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

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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.

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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-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.

1.2. Introduction

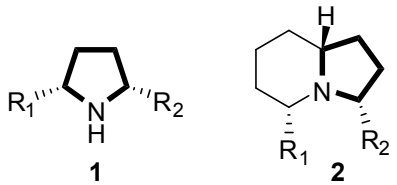
1.2.1. Amphibians

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.[1] 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.[1] The most common use of this toxin is by the Indians of western Colombia for poisoning blowgun darts for use in hunting.[1] 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.[2] 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.[2] However, when alkaloid-dusted fruit flies were fed to dendrobatid frogs the pyrrolidines accumulated poorly into the skin.[3] 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.[2] The 2,5-disubstituted pyrrolidines of the myrmicine ants serve as repellants for other ants and have insecticidal activity.[2] The 2,5-disubstituted pyrrolidines of these ant venoms and frog skin extracts have become attractive synthetic targets.

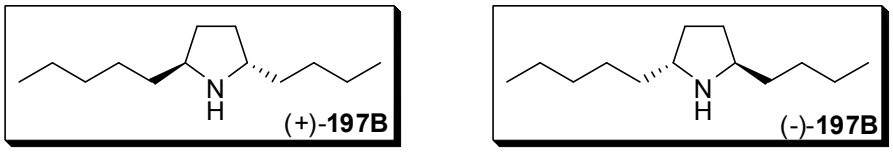
Figure 1.1: Amphibian alkaloid structures that contain cis-pyrrolidine subunit



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

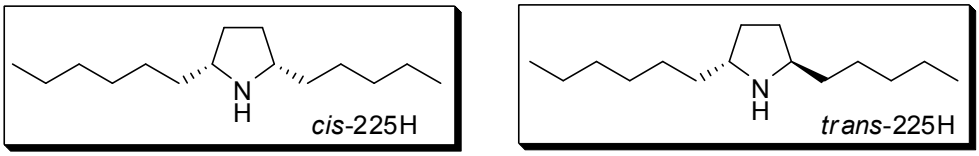
acetylcholine receptor in addition to other monocyclic and bicyclic alkaloids (Figure 1.1). However, the stereochemistry and absolute configurations have not been determined for many of these alkaloids. As yet, the structure of only one pyrrolidine **197B** isolated from a dendrobatid frog has been firmly established.[4]

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



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**



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.[6] 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.[7] 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.[6] As stated earlier amphibian alkaloids engage as noncompetitive blockers of nicotinic acetylcholine receptor ion channels.[4,8] These amphibian alkaloids block channel conductance and accelerate desensitization or inactivation of the nicotinic acetylcholine receptor channel.

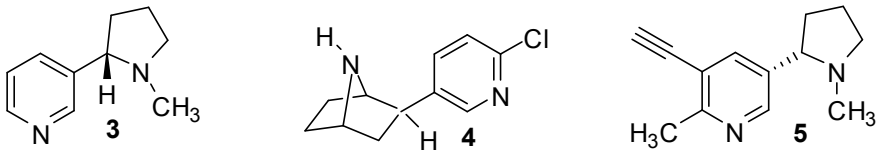
1.2.4. Therapeutic Targets

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.[6] 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.[6]

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



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.[11] According to the Alzheimer's Association, there are approximately 5.3 million people living with this disease.[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).[7,12-14]

There are four identifiable phases of Alzheimer's Disease: onset, loss, disability and victim apathetic.[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.[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.[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.[7] 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 granulovacula degeneration.[7,12-14] 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.[7] 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.[7] Granulovacula 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.[7,12-14] 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.[11] 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.[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).[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.[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.[16] The cells in the substantia nigra produce dopamine, which aids in coordination of muscles and movement.[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).[15-19] 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.[15-19] 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.[17] 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.[15-19] 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.[15-19] 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.[15-19] Anticholinergic medications reduce tremor or rigidity, but are used in elderly patients or those with cognitive problems.[15-19] 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.[15-19]

1.2.4.3. Smoking Cessation

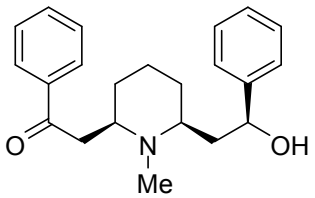
The nicotinic acetylcholine receptor has become the target in understanding various health consequences involved in smoking and its mechanisms of action. Nicotine (**3**) is an addictive drug and accounts for more deaths than cocaine and other hard drugs. The combination of nicotine (**3**) and other components are carcinogenic and can lead to a host of cancers.[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.[20]

Nicotine (**3**) stimulates acetylcholine receptors and increases the activity of dopaminergic neurons of the mesolimbic system.[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.[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.[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.[21] 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.[22]

Nicotine (**3**) is the main active ingredient in tobacco. It is an alkaloid named from Nicotiana tabacum and is a cholinergic agonist that micmics 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

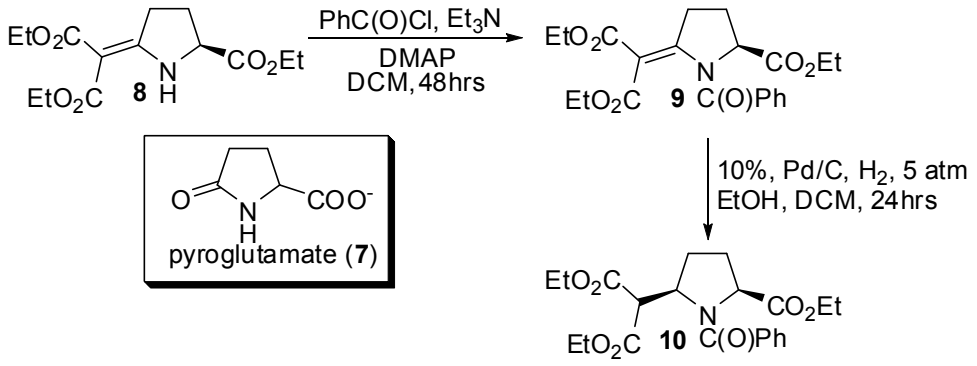


6

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

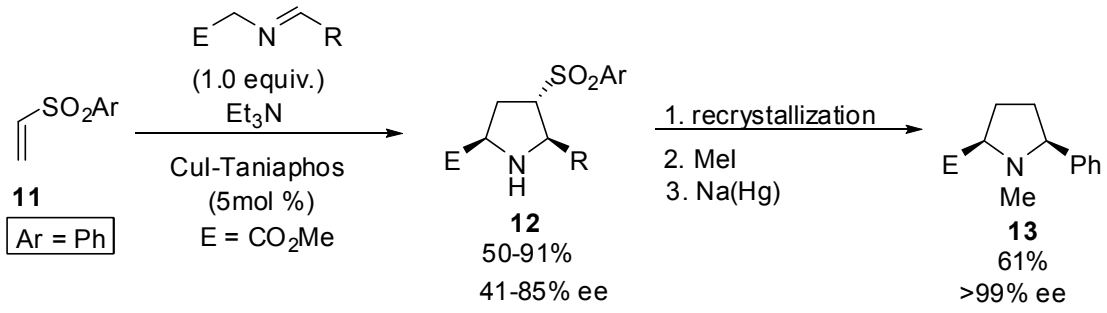


The Moloney group performed enamine reduction and subsequent regioselective and diastereoselective alkylations to construct cis-2,5-disubstituted pyrrolidines.[5,23] The starting material for the synthesis is pyroglutamic acid and the lactam carbonyl is manipulated through the Eschenmoser contraction 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.[5,23] Benzoylation of the amine **8** nitrogen gave a separable mixture of *cis* and *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.

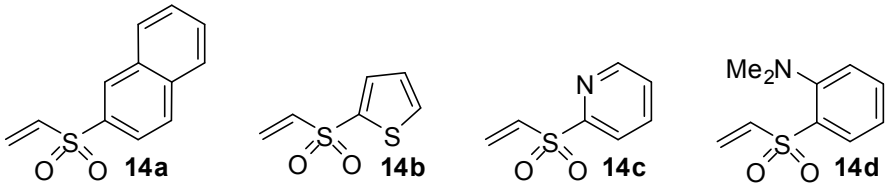
The Carretero group performed catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides with vinyl sulfones to construct *cis*-2,5-pyrrolidines.[24]

Scheme 1.2: Catalytic Enantioselection to obtain *cis*-pyrrolidines



The outlined procedure uses metal catalyzed asymmetric 1,3-cycloaddition to form the *cis*-pyrrolidine. The use of the Cu^{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.[24-23] Vinyl sulfones were employed due to the highly electron deficient nature of the carbon-carbon double bond (Figure 1.6).

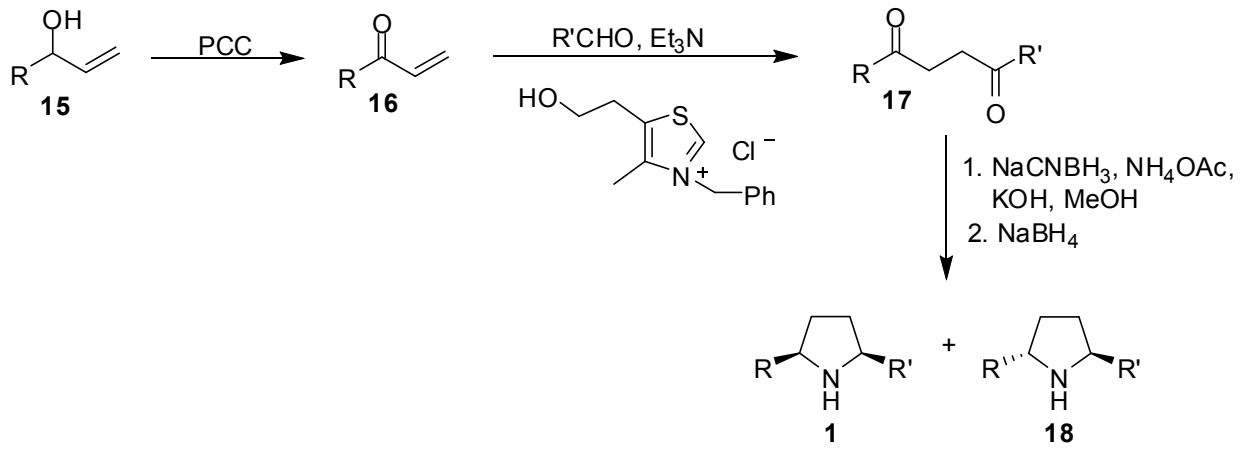
Figure 1.6: Aryl vinyl sulfones



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.[22] 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.[25-26]

Scheme 1.3: Reductive amination of 1,4-diketones

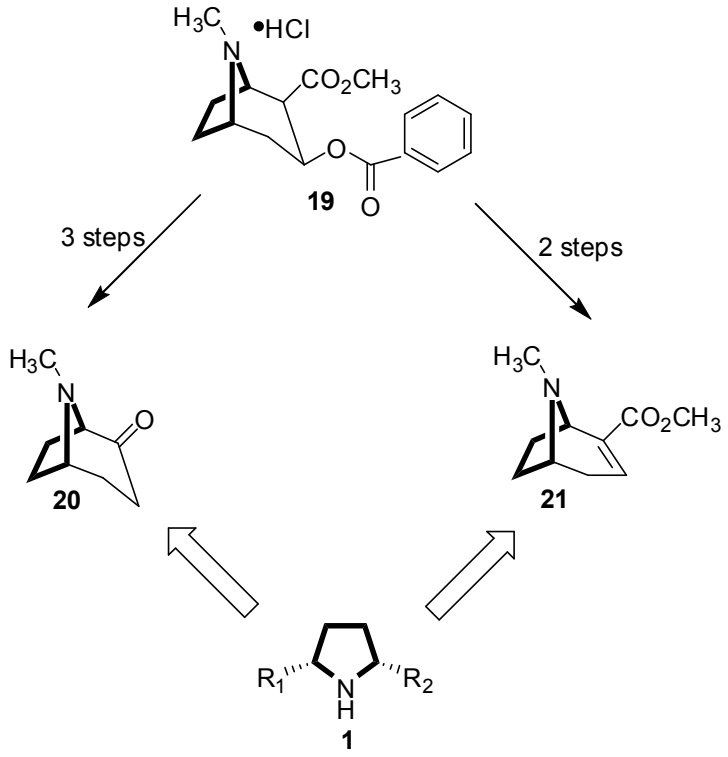


The 1,4-diketone was prepared from alcohol **15** by buffered pyridinium chlorochromate oxidation to give the unstable enone **16**.[25-26] Enone **16** was manipulated through the Stetter reaction when treated with the appropriate aldehyde, triethylamine, and a thiazolium salt catalyst. The condensation of enone **16** and the aldehyde gave the 1,4-diketone **17**. Treatment of the 1,4-diketone **17** with ammonium acetate, $NaBH_3CN$ 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.[25-26] The *trans*-pyrrolidine **225H** has been isolated from both the *Solenopsis molestra* 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-

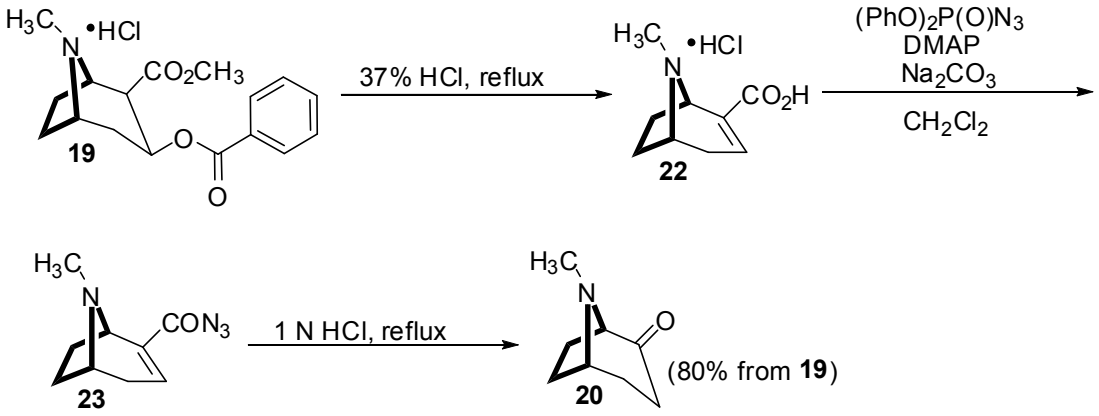
pot three-step synthesis. Typically performed on a 35g scale this process yields 10g of the optically pure chiral building block, 2-tropinone (**20**).[27] Through the degradation of cocaine, the inherent stereochemistry of C1 and C5 is exploited.

