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Synthesis and Development of Potential CB1 Receptor Neutral Antagonists

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Synthesis and Development of Potential CB_1 Receptor
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This thesis is dedicated to my family, advisor and my friends.

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Abstract

Cannabis and its derivatives have been used for both medicinal and recreational purposes. The study of this plant led to the discovery of over 60 cannabinoids, found exclusively in cannabis, that contribute to the behavioral effects of cannabis use, the most common is delta-9-tetrahydrocannabinol. Cannabinoid receptors function to increase activity in the mesolimbic dopamine reward system. Dopamine is a neurotransmitter that plays a major role in addition and its regulation plays a crucial role in mental and physical well-being. There is evidence that CB_1 receptors are important to the reinforcing effects and the development of physical dependence on opiate drugs. Studies have shown that increased levels of dopamine are consistent with addiction while reduced levels lead to a decline in recreational use.

The goal of this research is to design, synthesize and develop potential CB_1 receptors that exhibit a neutral cannabinoid antagonist pharmacological profile.

Keywords: Cannabinoids, Cannabinoid receptors, Dopamine, Benzhydryl Azetidines, Diols, Oximes, Amines

Introduction

Cannabis sativa, or marijuana, is an Indian hemp that was given its name and classification by Linnaeus in 1753.[1] For centuries, marijuana and its derivatives have been used for both medicinal and recreational purposes. An entire family of drugs, called cannabinoids (Figure 1), is found exclusively in cannabis, and each may contribute, directly or indirectly, to the behavioral effects associated with cannabis use.[1] Cannabis effects include enhanced moods (happiness or laughing), sensory alterations, enhanced appetite and greater insight/thinking.[2] The chemistry of cannabis is very complex, over 60 cannabinoids have been identified, the most common is the principal psychoactive ingredient Δ-9-tetrahydrocannabinol [Δ^9-THC (**1**)].[1] Other common natural cannabinoids or "phytocannabinoids" include cannabidiol [CBD (**2**)] and cannabinol [CBN (**3**)], which exhibit non-psychoactive properties.[2]

Δ-9-tetrahydrocannabinol
Δ^9- THC
(1)

Cannabidiol
CBD
(2)
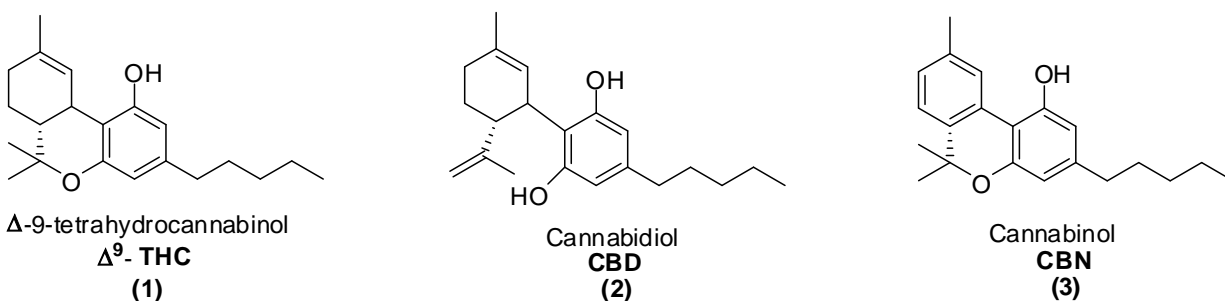
Cannabinol
CBN
(3)

Figure 1. "Phytocannabinoids" or Natural Cannabinoids[2]

The discovery of the cannabinoids led to the identification of the endogenous cannabinoid system (ECS), which is involved in many physiological processes, including appetite, sensation of pain, mood and memory.[3,4]   This system consists of two (G-protein)-coupled membrane receptors (CB_1 and CB_2), endogenous ligands (endocannabinoids), and the enzymes and proteins involved in their formation and metabolism.[3]   Modulation of this system may be crucial in discovering treatments for diseases, such as, drug addiction, obesity, and Alzheimer's.
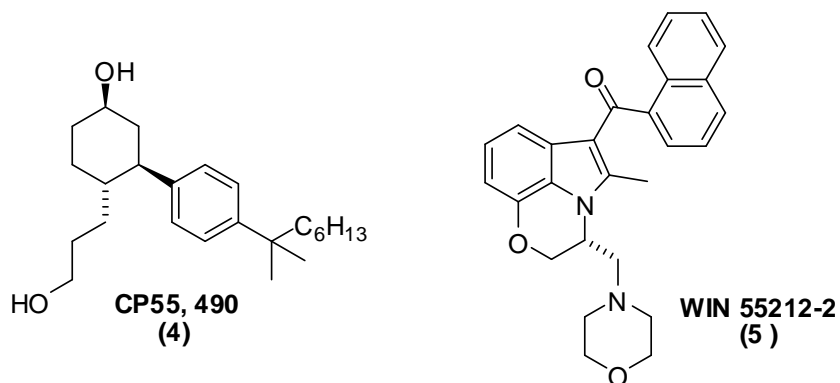
Figure 2. Examples of a Non-Classical Cannabinoid (**4**) and Aminoindole (**5**)[4]

Gaoni and Mechoulam (1964) successfully identified the correct chemical structure of THC and this discovery led to the synthesis of structurally similar analogs of **phytocannabinoids**, **nonclassical cannabinoids (4) and aminoindoles (5).** [4,5] The study of one such analog, **CP 55,940, (4)** provided evidence of the possible existence of a high-affinity and stereo-selective binding site, which allowed the

identification and characterization of a cannabinoid receptor.[6] Radioligands and autoradiography helped map these cannabinoid binding sites in the brain.[6] In 1990 and 1993 respectively, this mapping was essential to the identification and cloning of two cannabinoid G-protein coupled receptors (GCPRs).[7,8] These receptors (CB_1 and CB_2), belong to the Class A, rhodospin-like family of GPCRs. G-protein coupled receptors activate varying types of G-proteins on the intracellular side of the lipid membrane, thus eliciting biochemical responses through different signal transduction mechanisms.[9] CB_1 receptors are found primarily in the central nervous system, in areas including those that control movement (cerebellum and basal ganglia), cognition (cerebral cortex), memory and attention (hippocampus), and pain.[10] This receptor is also expressed in peripheral tissue (eye and bladder) and is responsible for mediating most of the behavioral effects of Δ^9-THC.[10] The CB_2 receptor is found mostly in peripheral tissue in cells of the immune system, including the spleen and tonsils,[11] and may play a pivotal role in mediating the immunosuppressive effects of cannabinoids.[10] A recent report described CB_2 receptors present in small amounts in the CNS, compared to CB_1 receptors.[12] CB_1 and CB_2 receptors can mediate different cannabinoid effects and make it possible to develop medications that selectively produce therapeutic effects with minimal side effects.[1]

There are four classes of ligands that characterize CB_1 receptor agonists: the classical cannabinoids [ex. Δ^9-THC (**1**)], the non-classical cannabinoids [ex. CP55,940 (**4**)], the aminoindoles [ex. WIN55212-2 (**5**)], and the endogenous cannabinoids [ex. Anandamide (**6**)].[11] These ligands have a low nanomolar affinity for CB_1 receptors and are usually non-selective for CB_1 over CB_2 receptors. Of the previous ligands, Anandamide (**6**) has shown a significant difference in binding affinities for each receptor type [K_i= 61 nM (CB_1) and K_i= 1930 nM (CB_2)].[13] Anandamide [AEA or N- arachidonyl ethanolamine (**6**)] was isolated from porcine brain and has similar properties to the naturally derived agonist Δ^9-THC. Another endogenous ligand is 2-arachidonoylglycerol [2-AG (**7**)], an important phosphoglyceride metabolism intermediate. [13]

Ananamide
AEA
(6)

2-Arachidonoylglycerol
2-AG
(7)
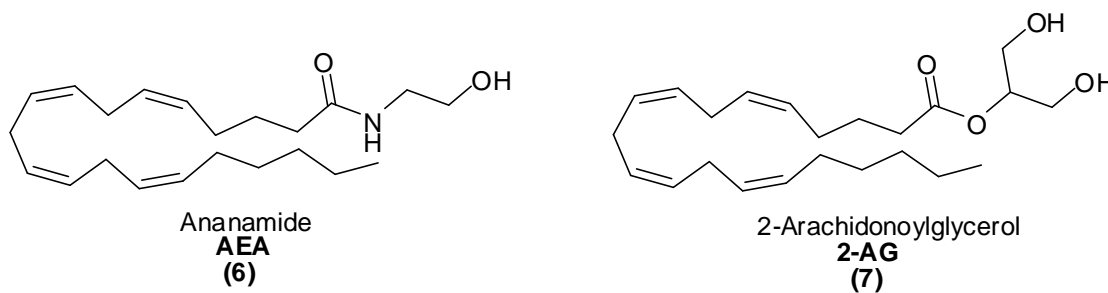
Figure 3. Examples of Endogenous Ligands [13]

Endocannabinoids (Figure 3) are thought to act as retrograde messengers in the nervous system. They are released by postsynaptic neurons and cross the synaptic cleft to stimulate CB_1 receptors on presynaptic termini.[13,14] The activated CB_1

receptors couple mainly through the G_i/G_o class of G proteins to control the potassium and calcium channels and reduce the chance of neurotransmitter release.[14,15] This suppression can result in inhibition or disinhibition of neuronal circuits, depending on whether the CB_1 receptor is expressed on glutamatergic or GABergic neurons.[14] The glutamatergic neurotransmitter system plays an important role in information processing and memory function. Ligands, AEA (**6**) and 2-AG (**7**), are produced from the metabolism of membrane phospholipids and are released immediately into extracellular space. Inactivation occurs in two steps: cellular reuptake, helped by a transporter protein known as anandamide membrane transporter (AMT) and enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) or by a monoacyglycerol lipase, for 2-AG (**7**).[13] AEA and 2-AG can be re-synthesized as needed. The therapeutic nature of these endogenous cannabinoid system receptors are of great interest because they represent targets for the development of new analgesic and anti-inflammatory drug agents.[13]

