) δ 4.75 (broad s, 1, OH), 5.04 (s, 2H), 6.43 (tt, J = 1.6 Hz, 2.0 Hz, 1H), 6.49 (t, J = 2.4 Hz, 1H), 6.56 (qq, J = 0.8 Hz, 0.8 Hz, 1H), 7.14 (t, J = 8.4 Hz, 1H), 7.31-7.44 (m, 5H). ¹³CNMR (400 MHz, (CD₃)₂CO) δ 69.7, 102.6, 106.3, 108.4, 127.8, 128.0(2), 128.7(2), 130.3, 137.8, 158.9, 160.6.
3-Benzyloxy-5-methyl-phenol (21b)

**General Method C.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 0.995 g (29%) of (21b) as a pale yellow oil: \(R_f\) 0.44 (EtOAc/hexane, 1:4). \(^1\)HNMR (400 MHz, (CD\(_3\)_2SO) \(\delta\) 2.18 (s, 3H), 5.00 (s, 2H), 6.24 (d, \(J = 4.4\) Hz, 2H), 6.29 (s, 1H), 7.31 (t, \(J = 4.0\) Hz, 3H), 7.35-7.43 (m, 2H), 9.30 (broad s, 1, OH). \(^{13}\)CNMR (400 MHz, (CD\(_3\)_2SO) \(\delta\) 21.3, 69.0, 99.4, 106.4, 108.9, 127.6(2), 127.7, 128.4(2), 137.4, 139.5, 158.5, 159.6.

3-Benzyloxy-5-ethylphenol (21c)

**General Method C.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane) to afford 0.379 g (18%) of (21c) as a yellow oil: \(R_f\) 0.47 (EtOAc/hexane, 1:4). \(^1\)HNMR (400 MHz, (CDCl\(_3\)) \(\delta\) 1.21 (t, \(J = 7.6\) Hz, 3H), 2.57 (q, \(J = 7.6\) Hz, 2H), 4.61 (broad s, 1, OH), 5.02 (s, 2H), 6.31 (q, \(J = 2.4\) Hz, 1H), 6.44 (s, 2H), 7.33-7.44 (m, 5H). \(^{13}\)CNMR (400 MHz, (CDCl\(_3\)) \(\delta\) 15.5, 29.1, 70.2, 99.7, 107.4, 107.8, 127.8(2), 128.2, 128.8(2), 137.2, 147.4, 156.7, 160.3.
3-Benzylxyloxy-5-propylphenol (21d)

**General Method C.** The residue was purified by column chromatography (SiO₂, gradient of hexane) to afford 0.256 g (19%) of (21d) as a yellow oil: R_f 0.51 (EtOAc/hexane, 1:4). ^1^HNMR (400 MHz, CDCl₃) δ 0.93 (t, J = 7.2 Hz, 3H), 1.50-1.66 (m, 2H), 2.53 (t, J = 7.2 Hz, 2H), 5.02 (s, 2H), 6.23 (d, J = 2.0 Hz, 1H), 6.23-6.47 (m, 2H), 7.09-7.44 (m, 5H). ^13^CNMR (400 MHz, CDCl₃) δ 13.9, 24.4, 38.2, 70.5, 104.6, 112.9, 113.0, 127.8(2), 128.4, 128.9(2), 136.6, 146.7, 160.4, 161.9.

3-Benzylxyloxy-5-butylphenol (21e)

**General Method C.** The residue was purified by column chromatography (SiO₂, gradient of hexane, 1:9, 1:7, 1:5) to afford 0.409 g (26%) of (21e) as a dark brown oil: R_f 0.67 (EtOAc/hexane, 3:7). ^1^HNMR (400 MHz, CDCl₃) δ 1.03-1.08 (m, 3H), 1.42-1.51 (m, 2H), 1.64-1.72 (m, 2H), 2.62 (dd, J = 7.6 Hz, 2.0, 2H), 5.07 (s, 2H), 6.38 (d, J = 4.4 Hz, 1H), 6.44 (s, 1H), 6.48 (d, J = 2.4 Hz, 1H), 6.49 (s, 1H), 7.26-7.53 (m, 5H). ^13^CNMR (400 MHz, CDCl₃) δ 14.3, 22.7, 33.6, 36.1, 70.5, 100.1, 108.4, 108.9, 128.0(2), 128.4, 129.0(2), 137.3, 146.2, 156.7, 160.3.
3-Benzylxoy-5-pentyl-phenol (21f)

**General Method C.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 0.457 g (31%) of (21f) as a brown oil: R\(_f\) 0.53 (EtOAc/hexane, 1:4). \(^1\)HNMR (400 MHz, (CD\(_3\))\(_2\) CO) \(\delta\) 0.89 (t, \(J = 6.8\) Hz, 3H), 1.26-1.34 (m, 4H), 1.55-1.63 (m, 2H), 2.49-2.56 (m, 2H), 5.02 (s, 2H), 7.30-7.44 (m, 5H), 8.21 (broad s, 1, OH). \(^{13}\)CNMR (400 MHz, (CD\(_3\))\(_2\) CO) \(\delta\) 13.7, 22.6, 31.1, 31.6, 36.0, 69.6, 99.8, 106.5, 108.4, 127.7(2), 127.9, 128.6(2), 138.0, 145.3, 158.6, 160.4.