Scheme 1.4: Chiral building blocks



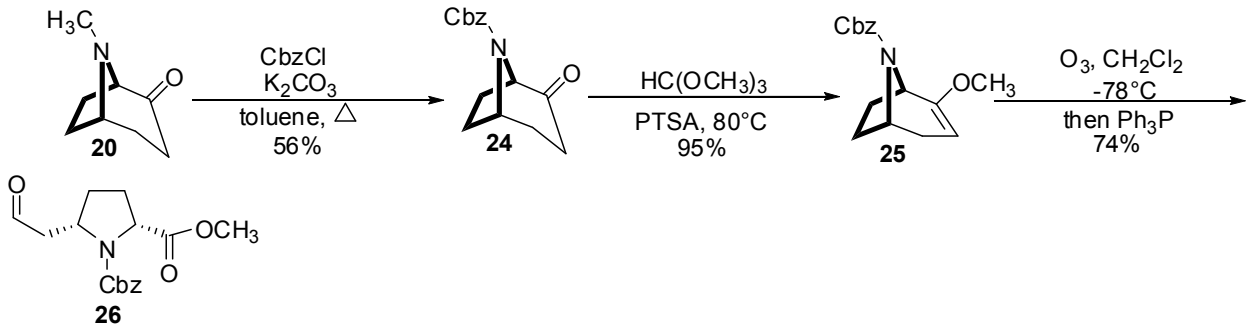
(+)-2-Tropinone (**20**) was identified as the initial chiral building block for the preparation of enantiopure *cis*-2,5-pyrrolidine **225H**.[27] This building block was the target for the complete synthetic procedure due to its availability and the ease in preparation. Confiscated grade (-)-cocaine•HCl **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]

Scheme 1.6: Synthesis of Cbz protected *cis*-2,5-disubsituted pyrrolidine

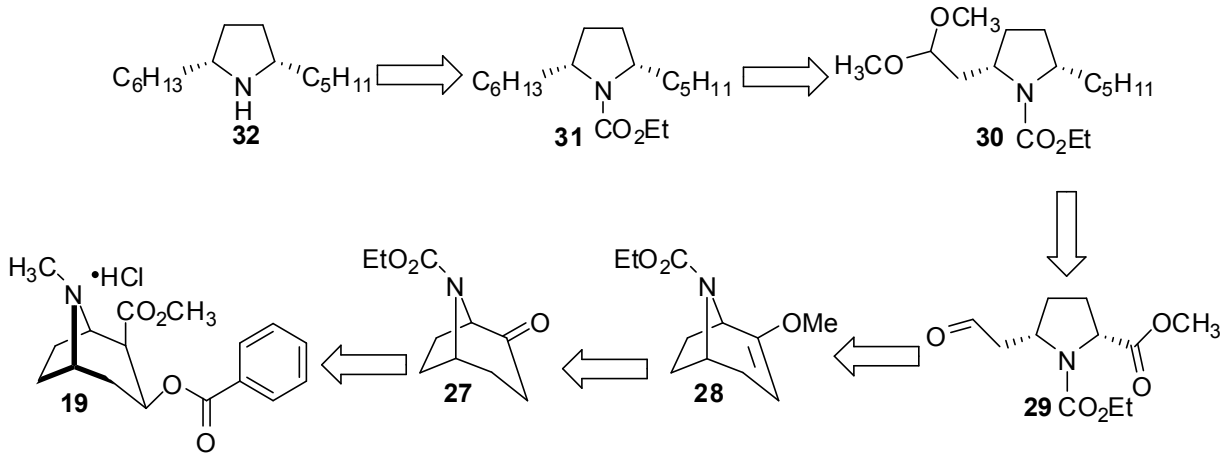


The Cbz protected 2-tropinone **24** was converted into the methyl enol ether **25** using trimethyl orthoformate catalyzed by p-toluenesulfonic acid. The double bond of the methyl enol ether **25** was cleaved by ozone at -78 ºC and subsequent reductive workup with triphenylphosphine furnished the enantiopure *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**).

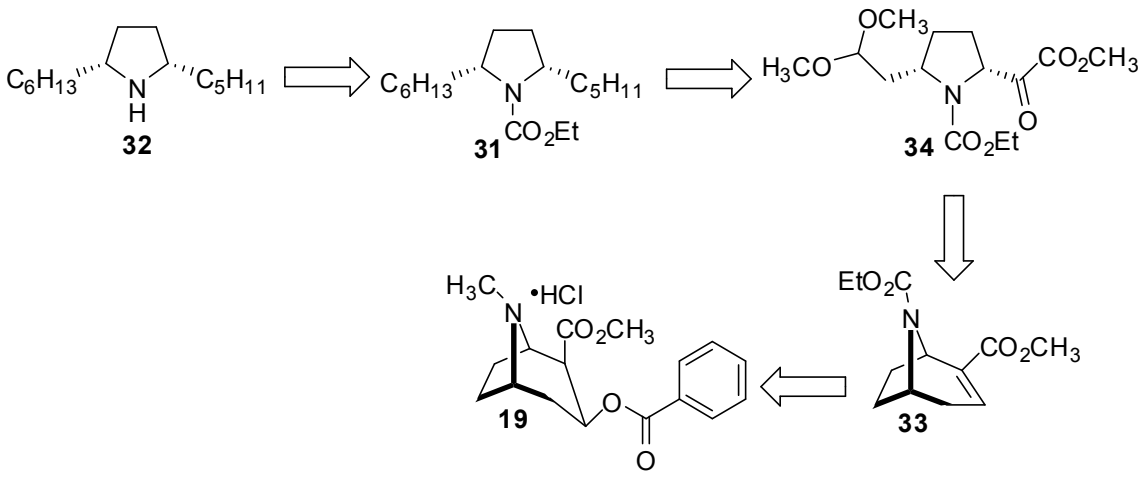
Scheme 1.7: Retrosynthetic approach via (+)-2-tropinone



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-(-)-anhydroecognine methyl ester



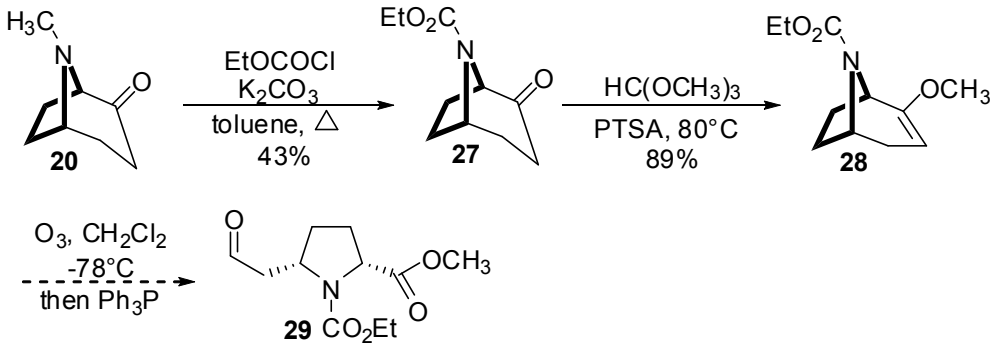
The synthesis was envisaged to start from confiscated grade (-)-cocaine•HCl **19**. The chiral building block, anhydroecgonine derivative **33**, will be explored as an intermediate in approaching amphibian alkaloid (+)-**225H** (**32**) as shown in Scheme 1.8. The synthesis will employ the deprotection 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).

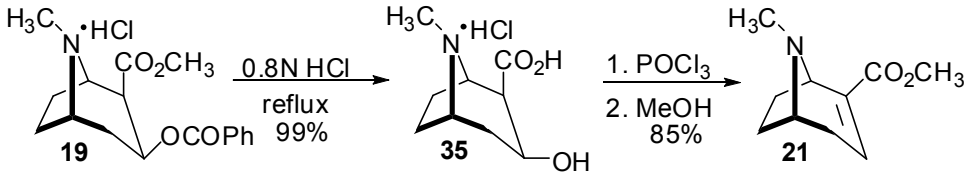
Scheme 1.9: Synthesis of carbamate protected *cis*-2,5-pyrrolidine disubstituted pyrrolidine



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

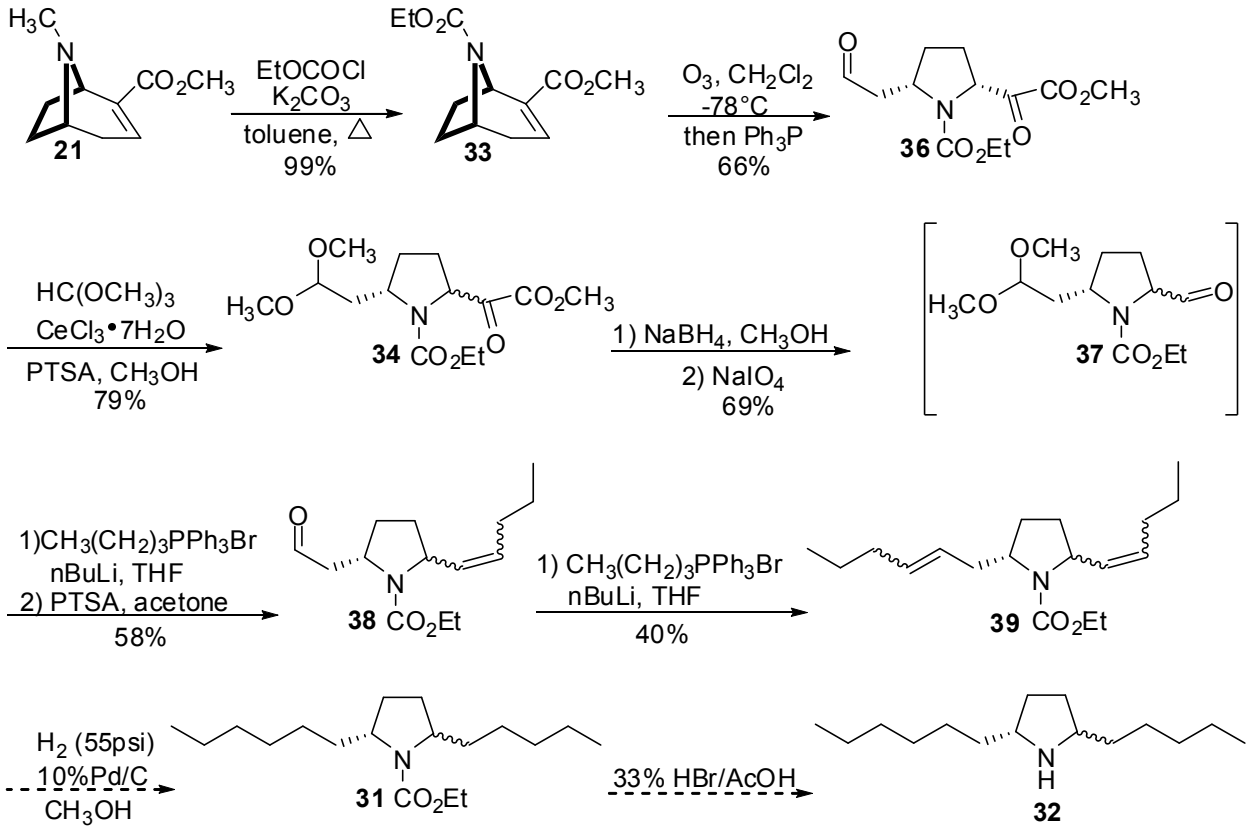


Subsequent dehydration with phosphorus oxychloride and concomitant esterification using methanol afforded the methyl ester **21** in 85% yield.

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**



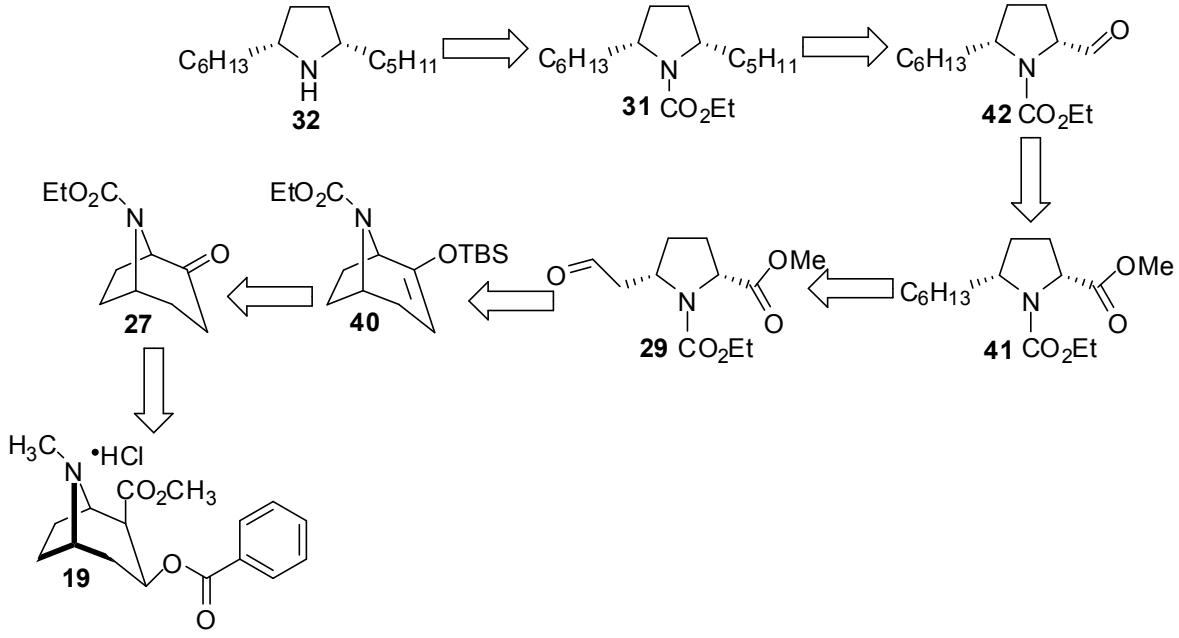
The carbon-carbon double bond of **33** was cleaved by ozonolysis at -78 ºC with a subsequent reductive workup with triphenylphosphine to afford the tricarbonyl compound **36** with a yield of 66% with a specific rotation of $[\alpha]_D^{25}$ = +25.7 (c = 1.0, EtOAc). Selective protection of the