Cannabinoid receptors and endocannabinoids appear to function as neuromodulators of many different neurotransmitters than as neurotransmitters themselves.[1] Cannabinoid receptors function to increase activity in the mesolimbic dopamine reward system. They perform this function by potentiating the effects of endogenous opioid peptides, which in turn function as neuromodulators of dopamine transmission.[1,15] Dopamine is a neurotransmitter that controls

movement, behavior, learning, motivation and reward. It plays a major role in addiction and its regulation plays a crucial role in mental and physical well-being.[2] CB_1 receptor agonists can increase intracellular dopamine levels in the brain similar to cocaine and there is evidence that the CB_1 receptors are important to the reinforcing effects and the development of physical dependence on opiate drugs.[2,15] Stimulants, such as cocaine, block the reuptake of dopamine in the synapse, resulting in prolonged availability of the neurotransmitter. Studies have shown that increased levels of dopamine are consistent with addiction, while reduced levels of dopamine are consistent with a reduction in drug self administration.[15]
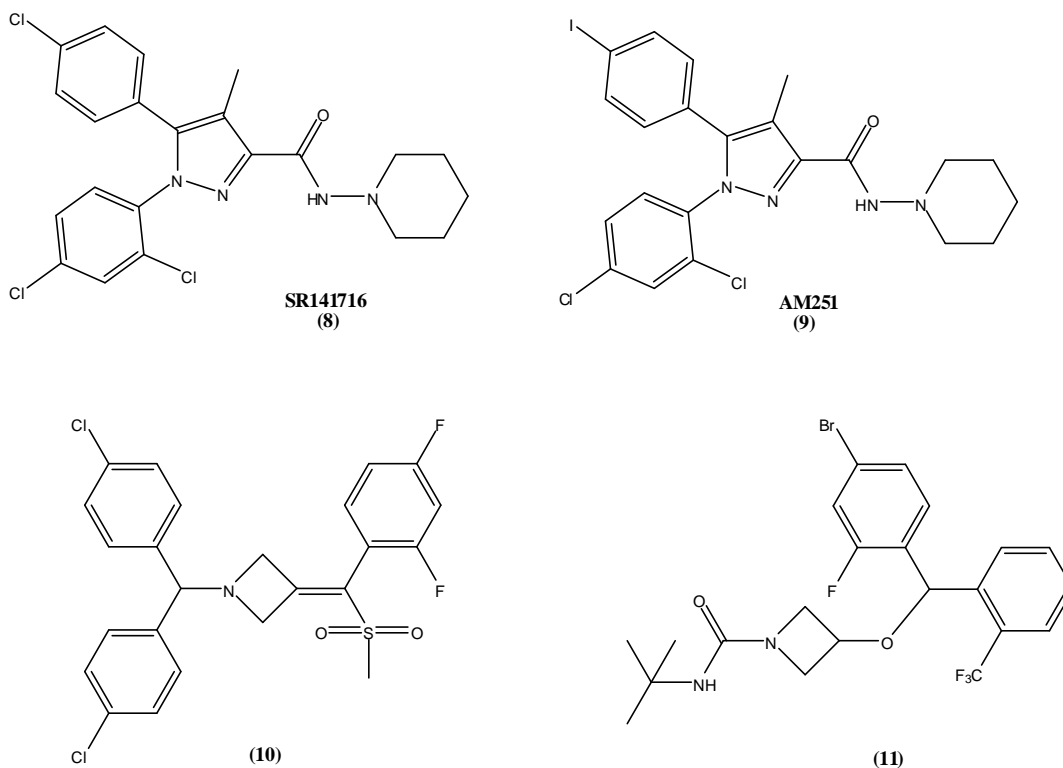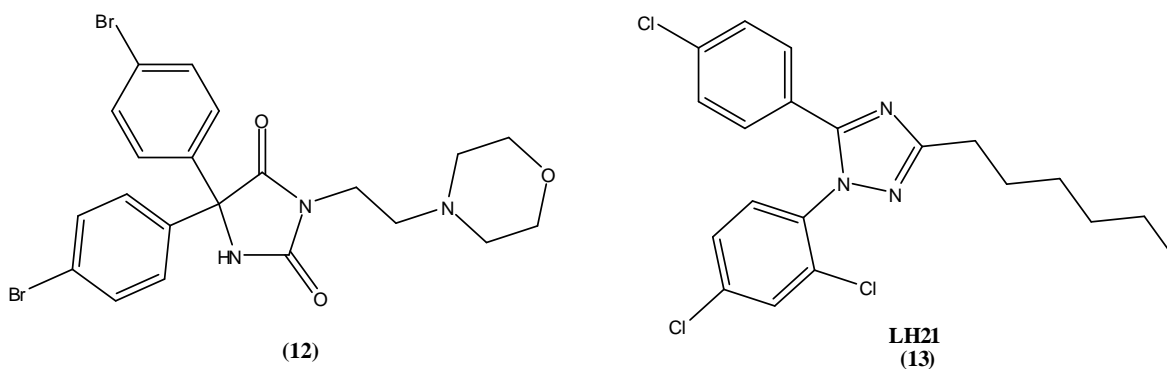

Figure 4. Examples of CB_1 Receptor Antagonists [3]

CB$_1$ receptor antagonists (Figure 4), such as SR-141716 [Rimonabant (**8**)], AM251 (**9**), and azetidine derivatives (**10,11**) bind to CB$_1$ receptors and block the effects of CB$_1$ agonists.[16] These compounds are potent and selectively inhibit the effects of some cannabinoid agonist, such as Δ^9-THC. CB$_1$ receptor antagonists block inhibition of adenlyl cyclase activity and block [^{35}S]GTPγS binding stimulation.[17,18] Rimonabant's profile also includes inverse agonist activity which is characterized by inhibition of [^{35}S]GTPγS binding and a decrease in K+ ion currents. [17,18] Clinical trials with Rimonabant (**8**) showed increased anxiety and depression in patients, which led to an increased incidence of suicide.[5] Due to the negative effects of this drug, CB$_1$ antagonists that have inverse agonist properties, may not be ideal medicinal targets.

In lieu of the results with Rimonabant, it has been suggested that a neutral cannabinoid receptor antagonists (Figure 5) would be a better target because of potentially reduced side effects.[19,20] However, to date neutral antagonists, such as arylimidazolidinone (**12**) and triazole LH21 (**13**), are less common and typically exhibit low potency at CB receptors.[21] To this end, it was the goal of this research

Figure 5. Examples of CB$_1$ Receptor Neutral Antagonists [20,21]

to design, synthesize and develop potential CB$_1$ receptors that exhibit a neutral cannabinoid antagonists pharmacological profile. The availability of a high affinity, potent, neutral CB$_1$ antagonist would undoubtedly prove to be a useful pharmacological tool to study a variety of cannabinoid mediated mechanisms and disease states.

Results and Discussion

Development of Azetidine-Based Cannabinoid Antagonists: Design Rationale

The patent literature has reported that *N*-benzhydryl azetidines exhibit CB$_1$ antagonist activity. [22] However, synthetic routes and biological data supporting these claims are not well documented. The known cannabinoid antagonist azetidine derivative **10** was identified as a lead compound to serve as a guide for the development of potential targets.
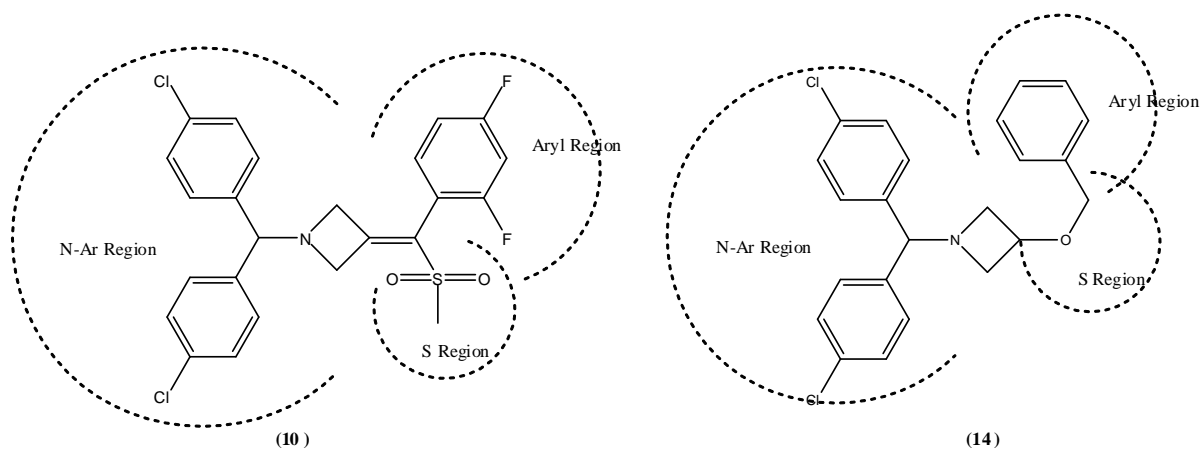
Figure 6. Pharmacophore Regions of *N*-Benzhydrylazetidine [3]

There is no reported structural-activity data for the series of azetidines represented by **10**. Therefore it was of interest to explore pharmacophore of **10** and develop novel compounds that exhibit high affinity and potency at cannabinoid receptors. The pharmacophore of **10** is composed of three major regions: the *N*-benzhydryl region (**N-Ar region**), the aryl substitute region (**Aryl region**) and the sulfonyl group region (**S region**). The focus of this research was to prepare a library of novel compounds based upon pharmacophore of **10**. To this end, a series of *N*-benzhydryl-3-benzyloxyazetidine derivatives were envisaged. The proposed syntheses of these series are shown below in **Scheme 1**.
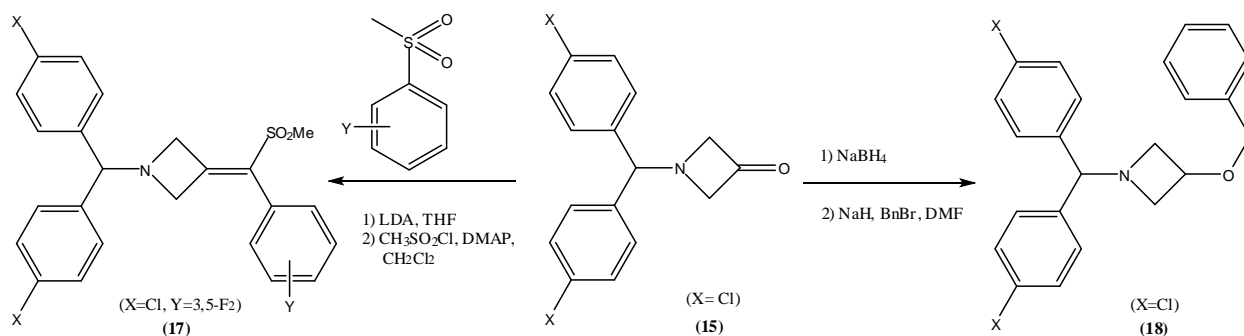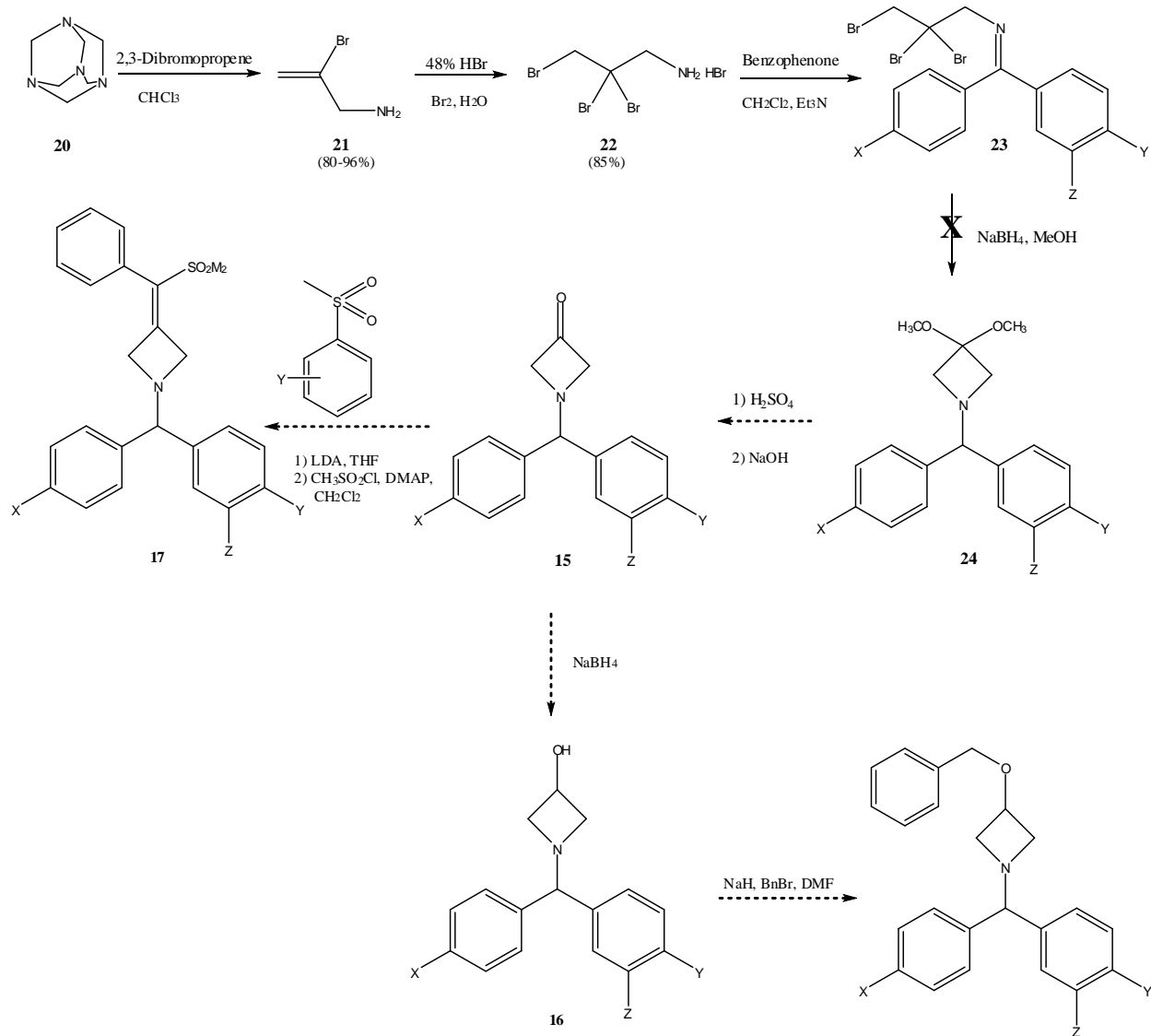
Scheme 1. Proposed Synthesis of **18** [22]