3-Benzylxoy-5-hexylphenol (21f)

**General Method C.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane) to afford 0.374 g (21%) of (21f) as a light brown oil: R\(_f\) 0.72 (EtOAc/hexane, 3:7). \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.95 (dt, \(J = 2.4\) Hz, 4.0 Hz, 3H), 1.31-1.40 (m, 6H), 1.62 (q, \(J = 7.6\) Hz, 2H), 2.56 (t, \(J = 8.0\) Hz, 2H), 5.03 (s, 2H), 5.75 (broad s, 1, OH), 6.36 (d, \(J = 8.8\) Hz, 1H), 6.38 (t, \(J = 2.4\) Hz, 1H), 6.50 (d, \(J = 1.2\) Hz,
1H), 7.35-7.48 (m, 5H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.3, 22.8, 29.2, 31.2, 31.9, 36.2, 70.2, 99.9, 108.0, 108.6, 127.8(2), 128.2, 128.8(2), 137.1, 146.0, 156.6, 160.1.

2-(3-Benzylxloxy-phenoxy)-6-trifluoromethyl-benzonitrile (22a)$^{57}$

**General Method D.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane, 1:10, 1:9, 1:4) to afford 0.325 g (23%) of (22a) as a white solid: R$_f$ 0.60 (EtOAc/hexane, 1:4). $^1$HNMR (400 MHz, (CD$_3$)$_2$SO) δ 5.16 (s, 2H), 6.82 (t, $J$ = 8.4 Hz, 1H), 6.94-7.00 (m, 2H), 7.24 (d, $J$ = 11.6 Hz, 1H), 7.33-7.45 (m, 6H), 7.65 (d, $J$ = 10.0 Hz, 1H), 7.82 (d, $J$ = 10.8 Hz, 1H). $^{13}$CNMR (400 MHz, (CD$_3$)$_2$SO) δ 70.1, 107.2(3), 112.5, 112.8, 120.8(2), 121.1, 127.8(3), 128.1(2), 128.7, 131.2, 135.2, 137.2, 155.9, 160.9, 161.0. MS (ESI) m/z 392.2 (M + Na), 387.3 (M + H$_2$O), 370.2 (M + 1). Anal. Calcd. For C$_{21}$H$_{14}$F$_3$NO$_2$:  C, 68.29; H, 3.82; N, 3.79. Found:  C, 68.21; H, 3.77; N, 3.81.

2-(3-Benzylxloxy-5-methyl-phenoxy)-6-trifluoromethyl-benzonitrile (22b)$^{57}$

**General Method D.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 1.35 g (91%) of (22b) as a pale yellow oil: R$_f$ 0.56 (EtOAc/hexane, 1:5). $^1$HNMR (400 MHz, (CD$_3$)$_2$CO) δ 2.34 (s, 3H),
5.14 (s, 2H), 6.66 (s, 1H), 6.73 (s, 1H), 6.84 (s, 1H), 7.25 (d, \( J = 8.8 \) Hz, 1H), 7.34 (d, \( J = 7.2 \) Hz, 1H), 7.39 (t, \( J = 7.2 \) Hz, 2H), 7.46 (d, \( J = 7.2 \) Hz, 2H), 7.65 (d, \( J = 7.6 \) Hz, 1H), 7.82 (t, \( J = 8.4 \) Hz, 1H). \(^{13}\) CNMR (400MHz, (CD\(_3\))\(_2\)CO) \( \delta \) 20.9, 70.1, 104.3(2), 113.2, 113.5, 120.7(2), 120.8, 121.1, 127.8(2), 128.1, 128.7(2), 135.2(2), 137.3, 141.9, 155.7, 160.6, 161.7.

2-(3-(Benzyloxy)-5-ethylphenoxy)-6-(trifluoromethyl)benzonitrile (22c)

**General Method D.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane) to afford 0.404 g (74%) of (22c) as a pale yellow oil: \( R_f \) 0.71 (EtOAc/hexane, 1:4). \(^1\) HNMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.23 (t, \( J = 7.6 \) Hz, 3H), 2.63 (q, \( J = 7.2 \) Hz, 2H), 5.04 (s, 2H), 6.53 (t, \( J = 2.4 \) Hz, 1H), 6.56 (s, 1H), 6.75 (s, 1H), 7.06 (d, \( J = 8.8 \) Hz, 1H), 7.32-7.44 (m, 2H), 7.53 (t, \( J = 8.8 \) Hz, 2H). \(^{13}\) CNMR (400 MHz, CDCl\(_3\)) \( \delta \) 15.4, 29.1, 70.5, 104.5(2), 112.4(2), 112.5, 120.1, 120.2(2), 127.8(2), 128.4, 128.9(2), 134.0(3), 148.2, 155.4, 160.5, 161.8.
2-(3-(Benzyloxy)-5-propylphenoxy)-6-(trifluoromethyl)benzonitrile (22d)

**General Method D.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane) to afford 0.279 g (64%) of (22d) as a pale yellow oil: R$_f$ 0.63 (EtOAc/hexane, 1:4). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.93 (t, J = 7.6 Hz, 3H), 1.60-1.66 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 5.04 (s, 2H), 6.54 (d, J = 1.6 Hz, 2H), 6.73 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.32-7.44 (m, 6H), 7.53 (t, J = 8.4 Hz, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 13.4, 24.4, 38.2, 70.5, 104.6(2), 112.9, 113.0, 115.6, 120.0, 120.1(2), 127.8(2), 128.3, 128.9(2), 134.0, 136.6, 146.7, 155.3, 160.4, 161.9.