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



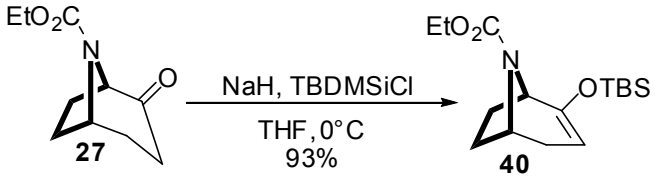
The chiral building block, (+)-2-tropinone (**20**), was revisited in order to revise the procedure for the *cis*-2,5 disubstituted pyrrolidine building block. The instability of the methyl enol ether **28** was envisaged to be avoided by preparation of the silyl enol ether **40**.[29] The retrosynthetic 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

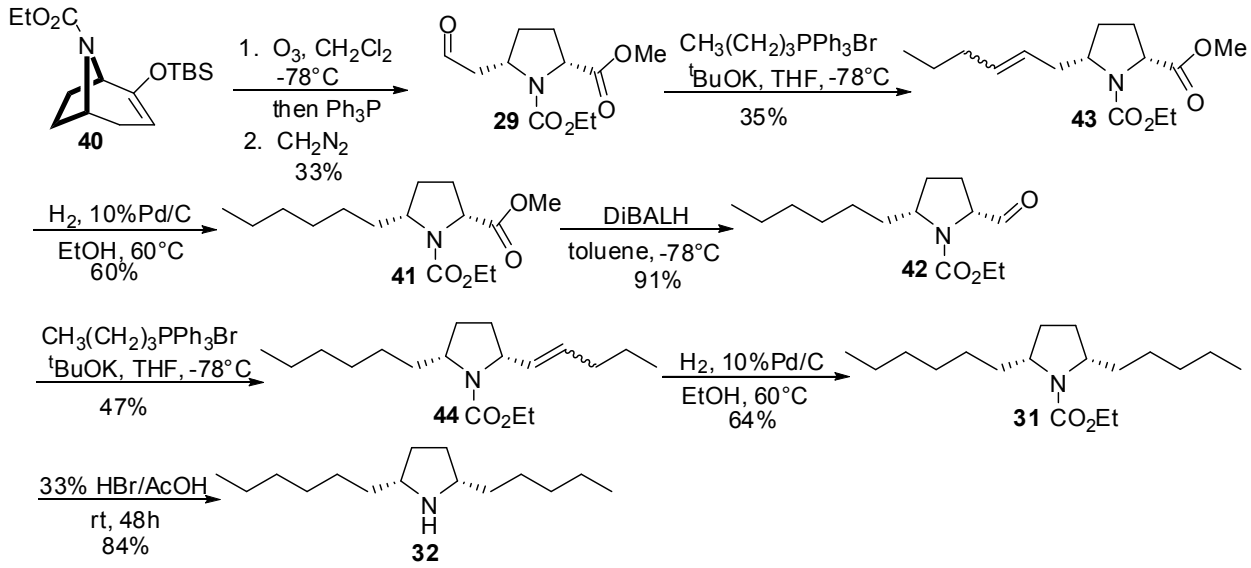
The ethyl carbamate protected 2-tropinone **27** was converted into the silyl enol ether **40** using sodium hydride and *tert*-butyl dimethyl silyl chloride at 0 ºC in 93% yield (scheme 1.13) with a specific rotation of $[\alpha]_D^{25} = -49.6$ (c = 0.6, MeOH).[29]

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 CH_2N_2 to furnish the enantiopure *cis*-2,5-disbustituted 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.

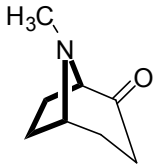
1.6. Conclusion

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_2Cl_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 Dragondorff'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.

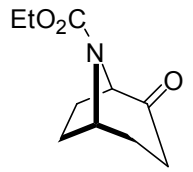


8-Methyl-8-azabicyclo[3.2.1]octan-2-one (20)[27]

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 (255mL) and extracted with Et_2O (2 x 127mL) 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 100ºC for 24 h. This afforded crude (-)-anhydroecgonine (19.2 g, 94%) without further purification was used in the next step.

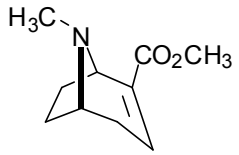
To the finely powder acid (5.16 g, 25.3 mmol) from the previous crude step were added Na_2CO_3 (7.62 g, 72 mmol) and DMAP (91.5 mg, 0.75 mmol), and the flask was sealed under nitrogen. To the flask dried CH_2Cl_2 (110 mL) was added followed by the addition of diphenylphosphorylazide (DPPA) (7.77 mL, 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_2O (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 ºC until CO_2 and N_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_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum. The resulting liquid was purified using the Kugelrohr (vacuum bulb to bulb distillation). This afforded **19** (1.11g, 31%, 3 steps) as a colorless liquid. ^{1}HNMR (400 MHz, $CDCl_3$) δ

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**)[30]

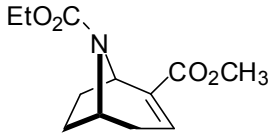
To a solution of **20** (0.643 g, 4.62 mmol), and K_2CO_3 (382 mg, 2.31 mmol) in toluene (8 mL) was added ethyl chloroformate (2.20 mL, 23.1 mmol). The reaction mixture was heated to reflux for 24 h. The solvent was removed under vacuum and the resulting residue was dissolved in deionized H_2O (9 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 9 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2, 3:7 CH_2Cl_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)[28]

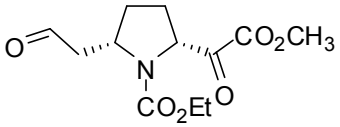
A solution of confiscated grade(-)-cocaine hydrochloride **19** (15.0 g, 44.4 mmol) in 0.8 N hydrochloric acid (200 mL) was heated to reflux for 24 h. The solution was cooled to room temperature, and extracted with Et_2O (200 mL). The aqueous layer was evaporated under vacuum to dryness. The solid was further dried under the vacuum at 100 ºC for 24 h. This afforded crude ecognine **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_2O (100 mL) and heated with a saturated ammonium hydroxide solution with NaCl. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined and dried over K_2CO_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)**[31]

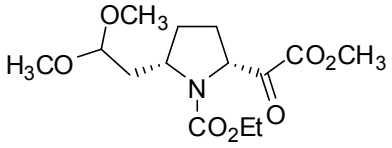
To a stirred solution of *R*-(-)-anhydroecgonine methyl ester **21** (6.1 g, 34 mmol), and K_2CO_3 (4.65g) in toluene (130 mL) under nitrogen, ethyl chloroformate (32 mL, 337 mmol) was added. The solution was heated to reflux for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue is purified by flash chromatography (SiO_2, 1:4 EtOAc/hexane) to afford **33** (6.16 g, 99%) as a pale yellow oil. $[\alpha]_D^{25}$ -82.0 (*c* 1.0, MeOH). ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (400 MHz, $CDCl_3$) 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 $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.24; H, 7.16; N, 5.85.



(2*R*,5*S*)-Ethyl 2-(2-methoxy-2-oxoacetyl)-5-(2-oxoethyl)pyrrolidine-1-carboxylate (36)

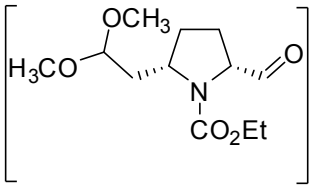
Ozone was bubbled through a solution of **33** (4.47 g, 18.7 mmol) in CH_2Cl_2 (40 mL) at -78 ºC until a slight blue color persisted. The mixture was flushed with nitrogen for 10 minutes. Then Ph_3P (9.80 g, 37.4 mmol) was added to the solution and the mixture stirred overnight. The solvent was evaporated to dryness under reduced pressure

and the residue was purified by flash column chromatography (SiO_2, 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, $CDCl_3$) 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). ^{13}C NMR (400 MHz, $CDCl_3$) 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 $C_{12}H_{17}NO_6 \cdot 1$ 1/2 H_2O: C, 49.06; H, 6.69; N, 4.77. Found: C, 49.27; H, 6.30; N, 4.80.



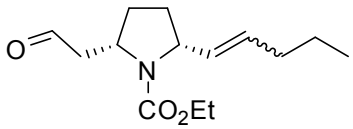
(2*S*,5*R*)-Ethyl 2-(2,2-dimethoxyethyl)-5-(2-methoxy-2-oxoacetyl)pyrrolidine-1-carboxylate (34)

To a solution of aldehyde **36** (2.52 g, 9.29 mmol) and $CeCl_3 \cdot 7H_2O$ (3.60 g, 9.66 mmol) in CH_3OH (50 mL), $HC(OCH_3)_3$ (10 mL, 82.2 mmol) was added. The reaction was stirred for 30 minutes at room temperature then quenched with saturated $NaHCO_3$ (10 mL). The reaction mixture was extracted with EtOAc (2 x 40 mL), washed with brine and dried over Na_2SO_4. The solvent was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography (SiO_2, 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, $CDCl_3$) 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). ^{13}C NMR (400 MHz, $CDCl_3$) δ13.8, 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.



(2*S*,5*R*)-Ethyl 2-(2,2-dimethoxyethyl-5-formylpyrrolidine-1-carboxylate (37)

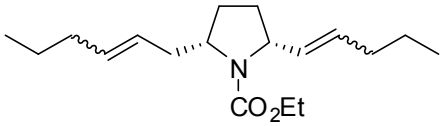
CH_3OH (6 mL) was added dropwise to a solution of acetal **34** (2.0 g, 6.4 mmol) and $NaBH_4$ (600 mg, 16 mmol) in THF (60 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes and then cooled to 0 ºC. $(CH_3)_2CO$ (4 mL), H_2O (30 mL) and Et_2O (50 mL) 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_2SO_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).



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

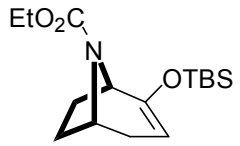
The aldehyde **37** was dissolved in toluene (20 mL) and added to a previously prepared solution of (*n*-butyl) triphenylphosphonium bromide and *t*-BuOK in toluene (57 mL) and stirred for 1.5 h. The reaction mixture was stirred at room temperature for 8 h. EtOAc (80 mL) and a solution of $Na_2S_2O_3$ (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_2SO_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_2Cl_2 (mL), washed with saturated $NaHCO_3$ solution, dried over Na_2SO_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).



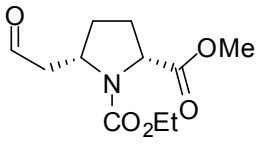
(2*S*,5*R*)-Ethyl 2-(hex-2-enyl)-5-(pent-1-enyl)pyrrolidine-1-carboxylate (39)

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 $Na_2S_2O_3$ solution (5 mL) was added to the reaction mixture and extracted with EtOAc (2 x 10 mL), washed with brine, dried over Na_2SO_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).



(1*R*,5*R*)-Ethyl 2-(*tert*-butyldimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (40)[29]

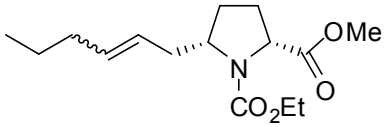
NaH (70 mg, 0.58 mmol) was suspended in dry THF (4 mL) under nitrogen at 0ºC with ice-NaCl bath. A solution of compound **27** (115 mg, 3 mmol) in dry THF (1 mL) was added dropwise and continued stirring at 0 ºC for 2 h. Then TBSCl (1.0 M in THF, 1.2 mL, 1.2 mmol) was added dropwise at 0 ºC. The reaction mixture was allowed to continue stirring overnight. At 0 ºC, H_2O (5 mL) was added slowly. The solution was extracted with Et_2O (3 x 10 mL). The organic portions were combined, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, hexane gradient, CH_2Cl_2) to afford **40** (169 mg, 93% yield) as a colorless oil. $[\alpha]_D^{25}$ -49.6 (*c* 0.6, MeOH). ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (400 MHz, $CDCl_3$) -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 $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50. Found: C, 61.86; H, 9.61; N, 4.38.



(2*R*,5*S*)-1-Ethyl 2-methyl 5-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (**29**)

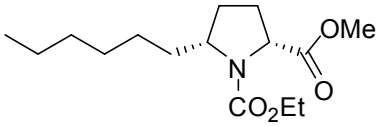
Ozone was bubbled through a solution of the TBS enol **40** (4.62 g, 14.8 mmol) in 40 mL CH_2Cl_2 at -78 ºC until a slight blue color persisted. The mixture was flushed with nitrogen for 10 minutes. Then Ph_3P (4.28 g, 16.3 mmol) was added to the solution and the mixture stirred overnight. The solvent was evaporated to dryness. The residue was triturated with 2N HCl (20 mL) and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ 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 Et_2O (25 mL) at 0 ºC, CH_2N_2 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 (SiO_2, hexane gradient, Et_2O, hexane) to afford **29** (1.19 g, 33%) a colorless oil. $[\alpha]_D^{25}$ +4.57 (*c* 0.2, MeOH). ^{1}HNMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{11}H_{17}NO_5 \cdot 1/4\ H_2O$: C, 53.32; H, 7.12; N, 5.65. Found: C, 53.00; H, 7.19; N, 5.32.



(2*R*,5*S*)-1-Ethyl 2-methyl 5-(hex-2-enyl)pyrrolidine-1,2-dicarboxylate (**43**)

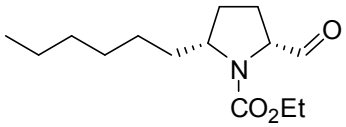
$CH_3CH_2CH_2CH_2PPh_3Br$ (5 g, 12 mmol) was suspended in dry THF (40 mL) under nitrogen at room temperature. *t*-BuOK (1.0 M in THF, 11.3 mL, 11.3 mmol) was added dropwise to the solution and stirred for 2 h. The aldehyde **29** (1.2 g, 4.9 mmol) was dissolved in THF (5 mL) and added dropwise to the reaction mixture. The combined reaction mixture was stirred for 8 h, then EtOAc (20 mL) and $Na_2S_2O_3$ solution (10 mL) was added. The reaction mixture was extracted with EtOAc (2 x 20 mL), washed with brine, dried over Na_2SO_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).