The bioisosteric analogues **18**, were envisaged to establish the role of the sulfonyl region for molecular-receptor recognition (H-bonding) and molecular lipophilicity. These new compounds will be used to determine optimal structural features and substitution patterns for the **N-Ar region** and **S region** of the azetidine targets.

Synthesis of Azetidines

Initially the N-4,4'-disubstitutedbenzhydryl azetidinones (**15**) were envisioned to be made using the sequence shown in Scheme 2 based upon previous work in our laboratories.[22-24] Hexamethylenetetramine (**20**) was treated with 2,3-dibromopropene and 2-bromopropeneamine (**21**) was isolated in good yields (80-96%). The bromopropeneamine was then brominated and 2,2,3-tribromopropyl amine HBr (**22**) was isolated (85% yield). The tribromoamine was reacted with a series of 4,4'-disubstituted benzophenone derivatives and imines **23 a-e** were isolated in good yields (**Table 1**).

Scheme 2. Proposed Synthesis of *N*-4,4'-Disubstituted Benzhydryl Azetidines [22-24]

Table 1. Tribromopropylimine Derivatives

23
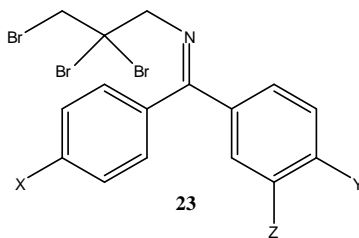
| entry	X	Y	Z	Yield %
23a	H	H	H	99
23b	Cl	Cl	H	70
23c	F	F	H	71
23d	Me	Me	H	72
23e	OMe	OMe	H	76

The imines **23** were treated with sodium borohydride and methanol to form the corresponding azetidines **24**. However, despite numerous attempted reaction conditions the azetidine ring wasn't formed. Presumably, the increased steric bulk of the benzhydryl moiety prevents the cyclization from occurring.
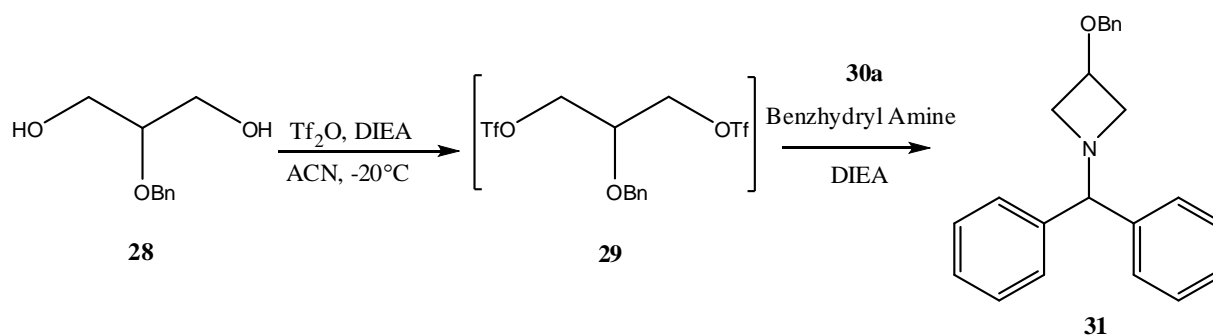
Table 2. *N*-Benzhydryl Azetidines
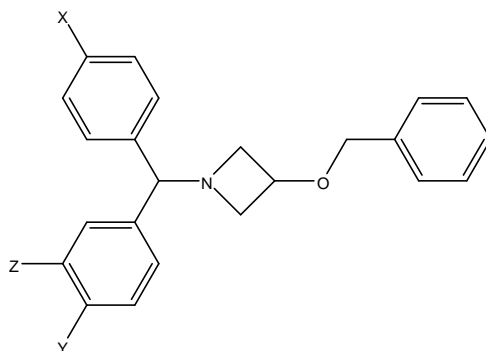
entry	X	Y	Z	Yield %
32a	H	H	H	75
32b	Cl	Cl	H	67
32c	F	F	H	60
32d	Me	Me	H	70
32e	OMe	OMe	H	65
32f	Cl	OMe	H	62
32g	F	OMe	H	69
32h	Cl	Cl	Cl	65

To prepare **18**, a different pathway to the N-benzhydryl azetidine reported by Hillier was investigated.[25] The azetidine ring system was synthesized from 1,3-disubstituted azetidines through the alkylation of primary amines with the bis-triflate of a 2-substituted-1,3-propanediol derivative (**Scheme 3**).[25] One of the reactions involved 2-oxybenzyl-1,3-propanediol (**28**) reacting with benzhydryl amine (**30a**) to form azetidine (**31**) in high yield (92%).[25] This reaction was

repeated (**Scheme 4**) and the target compound (**31**) was isolated in good yield (75%).
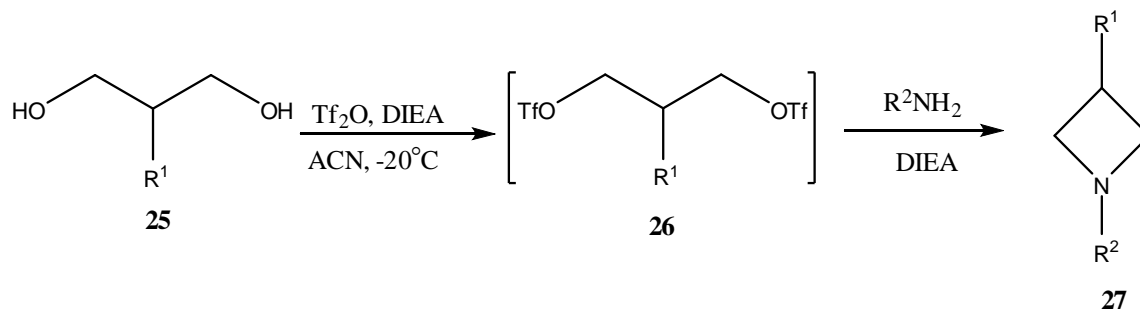
**Scheme 3.** Proposed Synthesis of 1,3-Disubstiuted Azetidines **(18)** [25]

**Scheme 4.** Synthesis of Benzhydryl Azetidines **(31)** [25]

Due to the efficiency of this reaction, the route illustrated in **Scheme 4** was used to make the azetidine derivatives **32** (Table 2) from different amine bases (**30b-h**). Benzhydryl amine **30a** is commercially available, but the other amine starting materials had to be synthesized from the various 4,4'-disubstituted benzophenone derivatives. Therefore, in order to pursue a structure activity study in this system, a convenient method for the preparation of the desired benzhydrylamines was investigated.

Synthesis of Benzhydryl Amine Derivatives

The first method involved forming an imine **34b-e** by treating 4,4'-disubstituted benzophenone derivatives with ammonia, followed by reduction to the corresponding amine. Unfortunately, the desired benzhydryl amines were not isolated in good yields using this approach (**Scheme 5**), so an alternative method was explored involving the conversion of an oxime into an amine (**Scheme 6**).
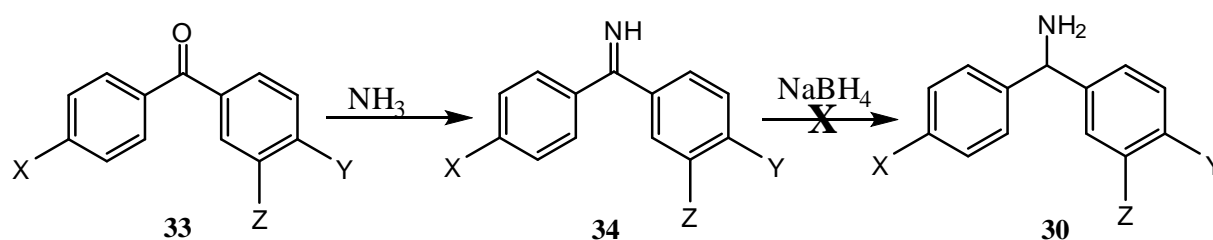
Scheme 5. Attempted Synthesis of Disubstituted N-Benzhydryl Amines through an Imine Intermediate (**34**)[26]
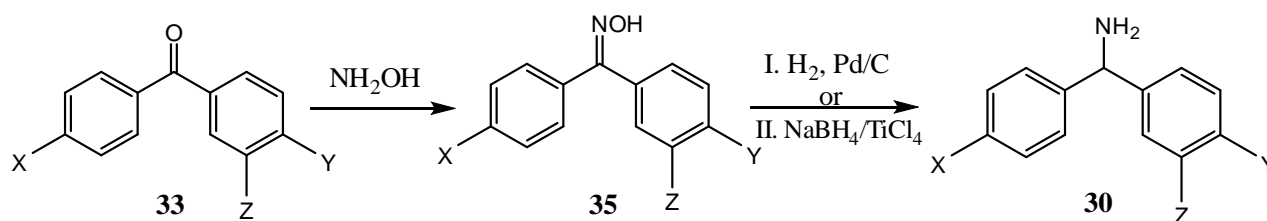
Scheme 6. Synthesis of Disubstituted N-Benzhydryl Amines through an Oxime Intermediate (**35**)[27]

The disubstituted benzophenone derivatives **33b-e** were treated with hydroxylamine·HCl and crystallized to afford the corresponding oximes **35b-e** in

good yields (60-90%). This reaction worked well and once crystallized the oximes were reduced by catalytic hydrogenation or with $NaBH_4$ and $TiCl_4$, to furnish the benzhydryl amines **30b-e** in good yields (63-86%).