2-(3-(Benzyloxy)-5-butylphenoxy)-6-(trifluoromethyl)benzonitrile (22e)

**General Method D.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane 3:7, CH$_2$Cl$_2$/Hexane 3:7) to afford 0.244 g (36%) of (22e) as a colorless oil: R$_f$ 0.80 (CH$_2$Cl$_2$/hexane, 3:7). $^1$HNMR (400 MHz, CDCl$_3$) δ 0.94 (t, J = 7.6 Hz, 3H), 1.28-1.41 (m, 2H), 1.56-1.64 (m, 2H), 2.61 (t, J = 6.8 Hz, 2H), 5.05 (s, 2H), 6.54-6.56 (m, 2H), 6.75 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.32-7.45 (m, 6H), 7.53 (t, J = 8.0 Hz, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 14.1, 22.5, 33.4, 35.9, 70.5,
104.6(2), 112.6, 112.9, 113.0, 120.1, 120.2(2), 127.8(2), 128.4, 128.9(2), 134.1(2), 136.7, 146.9, 155.3, 160.4, 161.9.

2-(3-Benzyloxy-5-pentyl-phenoxy)-6-trifluoromethyl-benzonitrile (22f)\textsuperscript{57}

**General Method D.** The residue was purified by column chromatography (SiO\textsubscript{2}, gradient of hexane) to afford 0.446 g (72%) of (22f) as a pale yellow oil: R\textsubscript{f} 0.36 (EtOAc/hexane, 1:9). \textsuperscript{1}HNMR (400 MHz, (CD\textsubscript{3})\textsubscript{2} CO) δ 0.88 (dd, J = 3.2 Hz, 6.8 Hz, 3H), 1.29-1.36 (m, 4H), 1.63 (q, J = 5.6 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H), 5.14 (s, 2H), 6.69 (t, J = 2.0 Hz, 1H), 6.75 (t, J = 2.4 Hz, 1H), 6.86 (t, J = 2.0 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.33-7.41(m, 3H), 7.46-7.48 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.79-7.83 (m, 1H). \textsuperscript{13}CNMR (400 MHz, (CD\textsubscript{3})\textsubscript{2} CO) δ 13.7, 30.9, 31.5, 32.5, 35.8, 70.1, 104.5(2), 112.7(2), 113.0, 120.6(2), 120.9, 127.8(2), 128.1, 128.7(2), 135.2(2), 137.3, 147.0, 155.6, 160.7, 161.8.
2-(3-(Benzyloxy)-5-hexylphenoxy)-6-(trifluoromethyl)benzonitrile (22g)

**General Method D.** The residue was purified by column chromatography (SiO₂, gradient of hexane) to afford 0.491 g (98%) of (22g) as a yellow oil: Rₓ 0.49 (EtOAc/hexane, 3:7). ¹H NMR (400 MHz, CDCl₃) δ 0.90 (t, J = 5.2 Hz, 3H), 1.31 (s, 6H), 1.59 (td, J = 2.8 Hz, 6.0 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H), 5.05 (s, 2H), 6.55 (d, J = 1.6 Hz, 2H), 6.75 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.32-7.45 (m, 6H), 7.55 (t, J = 8.4 Hz, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 14.3, 22.8, 29.1, 31.2, 31.9, 36.2, 70.5, 101.0, 104.6(2), 112.9, 113.0, 120.1(2), 120.2, 127.8(2), 128.4, 128.9(2), 134.1(2), 136.7, 147.0, 155.3, 160.4, 161.9.

2-(3-Hydroxy-phenoxy)-6-trifluoromethyl-benzonitrile (23a)

**General Method E.** The residue was purified by column chromatography (SiO₂, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:1) to afford 0.199 g (81%) of (23a) as a white solid: Rₓ 0.08 (EtOAc/hexane, 1:4); mp 106–108 °C. ¹H NMR (400 MHz, (CD₃)₂CO) δ 6.77-6.71 (m, 2H), 6.80-6.82 (m, 1H), 7.28-7.34 (m, 2H), 7.66 (d, J = 7.6
Hz, 1H), 7.84-7.88 (m, 1H), 8.81 (broad s, 1, OH). $^{13}$CNMR (400 MHz, (CD$_3$)$_2$CO) δ 101.6, 107.6, 111.1, 112.4, 113.2, 120.8(2), 121.7, 131.3, 135.3(2), 155.9, 159.5, 161.7.