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

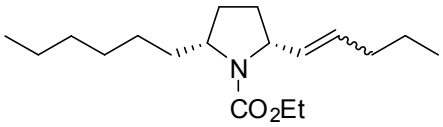
A solution of **43** (485 mg, 1.7 mmol), 10% Pd/C (108 mg) in EtOH (20 mL) was hydrogenated using a hydrogen balloon for 2 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, hexane) to afford **41** (292 mg, 60%) an oil. $[\alpha]_D^{25}$ -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, $CDCl_3$) δ 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.



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

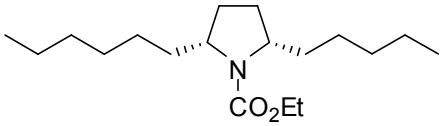
Ester **41** (180 mg, 0.63 mmol) was dissolved in toluene (3 mL) under nitrogen at -78 ºC. DIBAL-H (1.0 M in toluene, 0.69 mL, 0.69 mmol) was added dropwise over 45 minutes. The reaction mixture was allowed to continue stirring at -78 ºC for 15 minutes and then the cold bath is removed. Et_2O (10 mL), H_2O (4 mL) and 15% NaOH (6 mL) were added. The mixture was extracted with Et_2O (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, $CDCl_3$) δ 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).



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

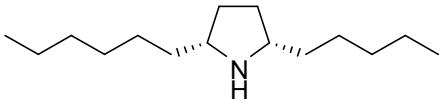
$CH_3CH_2CH_2CH_2PPh_3Br$ (570 mg, 1.4 mmol) was suspended in dry THF (20 mL) under nitrogen at room temperature. *t*-BuOK (1.0 M in THF, 1.3 mL, 1.3 mmol) was

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 $Na_2S_2O_3$ solution (5 mL) was added. The reaction mixture was extracted with EtOAc (2 x 10 mL), washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, hexane) to afford **44** (79.6 mg, 47%) an oil.



(2*R*,5*S*)-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 (SiO_2, hexane) to afford **44** (51.6 mg, 64%) an oil. $[\alpha]_D^{25}$ +9.26 (*c* 0.6, EtOAc). ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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 $C_{18}H_{35}NO_2$: C, 72.68; H, 11.86; N, 4.71. Found: C, 72.52; H, 11.76; N, 4.69.



(2*R*, 5*S*)-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. $NaHCO_3$ 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 Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, EtOAc/MeOH/Et_3N, 40:2:1). The purified oil was dissolved in CH_2Cl_2 (5 mL) and washed with sat. $NaHCO_3$ solution (5 mL) and the solvent was evaporated to dryness under reduced pressure to afford **32** (16 mg, 84%) a light yellow oil. $[\alpha]_D^{25}$ +15.6 (*c* 0.4, MeOH). ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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 $C_{15}H_{31}N$: C, 79.92; H, 13.86; N, 6.21. Found: C, 72.52; H, 11.76; N, 4.69.

1.8. References

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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

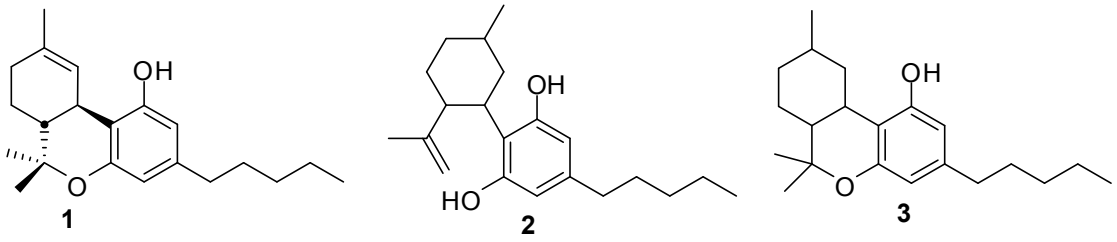
2.2.1. Drug Addicition

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-Δ^9-tetrahydrocannabinol (Δ^9-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).

Figure 2.1: Plant Cannabinoids



THC **1** is the major psychoactive constituent of marijuana. This psychoactive constituent has high lipid solubility and low water solubility.[6] 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**.[9] Unlike THC **1**, cannabidol (**2**) is not psychoactive and possess medical benefits such as relieving convulsion, inflammation, anxiety and nausea.[10] 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).[10] 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**).[11]

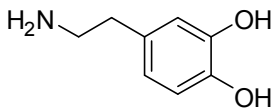
Currently, there are no effective treatments for marijuana abuse. Due to marijuana dependence being a major public health issue the development of new

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.[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.[15]

Figure 2.2: Structure of dopamine



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The abusive burden surrounding marijuana is produced by those reinforcing properties, which lead to repeated marijuana use.[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.[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.[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.[13,15]

Drug seeking behaviors are mediated by the release of dopamine (**4**). The more dopamine that is present allows for the increased activation of dopamine receptors (Figure 2.3).[15]

THC Binding to THC Receptors

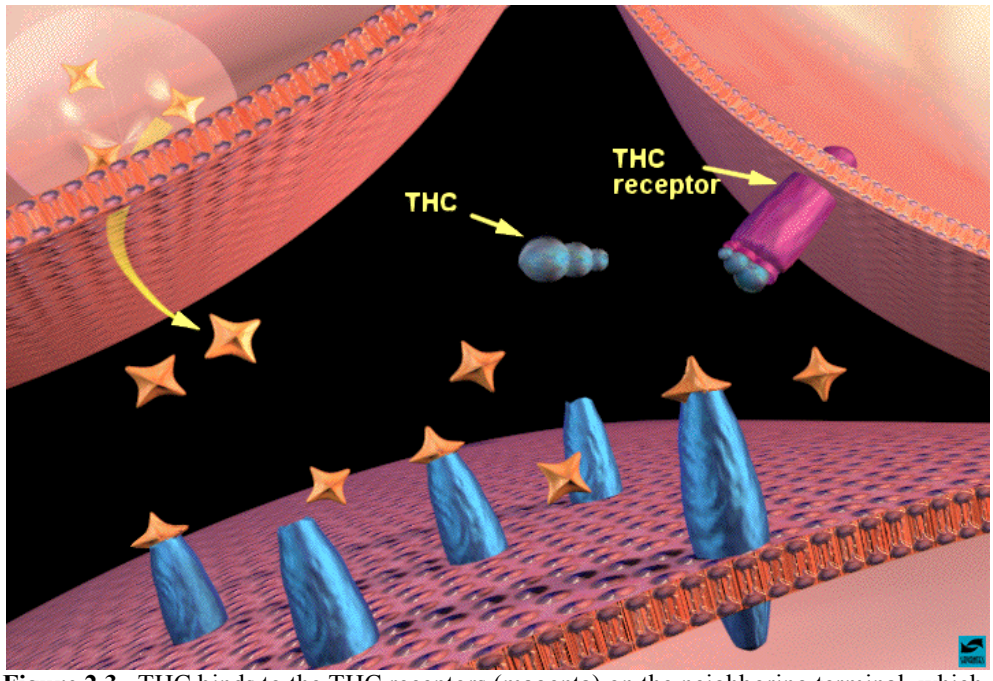


Figure 2.3. THC binds to the THC receptors (magenta) on the neighboring terminal, which sends a signal to the dopamine terminal to release more dopamine.[16]

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.[16] Besides drugs of

abuse, stress and other salient stiumuli 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.[17] 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.[17] The retrograde messengers inhibit a host of transmitters such as dopamine, serotonin, GABA, and acetylcholine.[14,17] The endocannabinoid transmission plays a significant role in the dependence/withdrawal to abused substances and drug seeking behavior through mediation of motivation.[15]

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 mesocorticolimbic dopamine systems which are located in the substantia nigra and ventral tegmental.[12,14,17] 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.[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.[15] Although the CB1 receptors have the ability to modulate effects of drug abuse, the exact mechanism of their interaction was uncertain.[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 **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[5], hunger stimulation in chemotherapy and AIDs patients[18], glaucoma, and as an analgesic.[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.[14,19] CB1 receptors are predominately found at nerve terminals and mediate inhibition of transmitter release.[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.[21] CB2 receptors are found in immune cells and modulate cytokine release.[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.

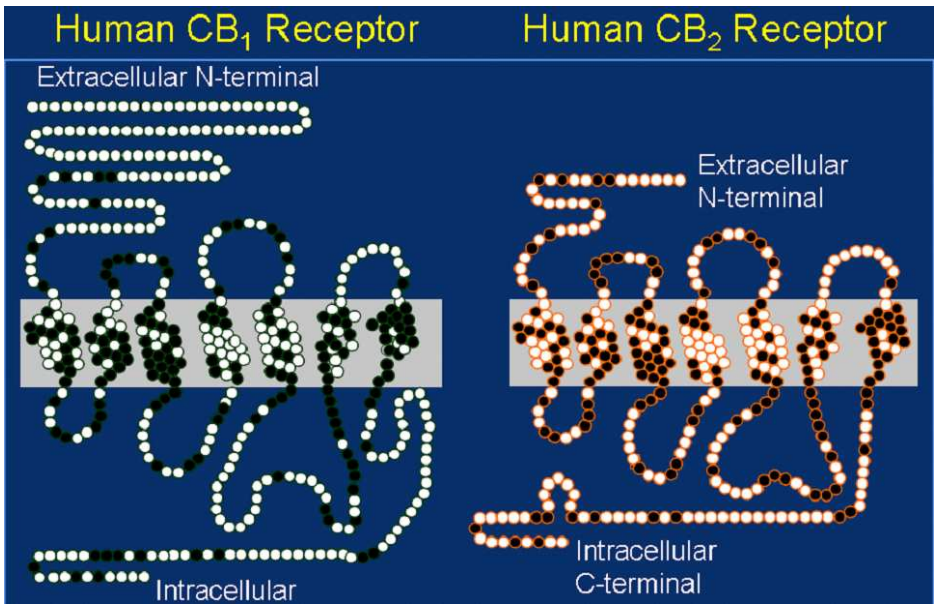


Figure 2.4: Structure of G-protein coupled receptors CB1 and CB2

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.[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.[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.[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.[25]

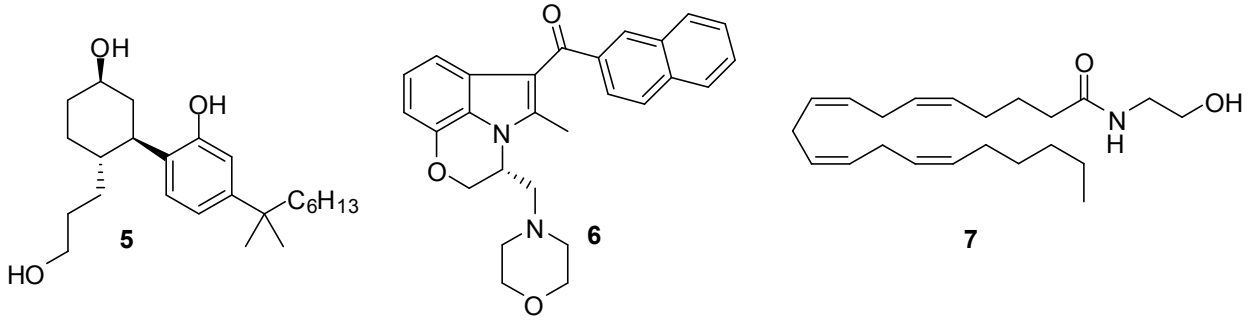
The binding of ligands to the receptor may shift the equilibrium toward the active receptor states.[26] There are two types of ligands that exist: agonists and or antagonists. Agonist are a class of ligands that favor the active states.[29] Within the agonist ligands there are low efficacy agonist deemed partial agonists. Among antagonists there are both antagonist and ligands that exhibit inverse agonist pharmacological profiles. Inverse

agonists favor the inactive states.[29] 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.[30-31]

2.2.3.1. CB1 Receptor Ligands

There are a five main chemical classes of cannabinoids: natural cannabinoids, synthetic cannabinoids, eicosanoids, 1,5-diarylpyrazoles, and aminoindoles. Natural "classical" cannabinoids are dibenzopyran derivatives.[30-31] Synthetic "nonclassical" cannabinoids are bicyclic and tricyclic analogues of Δ^9-THC **1**. However, eicosanoids "endocannabinoids" have a completely different structure.[30-31] The four classes of cannabinoid ligands that represent the essential characteristics of CB1 receptor agonist include classical cannabinoid, Δ^9-THC **1**; nonclassical cannabinoid,
CP 55,940 (**5**); aminoindole WIN 55,2112-2 (**6**) and the endogenous cannabinoid, anandamide (**7**).[31]

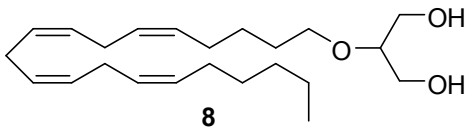
Figure 2.5: Structure of CB1 Receptor Agonists



CB1 receptor agonists are responsible for cAMP production inhibition[32], calcium influx inhibition[33], potassium channel activation[34], MAP Kinase pathway activation[35], and an increase in intracellular dopamine levels in the brain.[12,14,36-39]

In rat brain tissue, there was the discovery of a high affinity and pharmacologically distinct class of cannabinoid receptors.[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.

Figure 2.6: Structure of Endogenous Ligand



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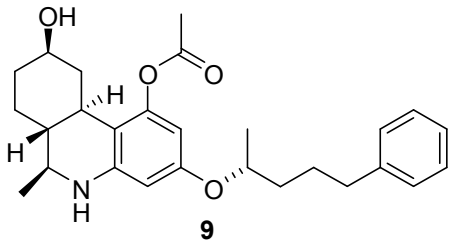
Anandamide (**7**) has a similar potency as THC **1** at the CB1 receptor and acts as a partial agonist. However, 2-AG **8** has the ability to bind to both the CB1 and CB2 receptors and act as a full agonist at both and has a higher concentration in the brain than anandamide (**7**).[40-41] Anandamide (**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



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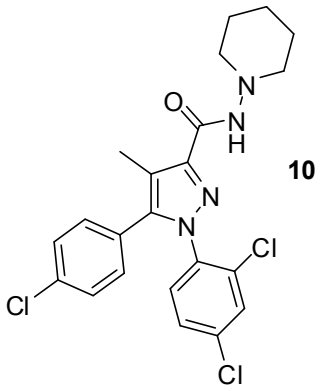
This cannabinoid compound was more potent than THC **1**, easier to administer, but had too many side effects.[42] From these early studies, CP55-940 (**5**), a synthetic analog of Δ^9-THC **1** was created and lead to the important discovery of CB1 receptor in 1988.