Table 3. Benzhydryl Oxime and Amine Derivatives

| Entry	X	Y	Z	Oxime (35) % Yield	Amine (30) % Yield
a	H	H	H	-	-
b	Cl	Cl	H	87	73
c	F	F	H	79	66
d	Me	Me	H	80	78
e	OMe	OMe	H	90	86
f	Cl	OMe	H	60	68
g	F	OMe	H	75	63
h	Cl	Cl	Cl	66	70

The 4,4'-disubstituted benzophenone derivatives **33f-h** were not commercially available, so the target amines required synthesis via alternative routes. The first approach was to use a Grignard method (**Scheme 7**). [26] This method involved reacting the corresponding Grignard reagent and a nitrile to form an imine followed by concomitant $NaBH_4$ reduction to yield the desired amine **38**.
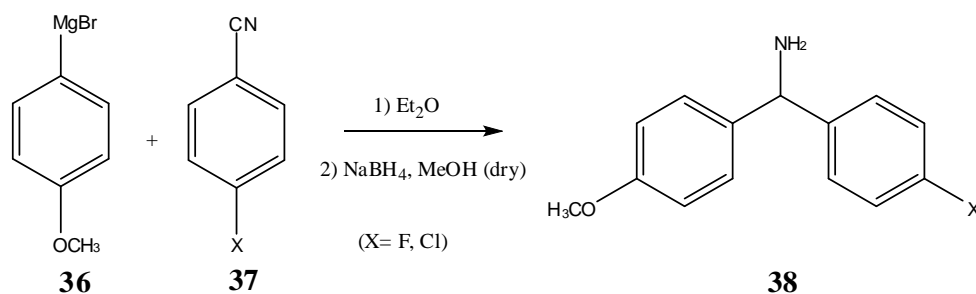
Scheme 7. Attempted Synthesis of Disubstituted Benzhydryl Amine **(38)** [26]

The Grignard reagent, 4-methoxyphenylmagnesium bromide (**36**) was reacted with 4-chlorobenzonitrile (**37**) in ether, then methanol was added to form the imine (**34**), followed by reduction with NaBH$_4$. Unfortunately the desired amine was not isolated. This method was repeated using 4-fluorobenzonitrile with similar poor results.

Using an alternative approach, the syntheses of **33f**, **33g** and **33h** was achieved by reacting a Grignard reagent with the corresponding aldehyde (**Scheme 8**) to form the desired benzhydryl alcohol derivatives (**40f-h**), which could then be oxidized to the benzophenone derivatives (**33f-g**). These derivatives could then be converted into the corresponding oximes (**35)** and benzhydrylamines (**30**) using the approach successfully employed previously (**Scheme 6**).
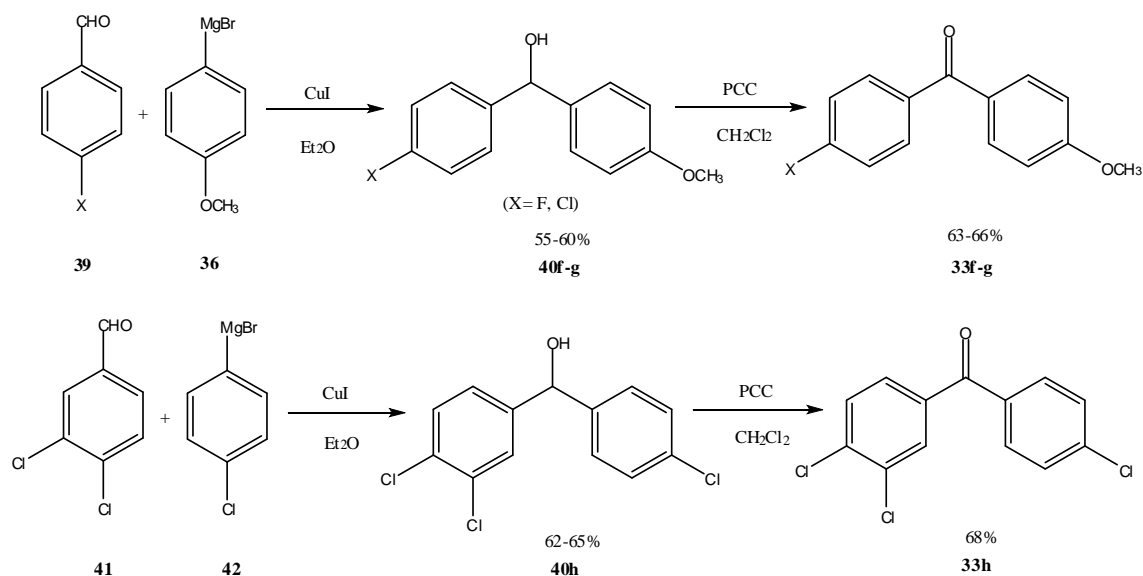
Scheme 8. Synthesis of Disubstituted and Trisubstituted Benzophenone Derivatives[28, 29]

The benzophenones **33f-h** were treated with hydroxyl amine and converted into an oxime followed by treatment with $NaBH_4$ and $TiCl_4$ resulting in benzhydryl amines **30f-h** (Table 3). With the substituted benzhydrylamines in hand, the azetidine derivatives **32f-h** were prepared using the bis-triflate method described previously (Table 2). As illustrated in **Scheme 4**, the substituted benzhydryl azetidines were synthesized in good yield from 2-oxybenzyl-1,3- propanediol.

Synthesis of 2-Benzyloxy Glycerol Derivatives

With the benzhydrylamine derivatives in hand, it was also of interest to develop an approach for the preparation of new 2-substituted-1,3-propanediol derivatives **50.**

(A= Me, OMe, Cl, F)
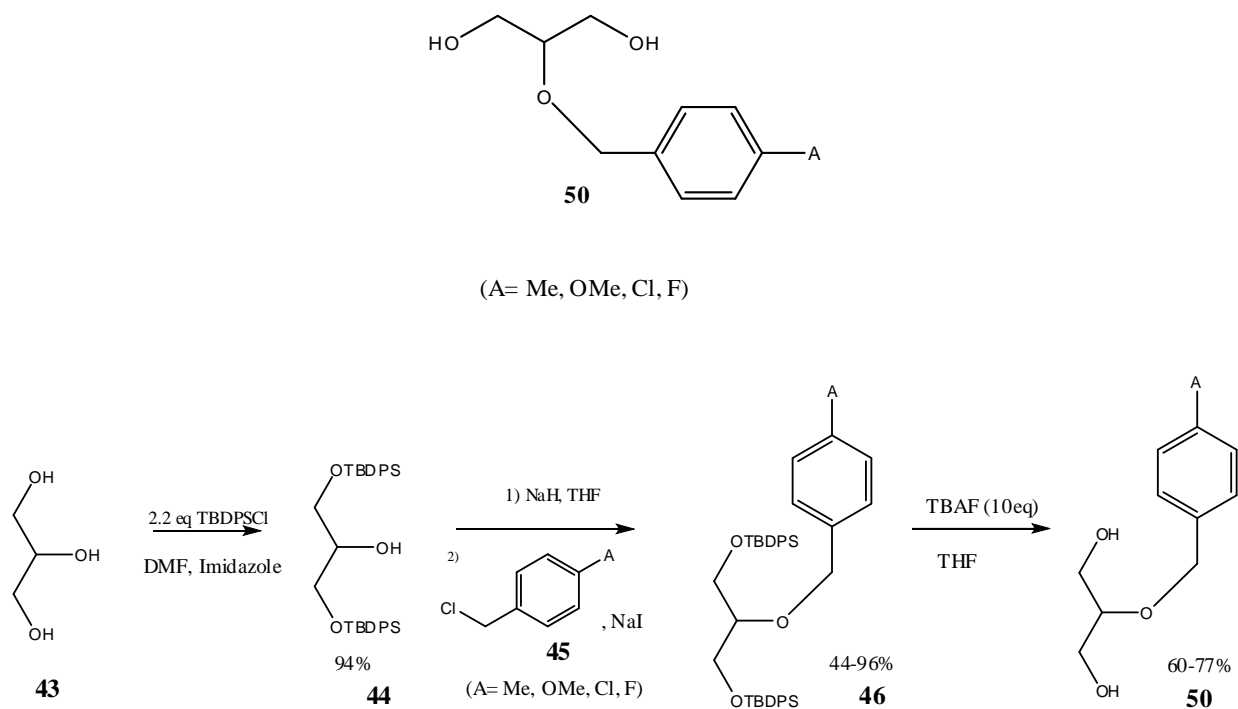
Scheme 9. Proposed Synthesis of 2-Substituted-1,3-Propanediol Derivatives (**50**)[30-32]

Glycerol (**43**) was used as the starting material to make the diol analogs and tert-Butyldiphenylsilyl chloride (TBDPSCl) was used to selectively protect the two primary alcohols of **43**. [30] Once the primary alcohols were protected, the 4-substituted benzyl group **45** was added to the secondary alcohol followed by treatment of tetrabutyl ammonium fluoride (TBAF) to remove the protecting groups.[31,32] This afforded the corresponding 2-benzyl glycerols **50** in good overall yield (Table 4).

Table 4. 2-Benzyloxy Glycerol Derivatives
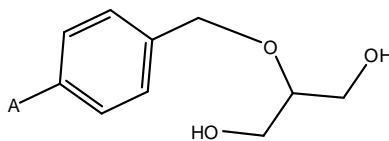
50

Entry	A	Yield %
50a	Me	70
50b	OMe	77
50c	Cl	60
50d	F	66

This method was successful on a small scale, but further attempts to scale-up the reaction were problematic due to the formation of a by-product at the deprotection stage. Numerous attempts were made to purify the diol intermediates but separation proved to be difficult. Various columns were run on each of the crudes, including: 3-25% hexane/ethyl acetate; 100% hexane; 33% ethyl ether/petroleum ether; 100% ethyl ether; 5-10% methanol/chloroform and 100% methanol. Unfortunately, none of these chromatographic conditions afforded the glycerol derivatives in sufficient purity to be synthetically useful.