2-(3-Hydroxy-5-methyl-phenoxy)-6-trifluoromethyl-benxonitrile (23b)

**General Method E.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:1) to afford 0.588 g (57%) of (23b) as a light brown solid: $R_f$ 0.19 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 73-75 ºC. $^1$HNMR (400 MHz, CDCl$_3$) δ 2.29 (s, 3H), 5.79 (broad s, 1, OH), 6.42-6.46 (m, 2H), 6.57 (d, $J$ = 0.8 Hz, 1H), 7.10 (d, $J$ = 8.8 Hz, 1H), 7.43 (d, $J$ = 7.6 Hz, 2H), 7.55-7.59 (m, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) δ 20.8, 101.2, 104.7(2), 111.9(2), 113.8, 120.6, 121.2, 135.2(2), 141.8, 155.7, 159.2, 161.8. MS (ESI) $m/z$ 292.1 (M - 1). Anal. Calcd. for C$_{15}$H$_{10}$F$_3$NO$_2$: C, 61.44; H, 3.44; N, 4.78. Found: C, 61.23; H, 3.77; N, 4.54.

2-(3-Ethyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23c)

**General Method E.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 0.279 g (89%) of
(23c) as a yellow oil: \( R_f \) 0.37 (EtOAc/hexane, 1:4). \(^1\)HNMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.21 (p, \( J = 13.0 \) Hz, 3H), 2.60 (q, \( J = 12.0 \) Hz, 2H), 5.32 (s, 1H), 6.43 (t, \( J = 2.4 \) Hz, 1H), 6.51 (broad s, 1, OH), 6.60 (t, \( J = 0.8 \) Hz, 1H), 7.11 (d, \( J = 8.4 \) Hz, 1H), 7.43 (d, \( J = 7.6 \) Hz, 1H), 7.57 (q, \( J = 8.0 \) Hz, 1H). \(^1\)CNMR (400 MHz, CDCl\(_3\)) \( \delta \) 15.3, 28.9, 105.3(2), 112.2, 112.7, 120.6, 120.3, 120.2(2), 134.2, 134.3, 148.5, 155.4, 157.4, 161.8. MS (ESI) \( m/z \) 342.1 (M + MeOH), 306.1 (M – O). Anal. Calcd. for C\(_{19}\)H\(_{18}\)F\(_3\)NO\(_2\): C, 62.54; H, 3.94; N, 4.56. Found: C, 62.44; H, 4.07; N, 4.35.

2-(3-Propyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23d)

**General Method E.** The residue was purified by column chromatography (SiO\(_2\), gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 90.4 mg (41%) of (67d) as a yellow oil: \( R_f \) 0.52 (EtOAc/hexane, 3:7). \(^1\)HNMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.92 (t, \( J = 7.2 \) Hz, 3H), 1.61 (q, \( J = 7.6 \) Hz, 2H), 2.52 (t, \( J = 7.6 \) Hz, 2H), 4.71 (broad s, 1, OH), 6.43 (s, 1H), 6.48 (s, 1H), 6.57 (s, 1H), 7.09 (d, \( J = 8.8 \) Hz, 1H), 7.43 (d, \( J = 7.6 \) Hz, 1H), 7.56 (t, \( J = 8.4 \) Hz, 1H). \(^1\)CNMR (400 MHz, CDCl\(_3\)) \( \delta \) 13.9, 24.3, 38.0, 100.2(2), 105.4(2), 112.6, 113.5(2), 120.1, 134.5(2), 146.9, 155.1, 157.6, 162.1. MS (ESI) \( m/z \) 364.3 (M + 1), 382.4 (M + H\(_2\)O), 386.2 (M + Na). Anal. Calcd. for C\(_{20}\)H\(_{20}\)F\(_3\)NO\(_2\)•1/2 H\(_2\)O: C, 64.51; H, 5.68; N, 3.76. Found: C, 64.62; H, 5.62; N, 3.64.
2-(3-Butyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23e)

**General Method E.** The residue was purified by column chromatography (SiO2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 86.7 mg (36%) of (23e) as a yellow solid: Rf 0.62 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 89-92 °C.  

$^1$H NMR (400 MHz, CDCl₃) δ 0.91 (q, $J = 7.6$ Hz, 3H), 1.30-1.37 (m, 2H), 1.52-1.59 (m, 2H), 2.54 (t, $J = 7.2$ Hz, 2H), 6.14 (broad s, 1, OH), 6.44 (t, $J = 2.4$ Hz, 1H), 6.47 (d, $J = 2.0$ Hz, 1H), 6.59 (dd, $J = 1.6$ Hz, 1.2 Hz, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.54-7.59 (m, 1H). $^{13}$C NMR (400 MHz, CDCl₃) δ 14.1, 22.4, 33.3, 35.7, 105.3(2), 112.6, 113.3, 120.1(2), 120.2(2), 134.2(2), 147.2, 155.3, 157.5, 161.9. MS (ESI) m/z 336.1 (M + 1), 353.3 (M + H₂O), 358.1 (M + Na). Anal. Calcd. for C₁₈H₁₆F₃NO₂: C, 64.47; H, 4.81; N, 4.18. Found: C, 64.71; H, 4.85; N, 4.06.