CP 55,940 (**5**) mimics the effects of THC **1** and is a full agonist at both CB1 and CB2 receptors.[31b] This synthetic analog allowed for radioligand binding assays that were not possible for Δ^9-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



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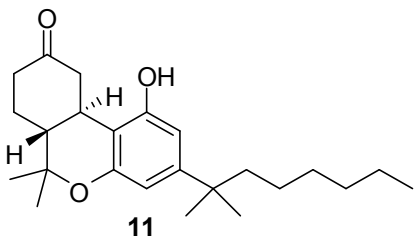
Rimonabant **10** was developed as an anti-obesity drug used for blockade of CB1 receptor that cause "munchies" among marijuana users.[12-14]

The aminoalkylindole derivative, WIN-55212-2 (**6**) is also a potent cannabinoid receptor agonist. This potent agonist has both analgesic[43] and neuropathic[44] properties and anti-inflammatory.[45] WIN-55212-2 (**6**) is a full agonist at the CB1 receptor with a higher affinity than THC **1** for the CB1 receptor.[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 Δ^9-THC **1** and is licensed for medical use.

Figure 2.9: Structure of Nabilone



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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.[29] 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.[29] However, if the physiologic 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 it's 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.[29] 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.[29] 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]

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

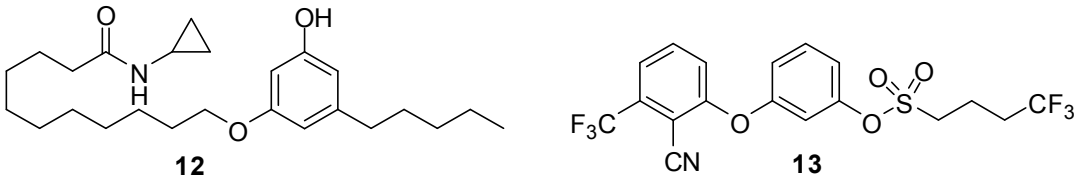
[S] is the substrate concentration and K_m is the substrate's affinity for an enzyme. The K_i or IC_{50} values display the binding affinity that the ligand binds to the receptor. Experimental values of the IC_{50} are variable based on radioligand concentration whereas K_i is an absolute value.

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

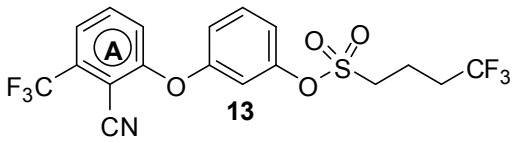
food intake and body weight, increased nocieptive sensitivity, and increased anxiety and depression, which is associated with Rimonabant (**53**).[50-53] An alternative to this approach is the development of partial agonist as therapy. Partial agonist stimulate dopamine, raise basal dopamine levels without 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.[54] However, CB25 (**12**) is very hydrophobic (ClogP = 6.2)[55] 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**).



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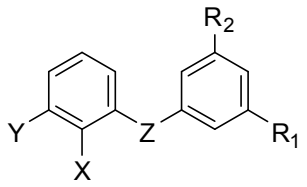
BAY 59-3074 (**13**) exhibits modest affinity (K_i = 55 nM)[56] and displays good lipophilicity (ClogP = 4.77)[55] compared to CB25 (**12**) and its analogues are more likely to be viable drug candidates. We want to synthesize these novel BAY 59-3074-CB25 hybrid analogues and characterize the binding 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



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

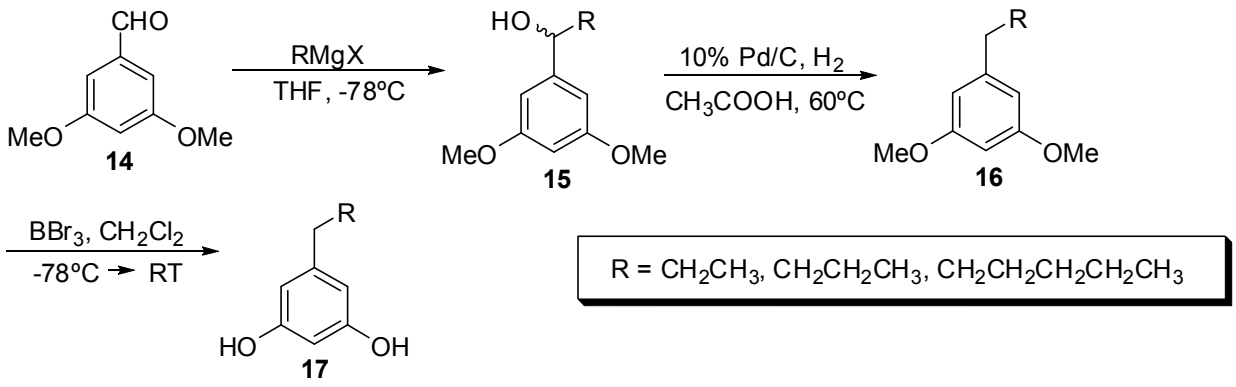
diaryl ether derivatives of BAY 59-3074 are the first class of compounds that will be prepared based on the basic scaffold since no SAR data for has been collected for BAY 59-3074 (**13**) at the CB receptors. The diaryl ether core will be derived from commercially available activated aryl fluoride and a 3-benzyloxyphenol. Microwave assisted uncatalyzed coupling reactions will be utilized to generate the diaryl ether scaffold in high yield.[57] 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.[58]

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.[57] 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).

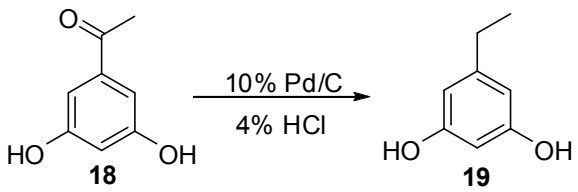
Scheme 2.1: Synthesis of 5-Alkylbenzene-1,3-diols[59]



The alcohol **15** was then deoxygenated under catalytic hydrogenolysis using 10%Pd/C and a hydrogen balloon in glacial acetic acid at 60 ºC to furnish the resorcinol dimethyl ether **16**. The dimethyl ether groups of **16** were deprotected with BBr_3 at -78 ºC 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).[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.

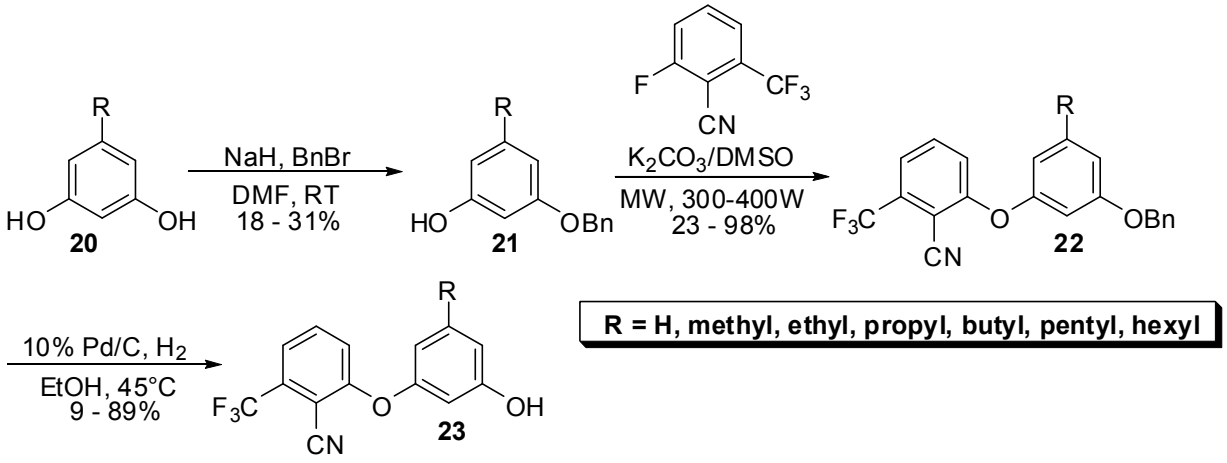
Scheme 16: Synthesis of 5-ethylbenzene-1,3-diol[60]



2.3.2. Synthesis of BAY 59-3074 and Alkyl Analogues

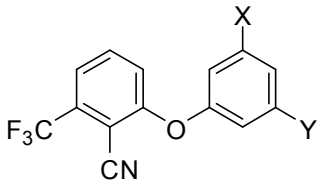
A variety of natural products and biologically interesting compounds contain a diaryl ether motif.[57] Diaryl ethers have been synthesized by coupling phenols to electron deficient aryl halides through S_NAr-based addition reactions with microwave irradiation within 5-10 minutes.[57] The synthesis of 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 alkylbenzoxyphenol **21** through microwave assisted uncatalyzed coupling reactions following the approach taken by the Wang group.[57] Debenzylation of the benzoxyphenol **22** was established under hydrogenolysis conditions with 10% Pd/C in EtOH at 45 ºC 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 affinites of the novel BAY 59-3074 alkyl analogues were determined at the cannabinoid receptor (CB1) by inhibition of [^{3}H]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



Cmpd.	Code #	X	Y	ClogP[a]	[^{3}H]SR141716A (CB1) *K*i (nM)[b]	CB1[c] (10 μM)	CB1[c] (100 μM)
23b	ARN 156	OH	CH_3	4.39	23,055±3217	16	30
23c	ARN 167	OH	CH_2CH_3	4.92		21	37
23d	ARN 180	OH	$CH_2CH_2CH_3$	5.45		24	60
23e	ARN 191	OH	$CH_2(CH_2)_2CH_3$	5.98		35	94
23f	ARN 158	OH	$CH_2(CH_2)_3CH_3$	6.50	293±107	39	41
23g	ARN 190	OH	$CH_2(CH_2)_4CH_3$	7.03		TBA	TBA
13	BAY 59-3074	H	$SO_2(CH_2)_3CF_3$	4.77	55[d]	61	65

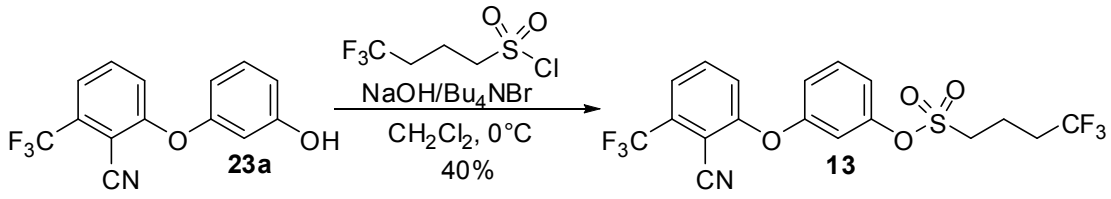
[a]The ClogP values were calculated using CS ChemDraw Ultra 10.0. [b]All the values are mean ± SEM of three experiments. [c]Binding affinities at CB1 receptor measured as % inhibition. [d]See reference 56.

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 **23c**-**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 0ºC to afford BAY 59-3074 (**13**) in 40% yield (Scheme 2.4).[62]

Scheme 2.4: Synthesis of BAY 59-3074[62]

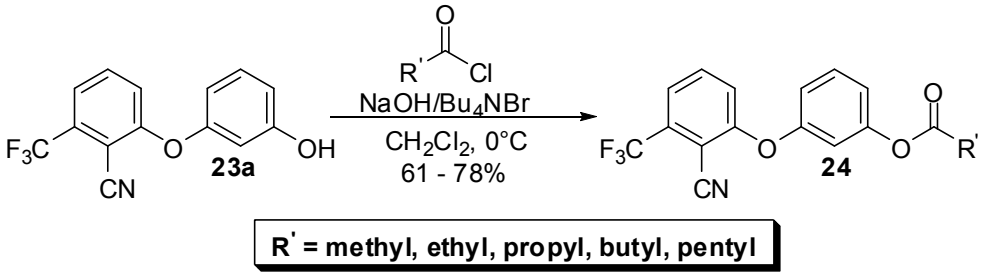


The binding affinity for the sulphonate ester **13** is presented in Table 2.1. The BAY 59-3074 has modest binding affinity (K_i = 55 nM)[56] and a greater affinity compared to the alkyl series reported in Table 2.1. Therefore, the syntheses of the ester analogues were attractive targets.

2.3.3. Synthesis of BAY 59-3074 Ester Analogues

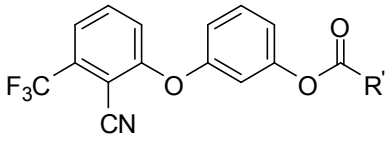
The same phase transfer catalysis utilized for BAY 59-3074 was employed to synthesize the diaryl ether ester analogues (Scheme 2.5).

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 ºC to afford the desired diaryl ether ester analogue **24**.

Table 2.2: [^{3}H]SR141716A uptake inhibition at CB1



Compound	Code #	R'	ClogP[a]	CB1[c] (10μM)	CB1[c] (100μM)
24a	ARN 199	CH_3	3.91	18	45
24b	ARN 200	CH_2CH_3	4.43	25	34
24c	ARN 201	$CH_2CH_2CH_3$	4.96	25	25
24d	ARN 202	$CH_2(CH_2)_2CH_3$	5.49	25	49
24e	ARN 203	$CH_2(CH_2)_3CH_3$	6.02	7	19

[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.

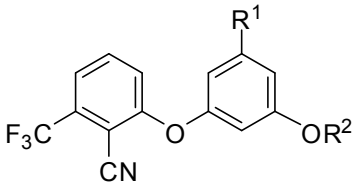
Upon evaluation of the ester series, there was significant improvement of the hydrophilicity **24a-24e** (ClogP 3.92 – 6.02)[55] compared to the alkyl series **23b-23g** (ClogP 4.39 – 7.03)[55]. The alkyl chain in the ester series increased in length the hydrophilicity decreased and the lipophilicity 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.