Alternative methods were used in an attempt to remove the tert-butyldiphenylsilyl group (Scheme 10). One method involved each of the protected diols being

dissolved in methanol and treated with varying concentrations (10-100%) of HCl at room temperature.[33] Numerous columns were run on the crudes and a by-product was still present. Another method involved each of the protected diols being dissolved in dry methanol and treated with a catalytic amount of acetyl chloride (AcCl) at room temperature.[34] 10% ethyl acetate/hexane was used to remove the byproduct and 5% methanol/chloroform was used to isolate the product in small yields.
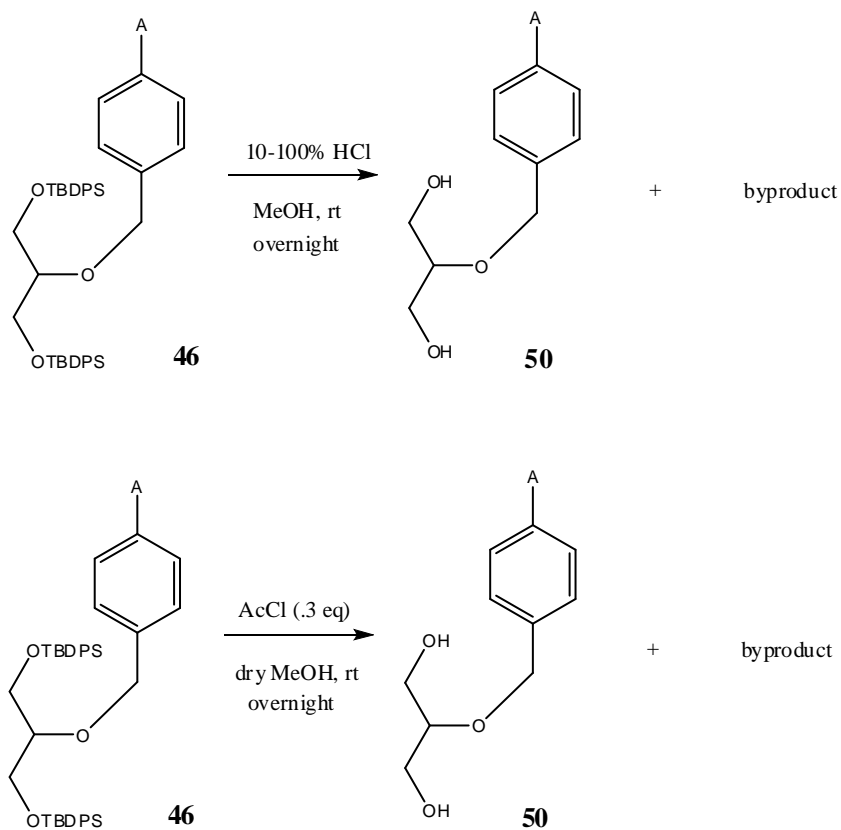
Scheme 10 : Synthesis of 2-Substituted-1,3-Propanediol Derivatives (**50**)[33,34]

A better method of producing the substituted 2-benzyoxy-1,3-propane diols was employed using a 1,3-dioxane derivative.[35] This could be done on a larger scale and involved only two steps. However, 2-phenyl-1,3-dioxan-5-ol (**47**) was slightly more expensive than *tert*-butyldimethylsilyl chloride.
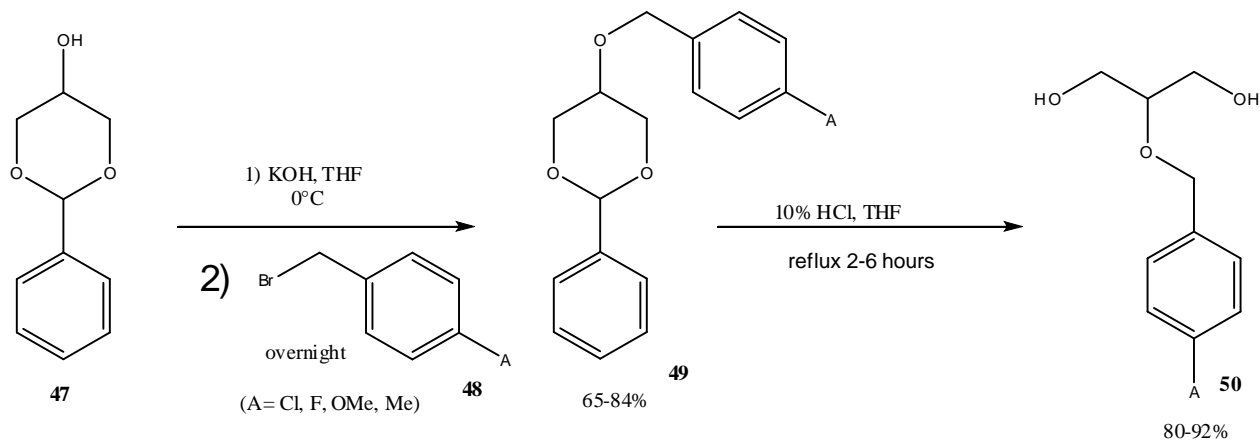
Scheme 11 . Synthesis of Substituted 2-Benzyloxy-1,3-Propane Diols (**50**)[35]
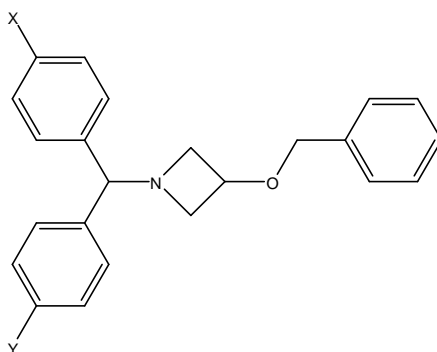
The reaction involved reacting 2-phenyl-1,3-dioxan-5-ol (**47**) with potassium hydroxide and substituted benzyl bromides (**48**).[35] The corresponding substituted 5-benzyloxy-2-phenyl-[1,3]dioxanes (**49**) were hydrolyzed to the diols (**50**) in good yields (80-92%).

Cannabinoid Receptor Affinity

The binding affinities of the azetidines derivatives (Table 5) were determined by the inhibition of [³H]SR141716 binding in homogenates of rat cerebellum

(Breivogel *et al*., 1997). For each compound, each concentration was tested in triplicate and each experiment was replicated three times.

Table 5. Cannabinoid Receptor Affinity

Compound[a]	X	Y	% inhibition @10 μM	% inhibition @100 μM
32a	H	H	11	43
32b	Cl	Cl	38	77
32c	F	F	12	36
32e	OCH$_3$	OCH$_3$	0	18

[a]All compounds were tested as the oxalate salt.

In general, *N*-benzhydryl-3-benzyloxyazetidines exhibited low affinities (IC$_{50}$ values would be > 10 μM). The dichloro analogue **32b** was the most potent compound of the series and exhibited 77% inhibition of [^{3}H]SR141716 at 100 μM. However, at a lower concentration of 10 μM, only 38% inhibition of [^{3}H]SR141716 was observed. Both the unsubstituted analog **32a** and the difluoro analog **32c** exhibited affinities less than **32b**, while the dimethoxy analog **32e** was nearly inactive.

Conclusion

A series of *N*-benzhydryl-3-benzyloxyazetidines were synthesized from commercially available 2-benzyloxy glycerol and a series of substituted benzhydryl amines. The *N*-benzhydryl-3-benzyloxyazetidines were obtained in good overall yields. In general, the *N*-benzhydryl-3-benzyloxyazetidines exhibited modest to low affinity for cannabinoid receptors. However, it appears that modification of the benzhydryl group can lead to improved receptor affinity. In addition, a series of substituted benzyloxy derivatives were prepared from 2-phenyl-1,3-dioxan-5-ol. The availability of novel substituted 2-benzyloxy glycerol will be useful for future structure-activity studies with the *N*-benzhydryl-3-benzyloxyazetidine derivatives.

Experimental Section

All the chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous THF was purchased from Mallindkrodt Baker. Anhydrous solvents toluene, dimethylformamide and acetonitrile were purchased from VWR International Co. and were used under argon without further purification. Chromatography refers to column chromatography on silica gel (Silica Gel 60, 230-400 mesh). Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 400 MHz spectrometer. Chemical

shifts are reported in δ values with tetramethylsilane (TMS), employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.
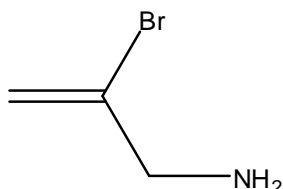

2-Bromopropeneamine (21).

In a three-neck flask, hexamethylenetetramine (63 g, 0.45 mol, 1.1 eq) was dissolved in $CHCl_3$ (600 mL). The solution was allowed to reflux and 2,3-dibromopropene (100 g, 0.50 mol, 1.0 eq) was added drop-wise over an hour. The reaction mixture was heated to reflux for 3 hours and allowed to stand overnight. The solution was cooled in ice bath, salt was collected by vacuum filtration and the yellow crude 2-bromoallylhexanimium was placed in a 4L beaker to air dry overnight. The 2-bromo-allyl hexaminium bromide (150 g, 0.58 mol) was collected and added to a warm solution of EtOH (2L), H_2O (400 mL) and 12 N HCl (480 mL). The mixture was stirred until all the solids had dissolved and let stand for 24 hours. The precipitate was collected using vacuum filtration and the liquid was evaporated to dryness. The residue was dissolved in H_2O (300 mL) and the pH was adjusted to pH = 10 with 6 N NaOH. The red-brown oil was separated

in a seperatory funnel and the aqueous layer was extracted with ethyl ether (3 x 100 mL). The combined oil and ether extracts were washed with saturated NaCl (50 mL) and dried over potassium carbonate. The solution was filtered and concentrated under reduced pressure to afford 2-bromopropeneamine (26 g, 83%). Mp 183-186 °C [lit. mp 184-186 °C].[23] ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.78 (s, 1H), 5.48 (s, 1H), 3.48 (s, 2H), 1.60 (s, 2H).[23]
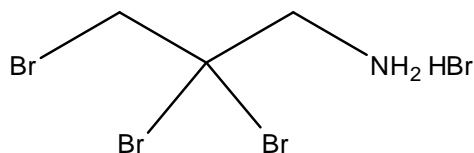

2,2,3-Tribromopropyl amine HBr (22).

2-Bromoallylamine (22.1 g, 0.163 mol, 1 eq) was dissolved in H$_2$O and 48% HBr (25 mL, 0.179 mol, 1.1 eq) was added slowly, followed by bromine (13 mL, 0.243 mol, 1.5 eq). This mixture was allowed to stir overnight and was then concentrated under reduced pressure. The solution was treated with solid sodium thiosulfate until colorless. Solid formed and 2,2,3-tribromopropyl amine HBr was confirmed by NMR (52 g, 85%). Mp 196-198 °C [lit. mp 196-198 °C]. [24] ^{1}H NMR (400 MHz, D$_2$O) δ 4.35 (s, 2H), 3.82 (s, 2H), 2.0 (s, 3H).[24]
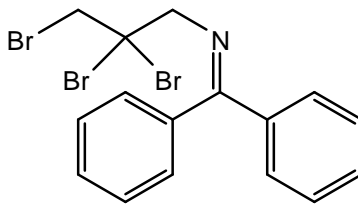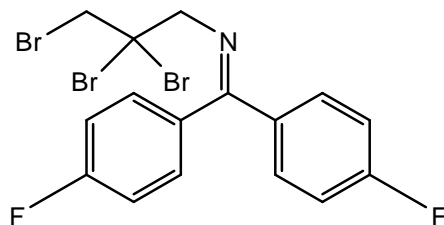
General Method A. 2,2,3-Tribromo-*N*-(diphenylmethylene)propan-1-amine (23a).