2-(3-Hydroxy-5-pentyl-phenoxy)-6-trifluoromethyl-benzonitrile (23f)

**General Method E.** The residue was purified by column chromatography (SiO₂, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:1) to afford 0.141 g (40%) of (23f) as a
white solid:  $R_f$ 0.23 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 85-86 °C. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 0.88 (q, $J$ = 4.4 Hz, 3H), 1.26-1.34 (m, 4H), 1.54-1.62 (m, 2H), 2.54 (t, $J$ = 7.6, 2H), 5.51 (broad s, 1, OH), 6.44 (t, $J$ = 2.0 Hz, 2H), 6.49 (d, $J$ = 2.0 Hz, 1H), 6.58 (s, 1H), 7.10 (d, $J$ = 8.4 Hz, 1H), 7.43 (d, $J$ = 8.0 Hz, 1H), 7.54-7.58 (m, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 14.2, 22.7, 30.9, 31.6, 35.9, 97.6, 105.2, 112.5, 112.9, 113.1, 115.6(2), 120.2(2), 134.1, 147.3, 155.4, 157.1, 161.8. MS (ESI) $m/z$ 372.2 (M + Na). Anal. Calcd. for C$_{19}$H$_{18}$F$_3$NO$_2$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.50; H, 5.14; N, 4.01.

![Structure of 2-(3-Hexyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23g)](image)

**2-(3-Hexyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23g)**

**General Method E.** The residue was purified by column chromatography (SiO$_2$, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 33.2 mg (8.4%) of (23g) as a yellow solid:  $R_f$ 0.68 (EtOAc/hexane, 3:7). The oily residue was induced to crystallize by the addition of hexane; mp 88-91 °C. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 0.86-0.89 (m, 3H), 1.24-1.33(m, 6H), 1.54-1.60 (m, 2H), 2.54 (t, $J$ = 8.0 Hz, 2H), 5.50 (broad s, 1, OH), 6.43 (t, $J$ = 2.0 Hz, 1H), 6.49 (s, 1H), 6.58 (s, 1H), 7.10 (d, $J$ = 8.4 Hz, 1H), 7.43 (d, $J$ = 7.6 Hz, 1H), 7.56 (t, $J$ = 8.4 Hz, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 14.3, 22.8, 29.1, 31.1, 31.8, 36.0, 105.3(2), 112.6(2), 112.8, 113.2, 120.1, 120.2, 134.1(2), 147.3, 155.4, 157.2, 161.8. MS (ESI) $m/z$ 364.3 (M + 1), 382.4 (M + H$_2$O), 386.2 (M +
Na). Anal. Calcd. for C_{20}H_{20}F_{3}NO_{2}\cdot\frac{1}{2}H_{2}O: C, 64.51; H, 5.68; N, 3.76. Found: C, 64.62; H, 5.62; N, 3.64.

![Chemical structure](image)

3-[2-Cyano-3-(trifluoromethyl)phenoxy]phenyl 4,4,4-trifluoro-1-butane-sulphonate (14)

**General Method F.** The residue was purified by preparative TLC (SiO\(_2\), gradient of hexane:CH\(_2\)Cl\(_2\) 3:7) to afford 0.129 g (40%) of 13 as a pale yellow oil: \(R_f\) 0.38 (CH\(_2\)Cl\(_2\)/hexane, 3:7). The oily residue was induced to crystallize by the addition of pentane; mp 59-60 °C. \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.25-2.41 (m, 4H), 3.38 (t, \(J = 7.6\) Hz, 2H), 7.05-7.10 (m, 2H), 7.14-7.20 (m, 2H), 7.47-7.54 (m, 2H), 7.64 (t, \(J = 8.4\) Hz, 1H), \(^1\){}CNMR (400 MHz, CDCl\(_3\)) \(\delta\) 17.1, 32.2 (q, \(J_{C-F} = 158\)), 49.6, 112.2, 114.5, 119.0, 119.3, 120.4, 120.7, 121.3(2), 124.1, 128.3, 131.7, 134.5, 149.8, 155.7, 160.5. MS (ESI) \(m/z\) 454.1 (M + 1).

![Chemical structure](image)

3-(2-Cyano-3-(trifluoromethyl)phenozy)phenyl acetate (24a)

**General Method G.** The residue was purified by flash chromatography (SiO\(_2\), gradient of hexane, CH\(_2\)Cl\(_2\), EtOAc) to afford 46.5 mg (67%) of (24a) as a colorless oil: \(R_f\) 0.30 (EtOAc/hexane, 1:4). \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.30 (s, 3H), 6.91 (t, \(J = 2.0\) Hz, 1H), 6.98-7.04 (m, 2H), 7.14 (d, \(J = 8.8\) Hz, 1H), 7.43 (dd, \(J = 8.0\) Hz, 8.8 Hz, 2H), 7.60 (t, \(J = 7.6\) Hz, 1H). \(^1\){}CNMR (400 MHz, CDCl\(_3\)) \(\delta\) 21.3, 98.6, 112.3, 114.4,
117.7(2), 119.3, 120.3, 120.7(2), 124.1, 131.0, 134.3(2), 152.1, 155.1, 161.2, 169.2. MS (ESI) m/z 322.3 (M + 1), 344.3 (M + Na), 339.3 (M + H$_2$O). Anal. Calcd. for C$_{16}$H$_{10}$F$_3$NO$_3$$\cdot$1/4 C$_7$H$_8$: C, 61.92; H, 3.51; N, 4.07. Found: C, 60.74; H, 3.66; N, 4.07.