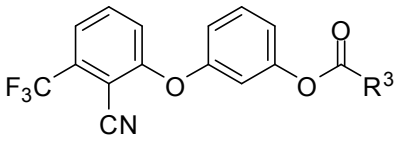
2.3.4. Evaluation of BAY 59-3074 Analogues

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



22a R^1 = H, R^2 = Bn
23a R^1 = H, R^2 = H
23f R^1 = $(CH_2)_4CH_3$, R^2 = H



24d R^3 = $(CH_2)_3CH_3$

Compound	Code #	ClogP[a]	CB1[c] (10μM)	CB1[c] (100μM)
13	BAY 59-3074	4.77	61	65
22a	AS 109	6.24	49	56
23a	ARN 142	3.89	3	37
23f	ARN 158	6.50	39	41
24d	ARN 202	5.49	25	49

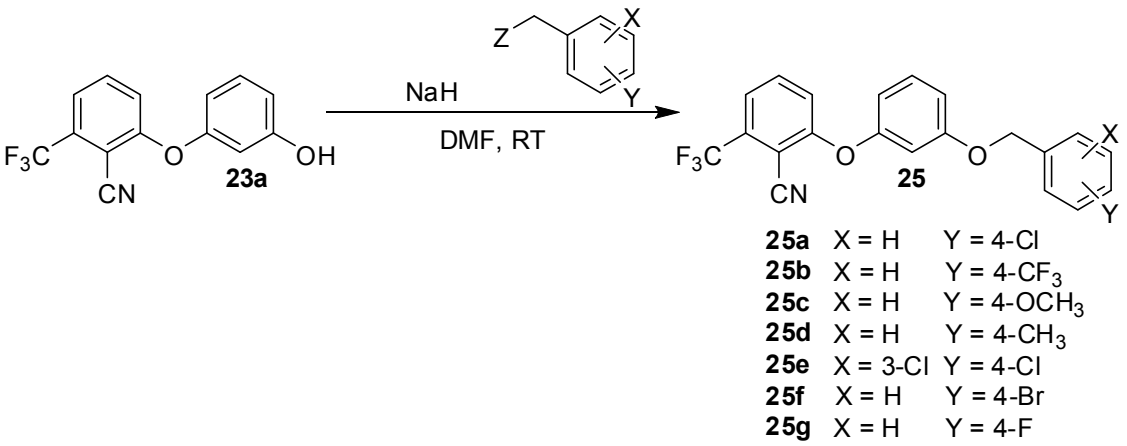
[a]The clogP values were calculated using CS ChemDraw Ultra 10.0. [b]All the values are mean ± SEM of three experiments. [c]Binding affinities at CB1 receptor measured as % inhibition.

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 modifiying 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_2Cl_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 Dragondorff'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[59]

To a stirred solution of 3,5-dimethoxybenzaldehyde (**14**) (1 equiv.) in THF and Et_2O at -78 ºC 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_4Cl. 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 $MgSO_4$, and evaporated to dryness under reduced pressure.

Deoxygenation Methodology[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 ºC. Upon completion the reaction mixture was diluted with Et_2O, 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 $NaHCO_3$. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure.

Demethylation Methodology[59]

To a stirred solution of 1-hexyl-3,5-dimethoxybenzene **16** (1 equiv.) in anhydrous CH_2Cl_2 at -78 ºC under an argon atmosphere was added BBr_3 (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 ºC, 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 $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure.

General Method B: Preparation of 2-ethylbenzene-1,3-diol[60]

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 Et_2O. The combined organic layers were dried over $MgSO_4$ 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 H_2O 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 Na_2SO_4, 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 Et_2O. The organic layers were combined, washed with 0.5 N HCl, washed with brine, dried over Na_2SO_4, and evaporated to dryness under reduced pressure.

General Method E: Preparation of Debenzylated Diaryl Ethers

A solution of 2-(3-(benzyloxy)-5-alkylphenoxy)-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.

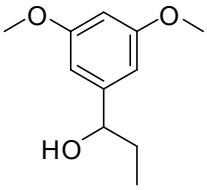
General Method F: Preparation of sulphonic ester, BAY 50-3074

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

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 $MgSO_4$.

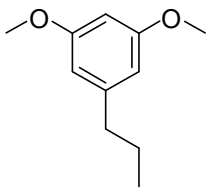
General Method G: Preparation of Esters

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 $MgSO_4$.



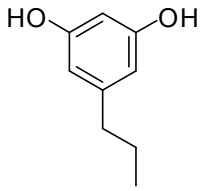
1-(3,5-Dimethoxyphenyl)propan-1-ol (15a)[59]

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, $CDCl_3$) δ 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, $CDCl_3$) δ 10.1, 31.9, 56.0(2), 77.8, 98.4, 104.7(2), 147.7, 160.9(2).



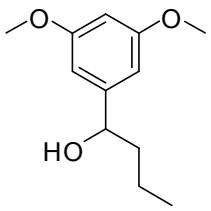
1-Propyl-3,5-dimethoxybenzene (16a)[59]

General Method A. The residue was purified by column chromatography (SiO_2, gradient of hexane, Et_2O/hexane, 1:9) to afford 0.910 g (43%) of (**16a**) as a pale yellow oil: R_f 0.78 (CH_2Cl_2/hexane, 3:7). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.67 (q, *J* = 7.6 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 3.80 (s, 6H), 6.33 (t, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 2H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 14.1, 24.6, 38.6, 55.4(2), 97.8, 106.8(2), 145.4, 161.0(2).



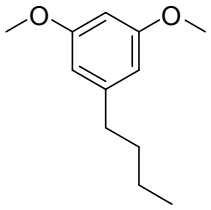
5-Propylbenzene-1,3-diol (17a)[59]

General Method A. No further purification to afford 0.839 g (99%) of (**17a**) as an amber oil: R_f 0.48 (EtOAc/hexane, 3:7). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.6 Hz, 3H), 1.60 (q, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 4.72 (broad s, 1, OH), 6.17 (s, 1H), 6.24 (d, *J* = 1.6 Hz, 2H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 14.0, 24.3, 38.1, 100.4, 108.3(2), 146.0, 159.2(2).



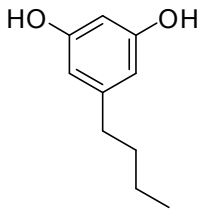
1-(3,5-Dimethoxyphenyl)butan-1-ol (15b)[59]

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, $CDCl_3$) δ 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, $CDCl_3$) δ 14.2, 19.2, 41.3, 55.5(2), 74.6, 99.5, 104.0(2), 147.9, 161.0(2).



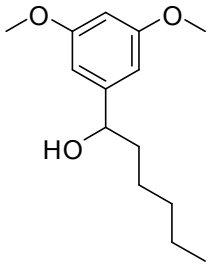
1-Butyl-3,5-dimethoxybenzene (16b)[59]

General Method A. The residue was purified by column chromatography (SiO_2, gradient of hexane, Et_2O/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, $CDCl_3$) δ 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, $CDCl_3$) δ 14.2, 22.7, 33.7, 36.3, 55.3(2), 97.8, 106.7(2), 145.6, 161.0(2).



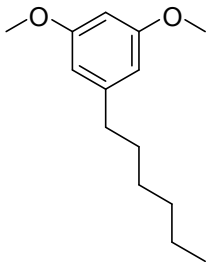
5-Butylbenzene-1,3-diol (17b)[59]

General Method A. The residue was purified by column chromatography (SiO_2, gradient of hexane, Et_2O/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).



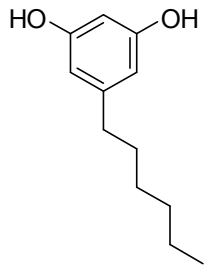
1-(3,5-Dimethoxyphenyl)hexan-1-ol (15c)[59]

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).



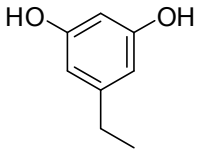
1-Hexyl-3,5-dimethoxybenzene (16c)[59]

General Method A. The residue was purified by column chromatography (SiO_2, gradient of hexane, Et_2O/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).



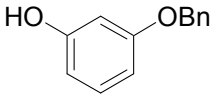
5-Hexylbenzene-1,3-diol (17c)[59]

General Method A. The residue was purified by column chromatography (SiO_2, gradient of hexane, Et_2O/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).



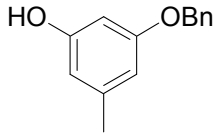
5-Ethylbenzene-1,3-diol (19)[60]

General Method B. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:4) to afford 1.31 g (72%) of (**19**) as a colorless oil: R_f 0.16 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 15.4, 28.9, 100.5, 107.6(2), 135.5, 157.0(2).



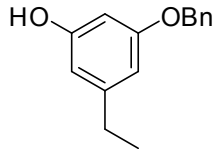
3-Benzyloxyphenol (21a)

General Method C. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 0.86 g (24%) of (**21a**) as an amber oil: R_f 0.46 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $(CD_3)_2CO$) 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). ^{13}CNMR (400 MHz, $(CD_3)_2CO$) 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.



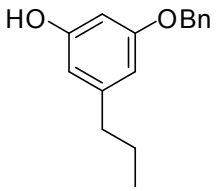
3-Benzyloxy-5-methyl-phenol (**21b**)

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, $(CD_3)_2SO$) δ 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, $(CD_3)_2SO$) δ 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.



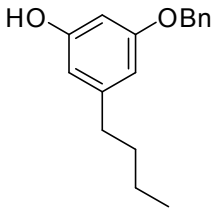
3-Benzyloxy-5-ethylphenol (**21c**)

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, $(CDCl_3)$ δ 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, $(CDCl_3)$ δ 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.



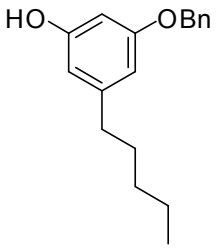
3-Benzyloxy-5-propylphenol (**21d**)

General Method C. The residue was purified by column chromatography (SiO_2, 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, $CDCl_3$) 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, $CDCl_3$) 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.



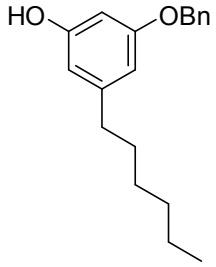
3-Benzyloxy-5-butylphenol (**21e**)

General Method C. The residue was purified by column chromatography (SiO_2, 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, ($CDCl_3$) 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, ($CDCl_3$) 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-Benzyloxy-5-pentyl-phenol (**21f**)

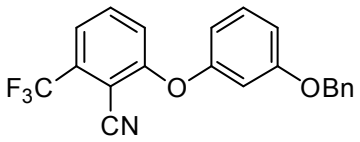
General Method C. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 0.457 g (31%) of (**21f**) as a brown oil: R_f 0.53 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $(CD_3)_2$ CO) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.26-1.34 (m, 4H), 1.55-1.63 (m, 2H), 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) δ 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-Benzyloxy-5-hexylphenol (**21f**)

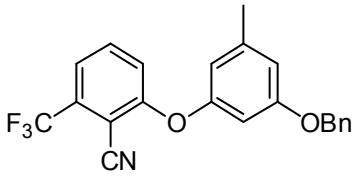
General Method C. The residue was purified by column chromatography (SiO_2, gradient of hexane) to afford 0.374 g (21%) of (**21f**) as a light brown oil: R_f 0.72 (EtOAc/hexane, 3:7). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.95 (dt, *J* = 2.4 Hz, 4.0 Hz, 3H), 1.31-1.40 (m, 6H), 1.62 (q, *J* = 7.6 Hz, 2H), 2.56 (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-Benzyloxy-phenoxy)-6-trifluoromethyl-benzonitrile (22a)[57]

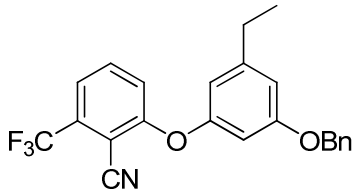
General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:10, 1:9, 1:4) to afford 0.325 g (23%) of (**22a**) as a white solid: R_f 0.60 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $(CD_3)_3SO$) δ 5.16 (s, 2H), 6.82 (t, *J* = 8.4 Hz, 1H), 6.94-7.00 (m, 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, $(CD_3)_3SO$) 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_2O), 370.2 (M + 1). Anal. Calcd. For $C_{21}H_{14}F_3NO_2$: C, 68.29; H, 3.82; N, 3.79. Found: C, 68.21; H, 3.77; N, 3.81.



2-(3-Benzyloxy-5-methyl-phenoxy)-6-trifluoromethyl-benzonitrile (22b)[57]

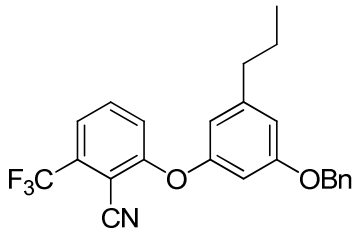
General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:5, 1:4) to afford 1.35 g (91%) of (**22b**) as a pale yellow oil: R_f 0.56 (EtOAc/hexane, 1:5). ^{1}HNMR (400 MHz, $(CD_3)_2CO$) δ 2.34 (s, 3H),

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, $(CD_3)_2CO$) δ 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.



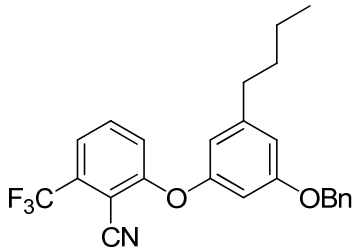
2-(3-(Benzyloxy)-5-ethylphenoxy)-6-(trifluoromethyl)benzonitrile (22c)[57]

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)[57]

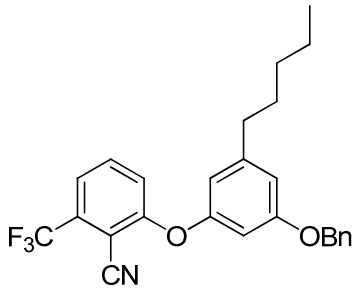
General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane) to afford 0.279 g (64%) of (**22d**) as a pale yellow oil: R_f 0.63 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, 3H), 1.60-1.66 (m, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 5.04 (s, 2H), 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, 95.7, 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)[57]

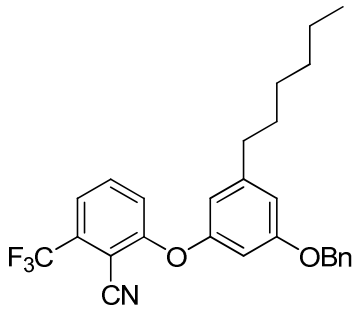
General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane 3:7, CH_2Cl_2/Hexane 3:7) to afford 0.244 g (36%) of (**22e**) as a colorless oil: R_f 0.80 (CH_2Cl_2/hexane, 3:7). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.6 Hz, 3H), 1.28-1.41 (m, 2H), 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.