Tribromopropyl amine HBr (1.17 g, 3.11 mmol, 1 eq), CH_2Cl_2 (20 mL), Et_3N (5 mL) and benzophenone (0.57 g, 3.13 mmol, 1 eq) were added to a 100 mL round bottom flask. The mixture was stirred for an hour, then H_2O (2 mL) was added and the mixture was stirred for an additional hour. The solution was extracted with CH_2Cl_2 (2 x 10 mL), dried over magnesium sulfate and concentrated using low heat under reduced pressure. A yellowish-white solid formed and 2,2,3-tribromo-*N*-(diphenylmethylene)propan-1-amine was confirmed by NMR (1.4 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8 Hz, 2H), 7.58 (t, J = 8 Hz, 3H), 7.48-7.44 (m, 5H), 4.22 (s, 2H), 3.39 (s, 2H).[24]
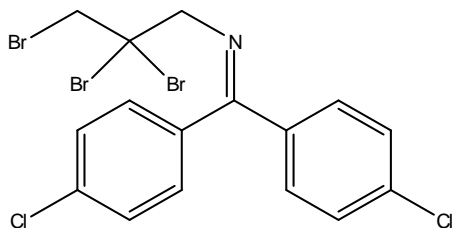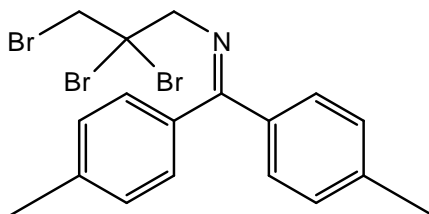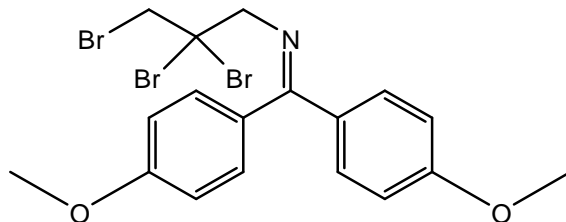

***N*-(Bis(4-chlorophenyl)methylene)-2,2,3-tribromopropan-1-amine (23b).**

Synthesized using General Method A and 4,4'-dichlorobenzophenone to yield a light orange solid (2.0 g, 70%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, J = 4 Hz, 4H), 7.63 (d, J = 4 Hz, 4H), 4.41 (s, 2H) 3.27 (s, 2H).

N-(Bis(4-fluorophenyl)methylene)-2,2,3-tribromopropan-1-amine (23c).

Synthesized using General Method A and 4,4'-difluorobenzophenone to yield a yellowish solid (0.99 g, 71%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82-7.78 (m, 4H), 7.40-7.30 (m, 4H), 4.41 (s, 2H), 3.29 (s, 2H).


N-(Bis(4-methylphenyl)methylene)-2,2,3-tribromopropan-1-amine (23d).

Synthesized using General Method A and 4,4'-dimethylbenzophenone to yield a yellowish solid (2.1 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J = 4 Hz, 4H), 7.30 (d, J = 4 Hz, 4H), 4.29 (s, 2H), 3.40 (s, 2H), 2.41 (s, 6H).

**N-(Bis(4-methoxyphenyl)methylene)-2,2,3-tribromopropan-1-amine (23e).**

Synthesized using General Method A and 4,4'-dimethoxybenzophenone to yield a yellowish solid (2.0 g, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 4 Hz, 4H), 7.05 (d, J = 4 Hz, 4H), 4.41 (s, 2H), 3.82 (s, 6H), 3.27 (s, 2H).
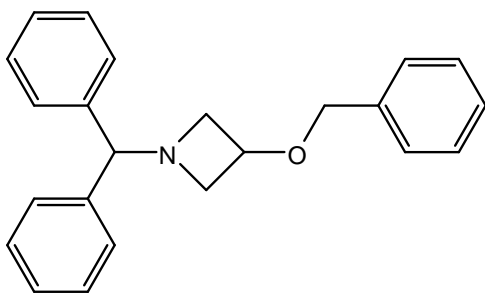
General Method B. Benzhydryl-3-(benzyloxy)azetidine (32a).

Under nitrogen, 2-oxybenzyl-1,3-propanediol (0.20 g, 1.05 mmol, 1.05 eq) was added to dry acetonitrile (10 mL) at 20 ℃. Tf$_2$O (0.39 mL, 2.30 mmol, 2.2 eq) was added slowly over 10-20 minutes, maintaining temperature below 10 ℃.   DIEA (0.47 mL, 2.71 mmol, 2.6 eq) was added over 10-20 minutes maintaining temperature below 10 ℃. The mixture was allowed to stir for 10 minutes and DIEA (0.47 mL, 2.71 mmol, 2.6 eq) was added to the mixture over 5 minutes. Benzhydrylamine (0.18 mL, 1.10 mmol, 1.1 eq) was added over 5 minutes and the

reaction was heated to 70 °C for 1-2 hours. The reaction was allowed to cool and the crude solid was purified via column chromatography (SiO_2) with 10% ethyl acetate/90% hexane column. Benzhydryl-3-(benzyloxy)azetidine was confirmed by NMR (0.26 g, 75%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 4H), 7.39-7.30 (m, 9H), 7.27-7.17 (m, 2H), 4.46 (s, 2H), 4.43 (s, 1H), 4.32-4.27 (m, 1H), 3.57 (dd, J = 6.1, 8.7 Hz, 1H), 3.57 (dd, J = 4.1, 6.7 Hz, 1H), 3.02 (dd, J = 6.1, 8.7 Hz, 1H), 3.02 (dd, J = 4.1, 6.7 Hz, 1H).[25] Anal. ($C_{23}H_{23}NO·C_2H_2O_4·½$ H_2O): C, 71.58; H, 6.01; N, 3.34. Found: C, 71.08; H, 5.97; N, 3.35.
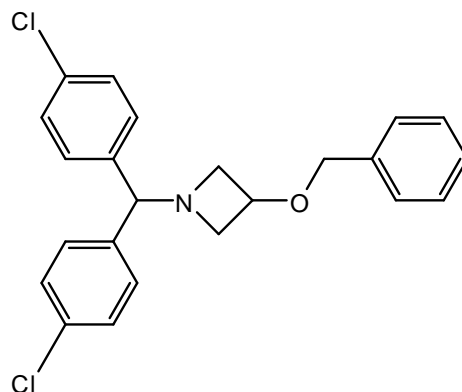
3-(Benzyloxy)-1-(bis(4-chlorophenyl)methyl)azetidine (32b).

Synthesized using General Method B and Bis(4-chlorophenyl)methyl amine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.42 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.37 (m, 8H), 7.38-7.30 (m, 5H), 4.49 (s, 2H), 4.41 (s, 1H), 4.32-4.27 (m, 1H), 3.58 (dd, J=6.1, 8.7 Hz, 1H), 3.58 (dd, J=4.1, 6.7 Hz, 1H), 3.02 (dd, J=6.1, 8.7 Hz, 1H), 3.02

(dd, *J*=4.1, 6.7 Hz, 1H). Anal. (C$_{23}$H$_{21}$Cl$_2$NO·C$_2$H$_2$O$_4$·½ H$_2$O): C, 61.48; H, 4.75; N, 2.87. Found: C, 62.14; H, 5.12; N, 2.79.
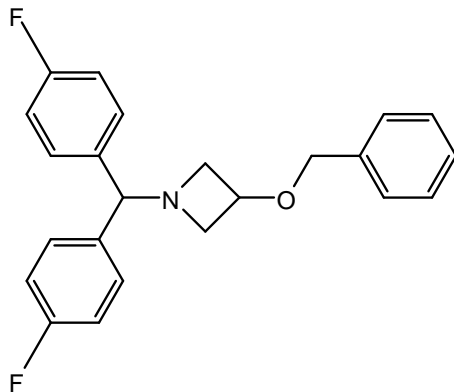
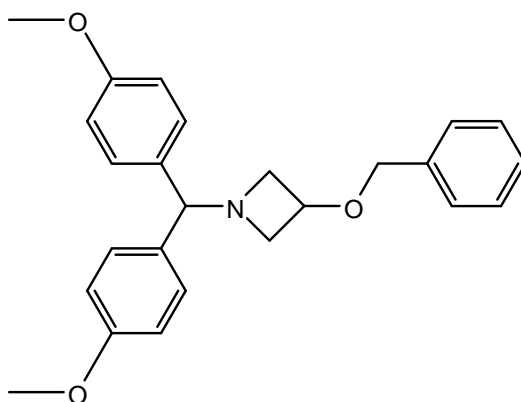**3-(Benzyloxy)-1-(bis(4-fluorophenyl)methyl)azetidine (32c).**

Synthesized using General Method B and Bis(4-fluorophenyl)methyl amine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.34 g, 60%). ^{1}H NMR (400 MHz, CDCl3) δ 7.50-7.30 (m, 4H), 7.22-7.13 (m, 6H), 7.10-6.95 (m, 3H), 4.44 (s, 2H), 4.43 (s, 1H), 4.32-4.25 (m, 1H), 3.58 (dd, *J*=6.1, 8.7 Hz, 1H), 3.58 (dd, *J*=4.1, 6.7 Hz, 1H), 3.02 (dd, *J*=6.1, 8.7 Hz, 1H), 3.02 (dd, *J*=4.1, 6.7 Hz, 1H). Anal. (C$_{23}$H$_{23}$F$_2$NO·C$_2$H$_2$O$_4$·½ H$_2$O): C, 64.07; H, 5.22; N, 2.99. Found: C, 64.49; H, 5.14; N, 2.88.
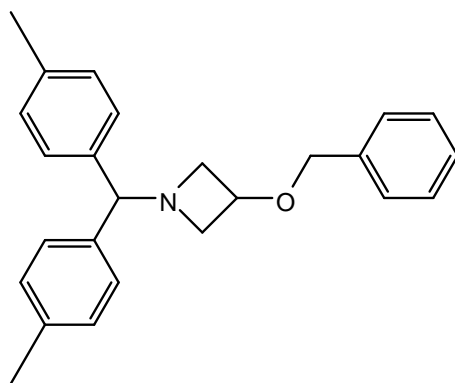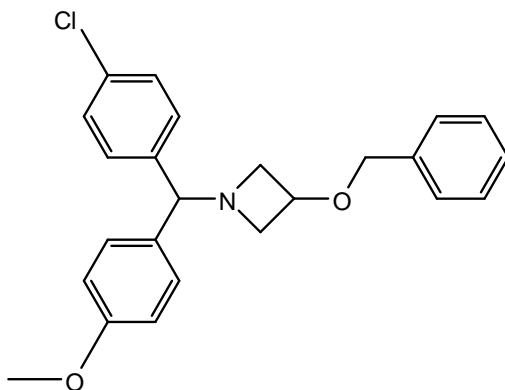
3-(Benzyloxy)-1-(bis(4-methylphenyl)methyl)azetidine (32d).