![Chemical Structure](image)

**3-(2-Cyano-3-(trifluoromethyl)phenoxy)phenyl propionate (24b)**

**General Method G.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc/hexane 1:4) to afford 70.8 mg (61%) of (24b) as a white solid: $R_f$ 0.25 (EtOAc/hexane, 1:4); mp 82-83 °C. $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 1.23 (t, $J = 7.5$ Hz, 3H), 2.59 (q, $J = 7.5$ Hz, 2H), 6.91 (s, 1H), 6.91-7.04 (m, 2H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.41-7.49 (m, 2H), 7.60 (t, $J = 8.1$ Hz, 1H). $^{13}$CNMR (300 MHz, CDCl$_3$) $\delta$ 9.16, 27.9, 101.4, 112.4, 114.5, 117.6, 119.3, 120.2, 120.6, 124.2, 127.8, 131.0, 134.3, 152.3, 155.0, 161.3, 172.8. MS (ESI) m/z 454.1 (M + 1). Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO$_3$$\cdot$1/4 H$_2$O: C, 60.09; H, 3.71; N, 4.12. Found: C, 60.20; H, 3.49; N, 4.16.

![Chemical Structure](image)

**3-(2-Cyano-3-(trifluoromethyl)phenoxy)phenyl butyrate (24c)**

**General Method G.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc/hexane 1:4) to afford 0.128 g (69%) of (24c) as a pale yellow oil: $R_f$ 0.54 (EtOAc/CH$_2$Cl$_2$, 1:4). $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 1.03 (t, $J = 7.6$ Hz, 3H), 1.77 (sextet, $J = 7.6$ Hz, 2H), 2.54 (t, $J = 7.6$ Hz, 2H), 6.90 (t, $J = 2.4$ Hz, 1H), 6.97-7.04 (m,
2H), 7.13 (d, J = 8.4 Hz, 1H), 7.42-7.48 (m, 2H), 7.57-7.62 (m, 1H). \textsuperscript{13}CNMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 13.8, 18.6, 36.4, 101.7, 112.4, 114.5, 117.6, 119.3, 120.2, 120.5, 120.6, 131.0, 134.3(2), 152.2, 155.0, 161.3, 172.0. MS (ESI) \(m/z\) 350.3 (M + 1), 372.3 (M + Na), 367.4 (M + H2O). Anal. Calcd. for C\textsubscript{20}H\textsubscript{20}F\textsubscript{3}NO\textsubscript{2}\cdot 1/2 H\textsubscript{2}O: C, 64.51; H, 5.68; N, 3.76. Found: C, 64.62; H, 5.62; N, 3.64.

3-(2-Cyano-3-(trifluoromethyl)phenoxy)phenyl pentanoate (24d)

To a stirred solution of phenol (23a) (57 mg, 0.20 mmol) in Et\textsubscript{3}N (5 mL) valeryl chloride (29 \(\mu\)L, 0.24 mmol, 1.2 equiv) was added and refluxed for 2 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO\textsubscript{2}, gradient of hexane, hexane/CH\textsubscript{2}Cl\textsubscript{2} 1:1, CH\textsubscript{2}Cl\textsubscript{2}, (CH\textsubscript{3})\textsubscript{2}CO) to afford 57.1 mg (78%) of (24d) as a white solid: \(R_f\) 0.50 (EtOAc/hexane, 1:4); mp 44-46 °C. \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.96 (t, \(J\) = 7.2 Hz, 3H), 1.39-1.48 (m, 2H), 1.69-1.76 (m, 2H), 2.56 (t, \(J\) = 7.2 Hz, 2H), 6.90 (t, \(J\) = 2.4 Hz, 1H), 6.97-7.03 (m, 2H), 7.13 (d, \(J\) = 8.8 Hz, 1H), 7.41-7.48 (m, 2H), 7.57-7.61 (m, 1H). \textsuperscript{13}CNMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 13.9, 22.4, 27.1, 34.2, 101.3, 112.4, 114.5, 117.7, 119.4, 120.2, 120.6, 120.7, 123.7, 131.0, 134.3, 152.3, 155.0, 161.3, 172.2. MS (ESI) \(m/z\) 454.1 (M + 1). Anal. Calcd. for C\textsubscript{20}H\textsubscript{20}F\textsubscript{3}NO\textsubscript{2}\cdot 1/2 H\textsubscript{2}O: C, 64.51; H, 5.68; N, 3.76. Found: C, 64.62; H, 5.62; N, 3.64.
3-(2-Cyano-3-(trifluoromethyl)phenoxy)phenyl hexanoate (24e)

**General Method G.** The residue was purified by preparative TLC (SiO₂, gradient of EtOAc:hexane 1:4) to afford 58.0 mg (74%) of (24e) as a colorless oil: Rᵥ 0.56 (EtOAc/hexane, 1:4). ¹HNMR (400 MHz, CDCl₃) δ 0.91-0.94 (m, 3H), 1.36-1.40 (m, 4H), 1.71-1.76 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 6.90 (t, J = 2.4 Hz, 1H), 6.97-7.03 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.42-7.48 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H). ¹³CNMR (400 MHz, CDCl₃) δ 14.1, 22.5, 24.7, 31.4, 34.4, 112.3, 114.5, 117.6, 119.3, 120.2, 120.6(2), 120.7, 123.7, 131.0, 134.3, 152.2, 155.0, 161.3, 172.1. MS (ESI) m/z 378.3 (M + 1), 400.4 (M + Na). Anal. Calcd. for C₂₀H₁₈F₃NO₃: C, 63.66; H, 4.81; N, 3.71. Found: C, 63.84; H, 4.90; N, 3.65.