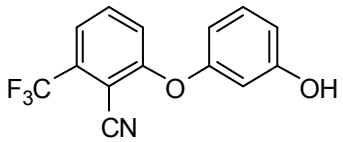
2-(3-Benxyloxy-5-pentyl-phenoxy)-6-trifluoromethyl-benzonitrile (22f)[57]

General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane) to afford 0.446 g (72%) of (**22f**) as a pale yellow oil: R_f 0.36 (EtOAc/hexane, 1:9). ^{1}HNMR (400 MHz, $(CD_3)_2$ 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). ^{13}CNMR (400 MHz, $(CD_3)_2$ 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)[57]

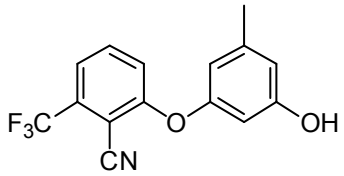
General Method D. The residue was purified by column chromatography (SiO_2, gradient of hexane) to afford 0.491 g (98%) of (**22g**) as a yellow oil: R_f 0.49 (EtOAc/hexane, 3:7). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 5.2 Hz, 3H), 1.31 (s, 6H), 1.59 (td, *J* = 2.8 Hz, 6.0 Hz, 2H), 2.60 (t, *J* = 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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)

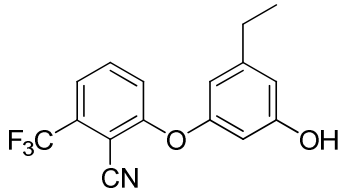
General Method E. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:1) to afford 0.199 g (81%) of (**23a**) as a white solid: R_f 0.08 (EtOAc/hexane, 1:4); mp 106–108 ºC. ^{1}HNMR (400 MHz, $(CD_3)_2CO$) δ 6.77-6.71 (m, 2H), 6.80-6.82 (m, 1H), 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, $(CD_3)_2CO$) 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**)

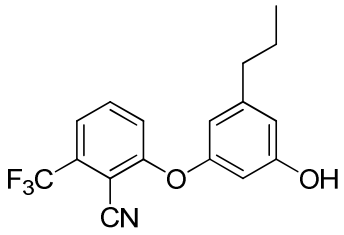
General Method E. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:1) to afford 0.588 g (57%) of (**23b**) as a light brown solid: R_f 0.19 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 73-75 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 $C_{15}H_{10}F_3NO_2$: 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**)

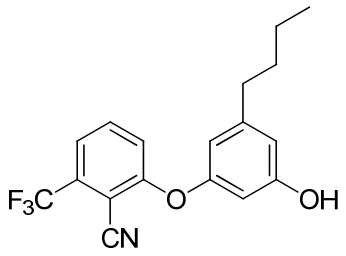
General Method E. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 0.279 g (89%) of

(**23c**) as a yellow oil: R_f 0.37 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) δ 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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 $C_{19}H_{18}F_3NO_2$: C, 62.54; H, 3.94; N, 4.56. Found: C, 62.44; H, 4.07; N, 4.35.



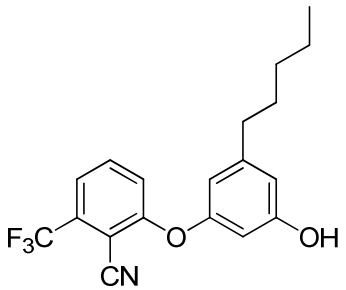
2-(3-Propyl-5-hydroxyphenoxy)-6-(trifluoromethyl)benzonitrile (**23d**)

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, $CDCl_3$) δ 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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_2O), 386.2 (M + Na). Anal. Calcd. for $C_{20}H_{20}F_3NO_2$•1/2 H_2O: 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**)

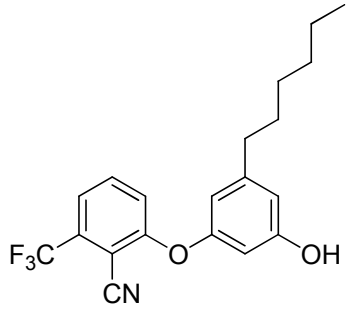
General Method E. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 86.7 mg (36%) of (**23e**) as a yellow solid: R_f 0.62 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 89-92 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) 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}CNMR (400 MHz, $CDCl_3$) 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 + H_2O), 358.1 (M + Na). Anal. Calcd. for $C_{18}H_{16}F_3NO_2$: 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 (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:1) to afford 0.141 g (40%) of (**23f**) as a

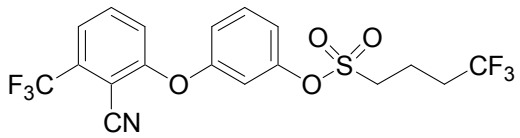
white solid: R_f 0.23 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 85-86 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.88 (q, *J* = 4.4 Hz, 3H), 1.26-1.34 (m, 4H), 1.54-1.62 (m, 2H), 2.54 (t, *J* = 7.6, 2H), 5.51 (broad s, 1, OH), 6.44 (t, *J* = 2.0 Hz, 2H), 6.49 (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, $CDCl_3$) δ 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 $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.50; H, 5.14; N, 4.01.



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

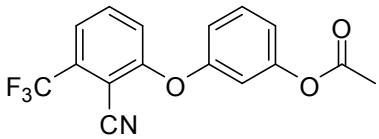
General Method E. The residue was purified by column chromatography (SiO_2, gradient of hexane, EtOAc/hexane, 1:9, 1:7, 1:5, 1:3, 1:1) to afford 33.2 mg (8.4%) of (**23g**) as a yellow solid: R_f 0.68 (EtOAc/hexane, 3:7). The oily residue was induced to crystallize by the addition of hexane; mp 88-91 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2O), 386.2 (M +

Na). Anal. Calcd. for $C_{20}H_{20}F_3NO_2$•1/2 H_2O: 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 4,4,4-trifluoro-1-butane-sulphonate (**14**)

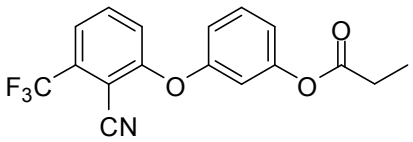
General Method F. The residue was purified by preparative TLC (SiO_2, gradient of hexane:CH_2Cl_2 3:7) to afford 0.129 g (40%) of **13** as a pale yellow oil: R_f 0.38 (CH_2Cl_2/hexane, 3:7). The oily residue was induced to crystallize by the addition of pentane; mp 59-60 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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), ^{13}CNMR (400 MHz, $CDCl_3$) δ 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).



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

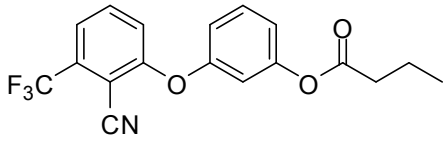
General Method G. The residue was purified by flash chromatography (SiO_2, gradient of hexane, CH_2Cl_2, EtOAc) to afford 46.5 mg (67%) of (**24a**) as a colorless oil: R_f 0.30 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.91 (t, J = 2.0 Hz, 1H), 6.98-7.04 (m, 2H), 7.14 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.0 Hz, 8.8 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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_2O). Anal. Calcd. for $C_{16}H_{10}F_3NO_3$•1/4 C_7H_8: C, 61.92; H, 3.51; N, 4.07. Found: C, 60.74; H, 3.66; N, 4.07.



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

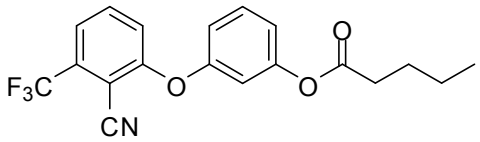
General Method G. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc/hexane 1:4) to afford 70.8 mg (61%) of (**24b**) as a white solid: R_f 0.25 (EtOAc/hexane, 1:4); mp 82-83 ºC. ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.5 Hz, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 6.91 (s, 1H), 6.91-7.04 (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, $CDCl_3$) δ 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 $C_{17}H_{12}F_3NO_3$•1/4 H_2O: C, 60.09; H, 3.71; N, 4.12. Found: C, 60.20; H, 3.49; N, 4.16.



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

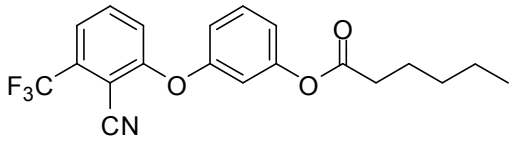
General Method G. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc/hexane 1:4) to afford 0.128 g (69%) of (**24c**) as a pale yellow oil: R_f 0.54 (EtOAc/CH_2Cl_2, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.6 Hz, 3H), 1.77 (sextet, *J* = 7.6 Hz, 2H), 2.54 (t, *J* = 7.6 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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 + H_2O). Anal. Calcd. for $C_{20}H_{20}F_3NO_2$•1/2 H_2O: C, 64.51; H, 5.68; N, 3.76. Found: C, 64.62; H, 5.62; N, 3.64.



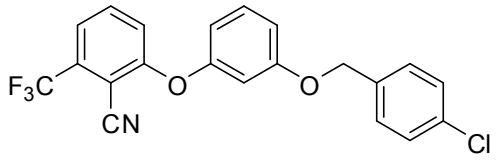
3-(2-Cyano-3-(trifluoromethyl)phenoxy)phenyl pentanoate (24d)

To a stirred solution of phenol (**23a**) (57 mg, 0.20 mmol) in Et_3N (5 mL) valeryl chloride (29 μL, 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_2, gradient of hexane, hexane/CH_2Cl_2 1:1, CH_2Cl_2, $(CH_3)_2CO$) to afford 57.1 mg (78%) of (**24d**) as a white solid: R_f 0.50 (EtOAc/hexane, 1:4); mp 44-46 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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 $C_{20}H_{20}F_3NO_2$•1/2 H_2O: 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**)

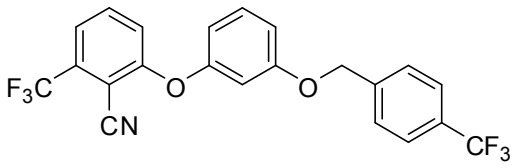
General Method G. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc:hexane 1:4) to afford 58.0 mg (74%) of (**24e**) as a colorless oil: R_f 0.56 (EtOAc/hexane, 1:4). ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.91-0.94 (m, 3H), 1.36-1.40 (m, 4H), 1.71-1.76 (m, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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 $C_{20}H_{18}F_3NO_3$: 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**)

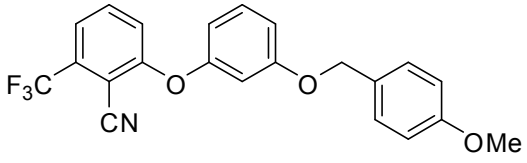
General Method C. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc:hexane 1:4) to afford 40.6 mg (56%) of (**25a**) as a colorless oil: R_f 0.40 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 46-48 °C. ^{1}HNMR (400 MHz, ($CDCl_3$) 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). ^{13}CNMR (400 MHz, ($CDCl_3$) 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,

160.4, 161.5. MS (ESI) *m/z* 404.3 (M + 1), 426.3 (M + Na). Anal. Calcd. for $C_{21}H_{13}ClF_3NO_2$: C, 62.47; H, 3.25; N, 3.47. Found: C, 62.47; H, 3.25; N, 3.47.



2-(Trifluoromethyl)-6-(3-(4-(trifluoromethyl)benzyloxy)phenoxy)benzonitrile (25b)

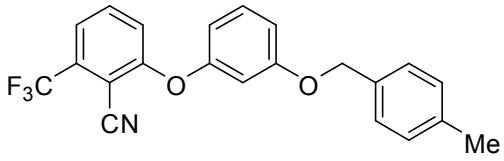
General Method C. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc:hexane 1:4) to afford 35.9 mg (71%) of (**25b**) as a colorless oil: R_f 0.37 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 65-66 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{13}F_6NO_2 \cdot H_2O$: 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)

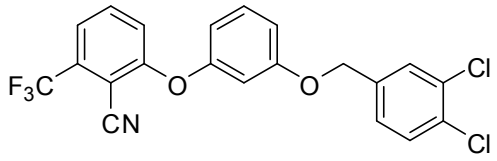
General Method C. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc:hexane 1:4) to afford 30.2 mg (64%) of (**25c**) as a white solid: R_f 0.45

(EtOAc/hexane, 1:4); mp 103-105 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.98 (s, 2H), 6.68 (dt, *J* = 1.6Hz, 2.0Hz, 2H), 6.87-6.93 (m, 3H), 7.06 (d, *J* = 8.4Hz, 1H), 7.33 (t, *J* = 8.4Hz, 3H), 7.44 (d, *J* = 7.6Hz, 1H), 7.55 (t, *J* = 8.4Hz, 1H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 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_2O), 422.4 (M + Na). Anal. Calcd for $C_{22}H_{16}F_3NO_3$: C, 66.16; H, 4.04; N, 3.51, Found: C, 66.11; H, 3.96; N, 3.51.