Synthesized using General Method B and Bis(4-methylphenyl)methyl amine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.39 g, 70%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48-7.40 (m, 4H), 7.36-7.28 (m, 6H), 7.26-7.21 (m, 3H), 4.41 (s, 2H), 4.39 (s, 1H), 4.27-4.21 (m, 1H), 3.52 (dd, J=6.1, 8.7 Hz, 1H), 3.52 (dd, J=4.1, 6.7 Hz, 1H), 2.98 (dd, J=6.1, 8.7 Hz, 1H), 2.98 (dd, J=4.1, 6.7 Hz, 1H), 2.37 (s, 6H).
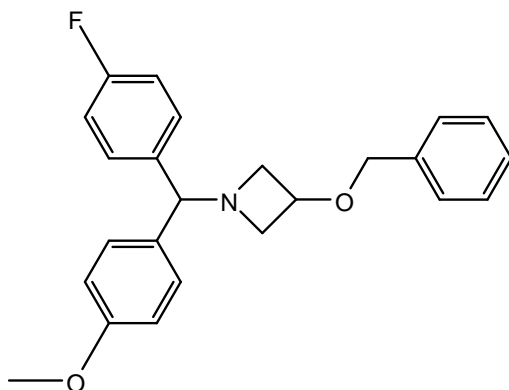

3-(Benzyloxy)-1-(bis(4-methoxyphenyl)methyl)azetidine (32e).

Synthesized using General Method B and Bis(4-methoxyphenyl)methyl amine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.40 g, 65%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41-7.29 (m, 8H), 6.90-6.80 (m, 5H), 4.41 (s, 2H), 4.37 (s, 1H), 4.31-4.24 (m, 1H), 3.77 (s, 6H), 3.59 (dd, J=6.1, 8.7 Hz, 1H), 3.59 (dd, J=4.1, 6.7 Hz, 1H), 3.02 (dd, J=6.1, 8.7 Hz, 1H), 3.02 (dd, J=4.1, 6.7 Hz, 1H). Anal. (C$_{23}$H$_{23}$NO·C$_2$H$_2$O$_4$·½ H$_2$O): C, 67.63; H, 6.10; N, 2.92. Found: C, 67.71; H, 6.10; N, 2.92.
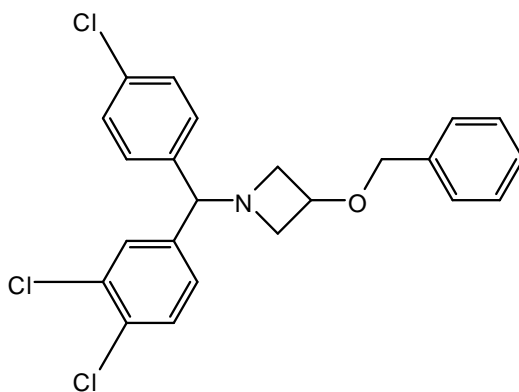

3-(Benzyloxy)-1-((4-chlorophenyl)(4-methoxyphenyl)methyl)azetidine (32f).

Synthesized using General Method B and (4-chlorophenyl)(4-methoxyphenyl) methanamine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.15 g, 62%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36-7.21 (m, 11H), 6.82-6.78 (m, 2H), 4.40 (s, 2H), 4.29 (s, 1H), 4.24-4.18 (m, 1H), 3.73 (s, 3H), 3.50 (dd, J=6.1, 8.7 Hz, 1H), 3.50 (dd, J=4.1, 6.7 Hz, 1H), 2.93 (dd, J=6.1, 8.7 Hz, 1H), 2.93 (dd, J=4.1, 6.7 Hz, 1H).

3-(Benzyloxy)-1-((4-fluorophenyl)(4-methoxyphenyl)methyl)azetidine (32g).

Synthesized using General Method B and (4-fluorophenyl)(4-methoxyphenyl) methanamine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.27 g, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43-7.23 (m, 11H), 6.96-6.82 (m, 2H), 4.40 (s, 2H), 4.37 (s, 1H), 4.31-4.26 (m, 1H), 3.75 (s, 3H), 3.51 (dd, *J*=6.1, 8.7 Hz, 1H), 3.51 (dd, *J*=4.1, 6.7 Hz, 1H), 2.95 (dd, *J*=6.1, 8.7 Hz, 1H), 2.95 (dd, *J*=4.1, 6.7 Hz, 1H).


3-(Benzyloxy)-1-((4-chlorophenyl)(3,4-dichlorophenyl)methyl)azetidine (32h).

Synthesized using General Method B and (4-chlorophenyl)(3,4-dichlorophenyl) methanamine to yield a brown oil. The oxalate salt was obtained by dissolving the azetidine in acetone and oxalic acid (0.30 g, 65%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50-7.18 (m, 12H), 4.41 (s, 2H), 4.30 (s, 1H), 4.24-4.18 (m, 1H), 3.46 (dd, J=6.1, 8.7 Hz, 1H), 3.46 (dd, J=4.1, 6.7 Hz, 1H), 2.91 (dd, J=6.1, 8.7 Hz, 1H), 2.91 (dd, J=4.1, 6.7 Hz, 1H).
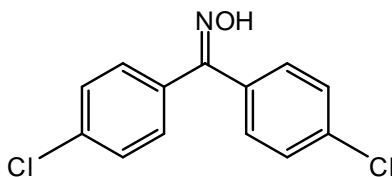
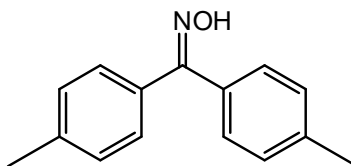**General Method C. Bis(4-chlorophenyl)methanone oxime (35b).**

A solution of Bis(4-chlorophenyl)methanone (4.00 g, 0.016 mol, 1 eq), NH$_2$OH·HCl (3.32 g, 0.048 mol, 3 eq) and Na$_2$CO$_3$ (5.07 g, 0.048 mol, 3 eq) in ethanol (70 mL) was stirred and heated to reflux for 6 hours. The solvent was concentrated under reduced pressure and the residue dissolved in an aqueous solution of potassium carbonate and filtered thru suction filtration. The resulting crystalline residue was dissolved in CH$_2$Cl$_2$, filtered and the solvent concentrated under reduced pressure. The crude was crystallized from hot methanol and bis(4-chlorophenyl)methanone oxime was confirmed by NMR (3.7 g, 87%). Mp 137 ºC [lit. mp 138 ºC].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.37 (d, J=8 Hz, 4H), 7.29 (d, J=8 Hz, 4H).[27]
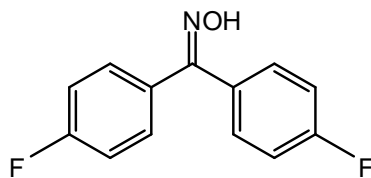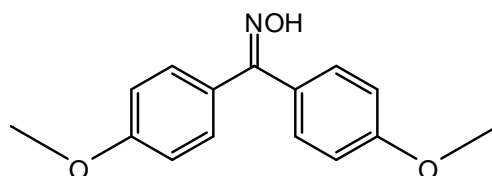
Bis(4-fluorophenyl)methanone oxime (35c).

Synthesized using General Method C from Bis(4-fluorophenyl)methanone and the oxime was crystallized using hot methanol (3.4 g, 79%). Mp 142 ℃ [lit. mp 142 ℃].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.43-7.10 (m, 8H).[27]
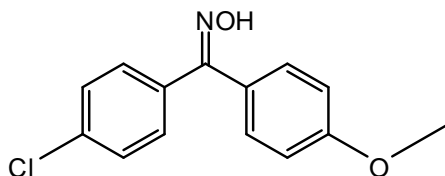

Bis(4-methylphenyl)methanone oxime (35d).

Synthesized using General Method C from Bis(4-methylphenyl)methanone and the oxime was crystallized using hot methanol (1.7 g, 80%). Mp 167 ℃ [lit. mp 168 ℃].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.27 (d, J = 8 Hz, 4H), 7.20 (d, J = 8 Hz, 4H), 2.38 (s, 6H).[27]
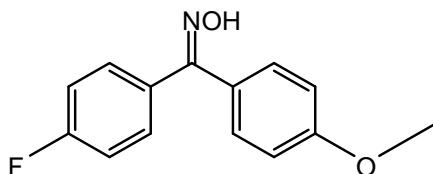

Bis(4-methoxyphenyl)methanone oxime (35e).

Synthesized using General Method C from Bis(4-methoxyphenyl)methanone and the oxime was crystallized using hot methanol (3.8 g, 90%). ^{1}H NMR (400 MHz, DMSO) δ 7.25 (d, J = 4 Hz, 4H), 6.80 (d, J = 4 Hz, 4H), 3.75 (s, 6H).

(4-Chlorophenyl)(4-methoxyphenyl) methanone oxime (35f).

Synthesized using General Method C from (4-chlorophenyl)(4-methoxyphenyl) methanone and the oxime was crystallized using hot methanol (0.24 g, 60%). ^{1}H NMR (400 MHz, DMSO) δ 7.42-7.21 (m, 4H), 7.00 (d, J = 4 Hz, 2H), 6.80 (d, J = 4Hz, 2H), 3.81 (s, 3H).
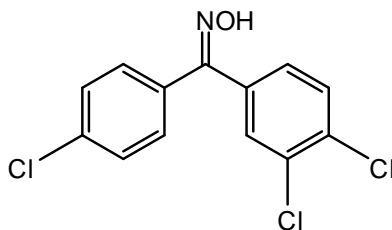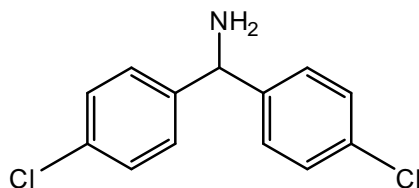

(4-Fluorophenyl)(4-methoxyphenyl) methanone oxime (35g).

Synthesized using General Method C from (4-fluorophenyl)(4-methoxyphenyl) methanone and the oxime was crystallized using hot methanol (0.32 g, 75%). ^{1}H NMR (400 MHz, DMSO) δ 7.40-7.33 (m, 4H), 6.93-6.89 (m, 4H), 3.83 (s, 3H).

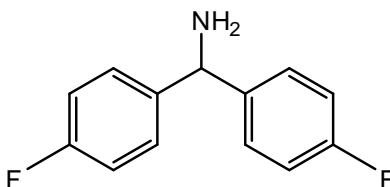**(4-Chlorophenyl)(3,4-dichlorophenyl) methanone oxime (35h).**

Synthesized using General Method C from (4-chlorophenyl)(3,4-dichlorophenyl) methanone and the oxime was crystallized using hot methanol (1.2 g, 66%). ^{1}H NMR (400 MHz, DMSO) δ 7.50-7.15 (m, 7H).