2-(3-(4-Chlorobenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25a)

**General Method C.** The residue was purified by preparative TLC (SiO₂, gradient of EtOAc:hexane 1:4) to afford 40.6 mg (56%) of (25a) as a colorless oil: Rᵥ 0.40 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 46-48 °C. ¹HNMR (400 MHz, CDCl₃) δ 5.03 (s, 2H), 6.70 (st, J = 6.8 Hz, 2H), 6.86 (td, J = 1.6 Hz, 2.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.31-7.37 (m, 5H), 7.45 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H). ¹³CNMR (400 MHz, CDCl₃) δ 69.7, 107.5, 112.5(2), 112.9, 120.3, 120.4, 120.5(2), 129.0(3), 129.1(2), 134.1(2), 135.0(2), 155.7,
2-(Trifluoromethyl)-6-(3-(4-(trifluoromethyl)benzyloxy)phenoxy)benzonitrile (25b)

**General Method C.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc:hexane 1:4) to afford 35.9 mg (71%) of (25b) as a colorless oil: $R_f$ 0.37 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 65-66 °C. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 5.13 (s, 2H), 6.72 (q, $J = 1.6$ Hz, 2.8 Hz, 2H), 6.87 (td, $J = 0.8$ Hz, 2.0 Hz, 1H), 7.06 (d, $J = 8.8$ Hz, 1H), 7.33-7.37 (m, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 10.8$ Hz, 3H), 7.65 (d, $J = 8.4$ Hz, 2H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 69.6, 107.4(3), 112.5, 113.0, 120.3, 120.5(2), 125.8(2), 129.9, 127.7(2), 131.2(2), 134.1(2), 140.6, 155.7, 160.2, 161.5. MS (ESI) $m/z$ 460.4 (M + Na). Anal. Calcd. for C$_{22}$H$_{13}$F$_6$NO$_2$·H$_2$O: C, 58.03; H, 3.32; N, 3.11. Found: C, 57.71; H, 2.88; N, 2.88.

2-(3-(4-Methoxybenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25c)

**General Method C.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc:hexane 1:4) to afford 30.2 mg (64%) of (25c) as a white solid: $R_f$ 0.45
(EtOAc/hexane, 1:4); mp 103-105 °C. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 3.82 (s, 3H), 4.98 (s, 2H), 6.68 (dt, $J = 1.6$Hz, 2.0Hz, 2H), 6.87-6.93 (m, 3H), 7.06 (d, $J = 8.4$Hz, 1H), 7.33 (t, $J = 8.4$Hz, 3H), 7.44 (d, $J = 7.6$Hz, 1H), 7.55 (t, $J = 8.4$Hz, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 55.5, 70.3, 107.5(3), 112.6, 114.3(3), 120.2, 120.3, 120.4, 128.5, 129.5(3), 131.1, 134.1, 155.6, 159.9, 160.7, 161.6. MS (ESI) $m/z$ 417.5 (M + H$_2$O), 422.4 (M + Na). Anal. Calcd for C$_{22}$H$_{16}$F$_3$NO$_3$: C, 66.16; H, 4.04; N, 3.51, Found: C, 66.11; H, 3.96; N, 3.51.

![Chemical Structure](image)

2-(3-(4-Methylbenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25d)

**General Method C.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc:hexane 1:4) to afford 38.5 mg (81%) of (25d) as a white solid: $R_f$ 0.50 (EtOAc/hexane, 1:4); mp 91-93 ºC. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 2.37 (s, 3H), 5.01 (s, 2H), 6.68-6.72 (m, 2H), 6.87-6.90 (m, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.29-7.35 (m, 3H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H). $^{13}$CNMR (400MHz, CDCl$_3$) $\delta$ 21.4, 70.5, 107.5(3), 112.6, 120.2, 120.3(2), 120.4, 127.9(2), 129.6(3), 133.5(2), 134.1, 138.3, 155.6, 160.7, 161.6. MS (ESI) $m/z$ 384.3 (M + 1), 406.3 (M + Na), 401.3 (M + H$_2$O). Anal. Calcd for C$_{22}$H$_{16}$F$_3$NO$_2$: C, 68.93; H, 4.21; N, 3.65. Found: C, 68.93; H, 4.21; N, 3.65.
2-(3-(3,4-Dichlorobenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25e)