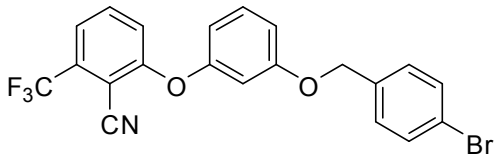
2-(3-(4-Methylbenzyloxy)phenoxy)-6-(trifluoromethyl)benzonitrile (**25d**)

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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2O). Anal. Calcd. for $C_{22}H_{16}F_3NO_2$: 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)

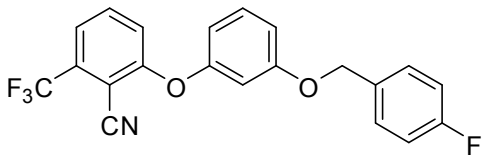
General Method C. The residue was purified by preparative TLC (SiO_2, gradient of EtOAc:hexane 1:4) to afford 35.4 mg (62%) of (**25e**) as a colorless oil: R_f 0.52 (EtOAc/hexane, 1:4). The oily residue was induced to crystallize by the addition of hexane; mp 66-68 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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 $C_{21}H_{12}Cl_2F_3NO_2$: 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 (SiO_2, gradient of EtOAc:hexane 1:4) to afford 50.5 mg (78%) of (**25f**) as a white solid: R_f 0.57 (EtOAc/hexane, 1:4); mp 85-86 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}CNMR (400 MHz, $CDCl_3$) δ 69.7, 107.5(3), 112.5, 112.9, 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_2O), 413.6 (M - Cl). Anal. Calcd. for $C_{21}H_{13}BrF_3NO_2$: C, 56.27; H, 2.92; N, 3.12. Found: C, 56.19; H, 2.88; N, 3.20.



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 ºC. ^{1}HNMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2O). Anal. Calcd. for $C_{21}H_{13}F_4NO_2$: C, 65.12; H, 3.38; N, 3.62. Found: C, 65.03; H, 3.65; N, 3.39.

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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)benzonitirile (**23a**).

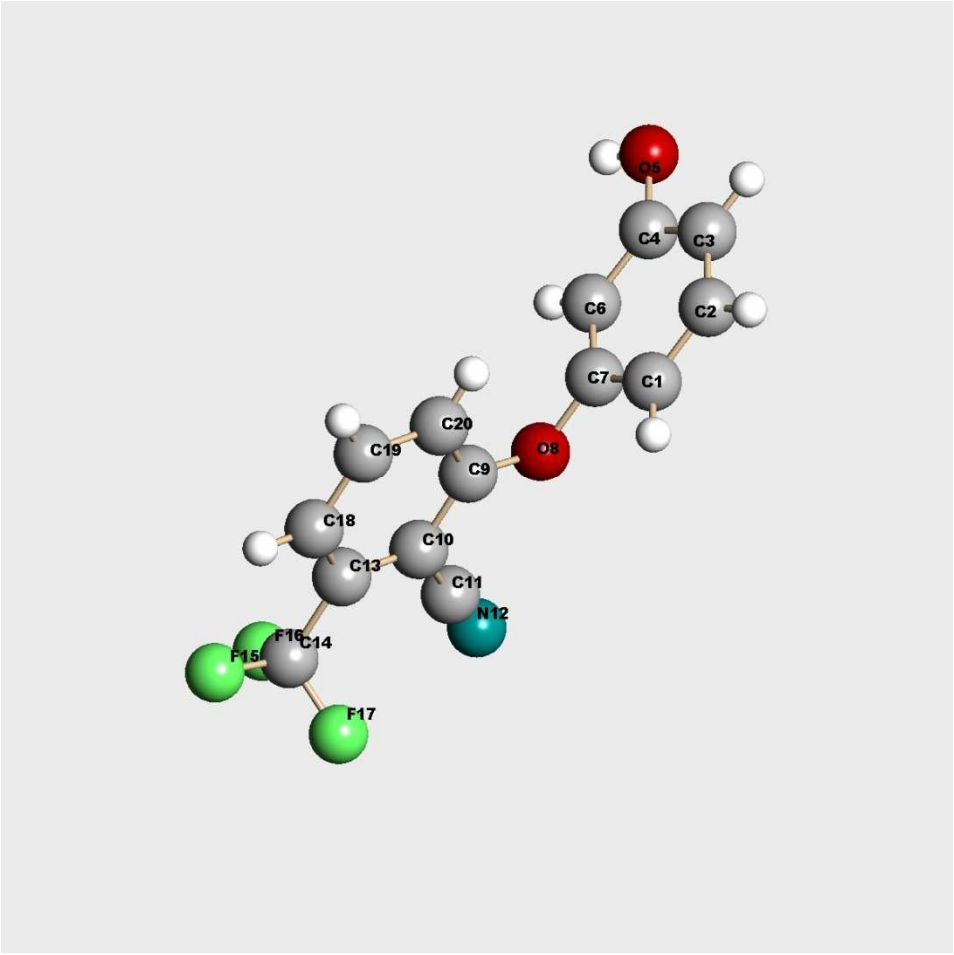

Table 1: Crystal data and structure refinement for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitirile

Empirical formula	$C_{14}H_8F_3NO_2$	
Formula weight	279.21	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 33.373(7) Å	α = 90º
	b = 5.60004(12) Å	β = 90.813(3)º
	a = 13.231(3) Å	γ = 90º
Volume	2472.7(9)Å^3	
Z	8	
Density (calculated)	1.500 Mg/m^3	
Absorption coefficient	0.131 mm^{-1}	
F(000)	1136	
Crystal size	0.50 x 0.50 x 0.01 mm^3	
Theta range for data collection	2.44 to 28.23º	
Index ranges	-43<=h<=43, -7<=k<=7, -17<=l<=17	
Reflections collected	14417	
Independent reflections	8410 [R(int) = 0.0283]	
Completeness to theta = 28.33	100%	
Absorption correction	emperical	
Max. and min. transmission	0.9987 and 0.9374	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2879/0/213	
Goodness-of-fit-on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1075	
R indices (all data)	R1 = 0.0533, wR2 = 0.1266	

Table 2: Atomic coordinates (Å x 10^4) and equivalent isotropic displacement parameter (Åx 10^3) for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitirile (**23a**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2994(5)	-1720(3)	7692(13)	29(3)
C(2)	2761(5)	-1948(3)	0.6815(13)	30(4)
H(2)	2576(6)	-3310(4)	0.6766(15)	32(5)
C(3)	2784(5)	-295(3)	0.6036(12)	28(3)
H(3)	2618(6)	-430(4)	0.5422(15)	32(5)
C(4)	3048(5)	1628(3)	0.6126(11)	25(3)
O(5)	3064(4)	3219(2)	0.5346(9)	32(3)
H(5)	3243(8)	4270(5)	0.5448(18)	51(7)
C(6)	3285(5)	1887(3)	0.6995(12)	24(3)
H(6)	3458(6)	3180(3)	0.7062(14)	25(4)
C(7)	3251(5)	2110(3)	0.7754(11)	25(3)
O(8)	3476(3)	650(2)	0.8644(8)	29(3)
C(9)	3788(4)	-810(3)	0.8885(11)	24(3)
C(10)	3990(4)	-239(3)	0.9792(11)	24(3)
C(11)	3846(5)	1774(3)	10350(11)	25(3)
N(12)	3726(4)	3421(3)	10763(10)	31(3)
C(13)	4323(5)	-1609(3)	10100(12)	26(3)
C(14)	4540(5)	-1001(3)	11072(13)	33(4)
F(15)	4862(4)	-2358(3)	11232(9)	61(4)
F(16)	4665(4)	1273(2)	11094(9)	51(3)
F(17)	4305(3)	-1272(2)	11874(7)	42(3)
C(18)	4450(5)	-3491(3)	9514(13)	31(4)
H(18)	4680(6)	-4450(4)	9735(16)	38(5)
C(19)	4249(5)	-4020(3)	8613(13)	31(4)
H(19)	4340(6)	-5290(4)	8217(17)	43(6)
C(20)	3921(5)	-2708(3)	8296(12)	28(3)
H(20)	3784(6)	-3060(4)	7679(16)	32(5)
H(1)	2972(6)	-2840(4)	8240(16)	35(5)

Table 3: Bond lengths [Å] and angles [º] for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitirile (**23a**)

C(1)-C(7)	1.383(2)
C(1)-C(2)	1.392(2)
C(2)-C(3)	1.389(2)
C(3)-C(4)	1.394(2)
C(4)-O(5)	1.3645(19)
C(4)-C(6)	1.394(2)
C(6)-C(7)	1.381(2)
C(7)-O(8)	1.4084(18)
O(8)-C(9)	1.3588(19)
C(9)-C(20)	1.393(2)
C(9)-C(10)	1.406(2)
C(10)-C(13)	1.406(2)
C(10)-C(11)	1.435(2)
C(11)-N(12)	1.147(2)
C(13)-C(18)	1.379(2)
C(13)-C(14)	1.505(2)
C(14)-F(15)	1.331(2)
C(14)-F(16)	1.340(2)
C(14)-F(17)	1.337(2)
C(18)-C(19)	1.392(2)
C(19)-C(20)	1.379(2)
C(7)-C(1)-C(2)	117.36(15)
C(3)-C(2)-C(1)	121.41(15)
C(2)-C(3)-C(4)	119.59(15)
O(5)-C(4)-C(6)	121.86(14)
O(5)-C(4)-C(3)	118.14(14)
C(6)-C(4)-C(3)	120.00(14)
C(7)-C(6)-C(4)	118.61(14)
C(6)-C(7)-C(1)	123.02(14)
C(6)-C(7)-O(8)	116.22(14)
C(1)-C(7)-O(8)	120.62(14)
C(9)-O(8)-C(7)	119.25(12)
O(8)-C(9)-C(20)	125.22(14)
O(8)-C(9)-C(10)	114.88(13)
C(20)-C(9)-C(10)	119.87(14)
C(13)-C(10)-C(9)	119.40(14)
C(13)-C(10)-C(11)	123.32(14)
C(9)-C(10)-C(11)	117.27(14)
N(12)-C(11)-C(10)	177.37(16)
C(18)-C(13)-C(10)	120.16(15)
C(18)-C(13)-C(14)	120.35(15)
C(10)-C(13)-C(14)	119.48(14)
F(15)-C(14)-F(16)	106.81(16)

F(15)-C(14)-F(17)	106.86(15)
F(16)-C(14)-F(17)	105.97(15)
F(15)-C(14)-C(13)	112.58(14)
F(16)-C(14)-C(13)	112.28(14)
F(17)-C(14)-C(13)	111.91(14)
C(13)-C(18)-C(19)	119.69(16)
C(20)-C(19)-C(18)	121.25(16)
C(19)-C(20)-C(9)	119.62(15)

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

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	311(9)	266(8)	294(8)	38(6)	21(6)	13(6)
C(2)	268(8)	257(8)	373(9)	-16(7)	-2(6)	-26(6)
C(3)	260(8)	283(8)	288(8)	-43(6)	-56(6)	14(6)
C(4)	276(8)	236(7)	225(7)	0(6)	-27(6)	31(6)
O(5)	419(7)	309(6)	239(6)	42(5)	-85(5)	-42(5)
C(6)	245(8)	234(7)	250(7)	-17(6)	-27(6)	-4(6)
C(7)	263(8)	265(7)	221(7)	-16(6)	-34(5)	46(6)
O(8)	366(6)	284(6)	223(5)	-23(4)	-75(4)	74(5)
C(9)	269(8)	247(7)	199(7)	37(6)	0(5)	2(6)
C(10)	270(8)	259(7)	189(7)	9(6)	18(5)	-4(6)
C(11)	265(8)	295(8)	184(7)	23(6)	-17(5)	-3(6)
N(12)	378(8)	312(7)	242(6)	-17(6)	-2(5)	27(6)
C(13)	246(8)	321(8)	221(7)	11(6)	2(6)	10(6)
C(14)	305(9)	416(9)	277(8)	-23(7)	-38(6)	65(7)
F(15)	484(7)	880(10)	458(7)	-216(7)	-230(5)	361(7)
F(16)	552(8)	541(7)	425(7)	-13(6)	-160(5)	-180(6)
F(17)	487(7)	552(7)	215(5)	8(5)	-20(4)	30(5)
C(18)	280(9)	354(9)	302(8)	-14(7)	-9(6)	61(7)
C(19)	332(9)	320(9)	289(8)	-50(7)	33(6)	44(7)
C(20)	327(9)	291(8)	207(7)	-18(6)	1(6)	-2(6)

Table 5: Torsion angles [º] for 2-(3-hydroxyphenoxy)-6-(trifluoromethyl)benzonitirile (**67**)

C(7)-C(1)-C(2)-C(3)	-0.5(2)
C(1)-C(2)-C(3)-C(4)	0.5(2)
C(2)-C(3)-C(4)-O(5)	179.95(14)
C(2)-C(3)-C(4)-C(6)	-0.2(2)
O(5)-C(4)-C(6)-C(7)	179.77(14)
C(3)-C(4)-C(6)-C(7)	-0.1(2)
C(4)-C(6)-C(7)-C(1)	0.1(2)
C(4)-C(6)-C(7)-O(8)	-175.64(13)
C(2)-C(1)-C(7)-C(6)	0.2(2)
C(2)-C(1)-C(7)-O(8)	175.74(14)
C(6)-C(7)-O(8)-C(9)	-112.10(16)
C(1)-C(7)-O(8)-C(9)	72.1(2)
C(7)-O(8)-C(9)-C(20)	2.7(2)
C(7)-O(8)-C(9)-C(10)	-179.27(13)
O(8)-C(9)-C(10)-C(13)	-178.64(13)
C(20)-C(9)-C(10)-C(13)	-0.5(2)
O(8)-C(9)-C(10)-C(11)	0.2(2)
C(20)-C(9)-C(10)-C(11)	178.32(14)
C(13)-C(10)-C(11)-N(12)	149(4)
C(9)-C(10)-C(11)-N(12)	-29(4)
C(9)-C(10)-C(13)-C(18)	0.1(2)
C(11)-C(10)-C(13)-C(18)	-178.61(15)
C(9)-C(10)-C(13)-C(14)	-179.98(14)
C(11)-C(10)-C(13)-C(14)	1.3(2)
C(18)-C(13)-C(14)-F(15)	3.7(2)
C(10)-C(13)-C(14)-F(15)	-176.23(16)
C(18)-C(13)-C(14)-F(16)	124.27(18)
C(10)-C(13)-C(14)-F(16)	-55.6(2)
C(18)-C(13)-C(14)-F(17)	-116.70(18)
C(10)-C(13)-C(14)-F(17)	63.4(2)
C(10)-C(13)-C(18)-C(19)	0.4(3)
C(14)-C(13)-C(18)-C(19)	-179.53(16)
C(13)-C(18)-C(19)-C(20)	-0.5(3)
C(18)-C(19)-C(20)-C(9)	0.1(3)
O(8)-C(9)-C(20)-C(19)	178.31(15)
C(10)-C(9)-C(20)-C(19)	0.4(2)

Symmetry transformations used to generate equivalent atoms

VITA

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