**General Method C.** The residue was purified by preparative TLC (SiO₂, gradient of EtOAc:hexane 1:4) to afford 35.4 mg (62%) of (25e) as a colorless oil: Rₐ 0.52 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 66-68 °C. ¹H NMR (400 MHz, CDCl₃) δ 5.01 (s, 2H), 6.69-6.74 (m, 2H), 6.84-6.87 (m, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.23-7.26 (m, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.45-7.47 (m, 2H), 7.54 (td, J = 8.0 Hz, 0.4 Hz, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 69.0, 107.4(3), 112.4, 113.1, 120.3, 120.5(2), 126.8, 129.5, 130.9, 132.4(2), 133.1, 136.8, 134.1, 155.7, 160.1, 161.5, 131.2. MS (ESI) m/z 437.5 (M - 1). Anal. Calcd. for C₂₁H₁₂Cl₂F₃NO₂: C, 57.56; H, 2.76; N, 3.20. Found: C, 57.56; H, 2.76; N, 3.20.

2-(3-(4-Bromobenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25f)

**General Method C.** The residue was purified by preparative TLC (SiO₂, gradient of EtOAc:hexane 1:4) to afford 50.5 mg (78%) of (25f) as a white solid: Rₐ 0.57 (EtOAc/hexane, 1:4); mp 85-86 °C. ¹H NMR (400 MHz, CDCl₃) δ 5.01 (s, 2H), 6.71 (t, J = 2.1 Hz, 2H), 6.84 (dd, J = 1.5 Hz, 2.1 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 7.25-7.35 (m, 3H), 7.43-7.58 (m, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 69.7, 107.5(3), 112.5, 112.6, 120.3, 120.4, 120.5, 122.3, 129.3(3), 131.1(2), 132.2, 134.5, 135.6, 155.6, 160.3, 161.5.
MS (ESI) $m/z$ 430.6 (M - H$_2$O), 413.6 (M - Cl). Anal. Calcd. for C$_{21}$H$_{13}$BrF$_3$NO$_2$: C, 56.27; H, 2.92; N, 3.12. Found: C, 56.19; H, 2.88; N, 3.20.

![Chemical Structure](image.png)

2-(3-(4-Fluorobenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (25g)

**General Method C.** The residue was purified by preparative TLC (SiO$_2$, gradient of EtOAc:hexane 1:4) to afford 36.9 mg (71%) of (25g) as a colorless oil: $R_f$ 0.47 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 70-72 °C. $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 5.03 (s, 2H), 6.72 (d, $J = 5.6$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 1H), 7.07 (sd, $J = 8.4$ Hz, 3H), 7.27-7.42 (m, 3H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.56 (t, $J = 8.4$ Hz, 1H). $^{13}$CNMR (400 MHz, CDCl$_3$) $\delta$ 69.9, 102.6, 107.5(3), 112.5, 115.7(3), 120.4(2), 123.7, 129.6(2), 129.7, 132.3, 134.1(2), 155.7, 160.5, 161.6, 164.1. MS (ESI) $m/z$ 388.4 (M + 1), 410.4 (M + Na), 405.4 (M + H$_2$O). Anal. Calcd. for C$_{21}$H$_{13}$F$_4$NO$_2$: C, 65.12; H, 3.38; N, 3.62. Found: C, 65.03; H, 3.65; N, 3.39.

2.6. References


55. The ClogP values were calculated using ChemDraw 11.0.


APPENDIX

Synthesis of Diaryl Ether Analogues of BAY 59-3074 as Therapeutics of Marijuana Abuse

X-ray Crystallographic Data, Positional Parameters, Thermal Displacement Parameters, Bond Distances, Bond Angles and Torsional Angles for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23a).
Table 1: Crystal data and structure refinement for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile

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<th>Property</th>
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</tr>
<tr>
<td>Temperature</td>
<td>120(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
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</tr>
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<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>C2/c</td>
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<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>α = 90°, β = 90.813(3)°, γ = 90°</td>
</tr>
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<td>Volume</td>
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<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
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<tr>
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<tr>
<td>F(000)</td>
<td>1136</td>
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<tr>
<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<tr>
<td>Reflections collected</td>
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</tr>
<tr>
<td>Independent reflections</td>
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<td>Completeness to theta = 28.33</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>R indices (all data)</td>
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Table 2: Atomic coordinates (Å x 10^4) and equivalent isotropic displacement parameter (Åx 10^3) for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23a). U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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Table 3: Bond lengths [Å] and angles [°] for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile ($\text{23a}$)

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Table 4: Anisotropic displacement parameters ($\text{Å}^2 \times 10^4$) 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (23a). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^* U^{11} + \ldots + 2h k a^* b^* U^{12}]$

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Table 5: Torsion angles [°] for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (67)

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</table>

Symmetry transformations used to generate equivalent atoms
VITA

The author was born in New Orleans, Louisiana on July 4, 1982. She graduated from the New Orleans Center for Science and Mathematics and McDonogh 35 Senior High School in May 2000. She received her B. Sc. Degree at Xavier University of Louisiana, New Orleans, Louisiana in 2004. In the Fall of 2004, she came to the University of New Orleans. She completed the requirements for the degree of Doctor of Philosophy in Organic Chemistry in December 2009 under the supervision of Professor Mark L. Trudell.