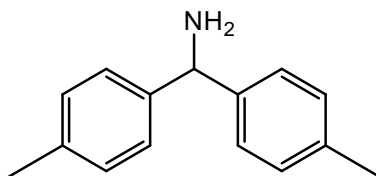

General Method D. Bis(4-chlorophenyl)methyl amine (30b).

General Method D. NaBH$_4$ (1.57 g, 0.042 mol, 4.1eq) was added to a solution of bis(4-chlorophenyl)methanone oxime (2.70 g, 0.010 mol, 1 eq) in 1,2 dimethoxyethane (10 mL) and TiCl$_4$ (4.04 g, 0.021 mol, 2.1 eq) was added slowly under nitrogen atmosphere at 0 °C. The solution was warmed to room temperature and stirred for 24 hours. Cold water (100 mL) was added and the solution was adjusted to pH = 10 with ammonia. The solution was then extracted with ethyl acetate and the organic layer was washed with saturated NaCl solution, dried over sodium sulfate and concentrated under reduced pressure. Bis(4-

chlorophenyl)methyl amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (1.8 g, 73%). [lit. mp 262 ºC].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.39 (d, *J*=8 Hz, 4H), 7.31 (d, *J*=8 Hz, 4H), 5.10 (s, 1H).[27]

Bis(4-fluorophenyl)methyl amine (30c).

Synthesized from General Method D using Bis(4-fluorophenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (2.0 g, 66%). [lit. mp 250 ºC].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.48-7.03 (m, 8H), 5.20 (s, 1H).[27]

Bis(4-methylphenyl)methyl amine (30d).

Synthesized from General Method D using Bis(4-methylphenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (1.1 g, 78%). [lit. mp 246 ºC].[27] ^{1}H NMR (400 MHz, DMSO) δ 7.28 (d, *J*=8.0 Hz, 4H), 7.18 (d, *J*=8.0 Hz, 4H), 5.20 (s, 1H), 2.38 (s, 6H).[27]
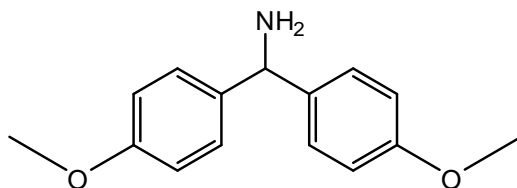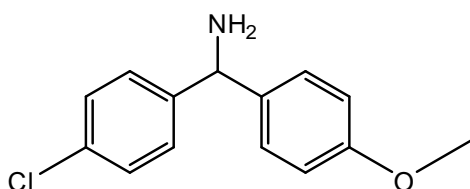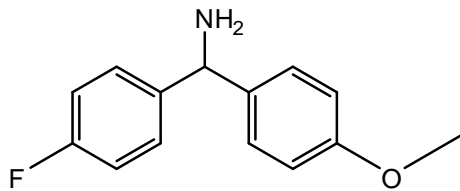
Bis(4-methoxyphenyl)methyl amine (30e).

Synthesized from General Method D using Bis(4-chlorophenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (2.1 g, 86%). ^{1}H NMR (400 MHz, DMSO) δ 7.28 (d, J = 4 Hz, 4H), 6.81 (d, J = 4Hz, 4H), 5.01 (s, 1H). 3.71 (s, 6H).

(4-Chlorophenyl)(4-methoxyphenyl)methanamine (30f).

Synthesized from General Method D using (4-chlorophenyl)(4-methoxyphenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (0.16 g, 68%). ^{1}H NMR (400 MHz, DMSO) δ 7.39-7.13 (m, 4H), 6.93-6.80 (m, 4H), 5.17 (s, 1H), 3.81 (s, 3H).
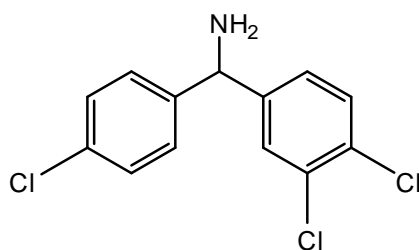
(4-Fluorophenyl)(4-methoxyphenyl)methanamine (30g).

Synthesized from General Method D using (4-fluorophenyl)(4-methoxyphenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (0.19 g, 63%). ^{1}H NMR (400 MHz, DMSO) δ 7.41-7.32 (m, 4H), 6.94-6.85 (m, 4H), 5.20 (s, 1H), 3.83 (s, 3H).
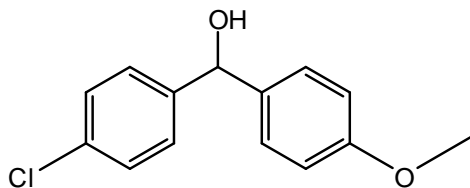

(4-Chlorophenyl)(3,4-dichlorophenyl)methanamine (30h).

Synthesized from General Method D using (4-chlorophenyl)(3,4-dichlorophenyl)methanone oxime and the amine was crystallized as a hydrochloride salt from ethanol/ethyl ether (0.81 g, 70%). ^{1}H NMR (400 MHz, DMSO) δ 7.51-7.13 (m, 7H), 5.17 (s, 1H).
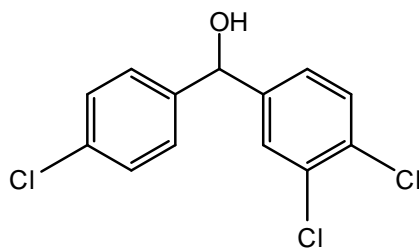
(4-Chlorophenyl)(4-methoxyphenyl)methanol (40f).

4-Methoxyphenyl magnesium bromide (6.30 mL, 1M in THF, 1eq) was syringed into a flask under nitrogen. A catalytic amount of CuI (0.006 g, 0.032 mmol) and 4-chlorobenzaldehyde (4.0 g, 0.028 mol, 1 eq), dissolved in ethyl ether (50 mL), was added slowly over 5-10 minutes with stirring. A small amount of heat was used for 5-10 minutes and the mixture was stirred overnight. Ethanol (20 mL) was added drop wise, with stirring, followed by 3 M HCl (20 mL) in 1 mL increments. The solution was extracted using HCl (3 x 20 mL) and the ether layer was washed with saturated NaCl solution and dried over sodium sulfate. The solution was filtered and concentrated under reduced pressure. (4-Chlorophenyl)(4-methoxyphenyl)methanol was crystallized using hexane and confirmed by NMR (1.9 g, 55%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (d, J = 4 Hz, 2H), 7.69 (d, J = 4 Hz, 2H), 7.43 (d, J = 4 Hz, 2H), 6.98 (d, J = 4 Hz, 2H), 5.35 (s, 1H), 3.83 (s, 3H).[28]
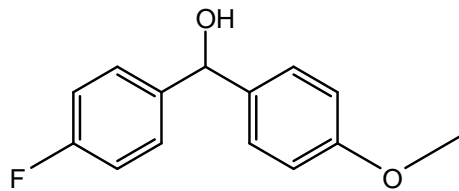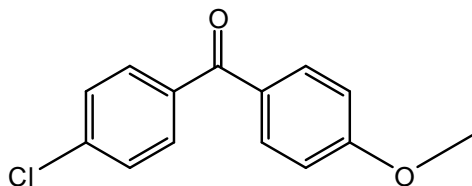
(4-Fluorophenyl)(4-methoxyphenyl)methanol (40g).

4-Methoxyphenyl magnesium bromide (7.13 mL, 1 M in THF, 1eq) was syringed into a flask under nitrogen. A catalytic amount of CuI (.005 g, 0.026 mmol) and 4-fluorobenzaldehyde (1.70 g, 0.014 mol, 1eq), dissolved in dry THF (20 mL), was added slowly and the mixture was stirred overnight. Ethanol (20 mL) was added drop wise, with stirring, followed by 3 M HCl (3 x 20 mL) in 1 mL increments. The solution was extracted using HCl (3 x 20 mL) and the ether layer was washed with saturated NaCl solution, dried over sodium sulfate, filtered using vacuum filtration and concentrated under reduced pressure. (4-Fluorophenyl)(4-methoxyphenyl)methanol was crystallized using hexane/ether and confirmed by NMR (1.9 g, 60%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49-7.38 (m, 2H), 7.30-7.23 (m, 2H), 7.18-7.10 (m, 2H), 7.03-6.93 (m, 2H), 5.42 (s, 1H), 3.81 (s, 3H).[28]

**(4-Chlorophenyl)(3,4-dichlorophenyl)methanol (40h).**

4-Chlorophenyl magnesium bromide (5.56 mL, 1 M in THF, 1eq) was syringed into a flask under nitrogen. A catalytic amount of CuI (0.005 g, 0.026 mmol) and 3,4-dichlorobenzaldehyde (4.0 g, 0.023 mol, 1eq), dissolved in ethyl ether (60 mL), was added slowly over 5-10 minutes with stirring. A small amount of heat was used for 5-10 minutes and the mixture was stirred overnight. Ethanol (20 mL) was added drop wise, with stirring, followed by 3 M HCl (20 mL) in 1 mL increments. The solution was extracted using HCl (3 x 20 mL), washed with saturated NaCl solution and the ether layer was dried over sodium sulfate, filtered using vacuum filtration and concentrated under reduced pressure. (4-Chlorophenyl)(3,4-dichlorophenyl)methanol was crystallized using hexane and confirmed by NMR (4.3 g, 65%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95-7.41 (m, 7H), 5.41 (s, 1H). [28]
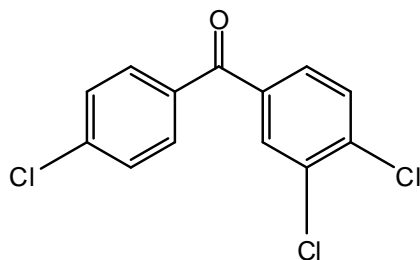

(4-Chlorophenyl)(4-methoxyphenyl)methanone (33f).

PCC (0.55g, 2.53 mmol, 1.25eq) was added to (4-chlorophenyl)(4-methoxyphenyl) methanol (0.50 g, 2.01 mmol, 1eq) dissolved in CH$_2$Cl$_2$ (15 mL) and allowed to stir under nitrogen overnight. The mixture was filtered through a Celite plug, rinsed with ethyl ether and concentrated under reduced pressure. (4-Chlorophenyl)(4-

methoxyphenyl)methanone was confirmed using NMR (0.31 g, 63%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (d, J = 4Hz, 2H), 7.70 (d, J = 4Hz, 2H), 7.44 (d, J = 4Hz, 2H), 6.93 (d, J = 4Hz, 2H), 3.83 (s, 3H).[29]
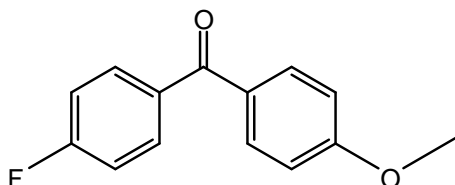
(4-Fluorophenyl)(4-methoxyphenyl)methanone (33g).

PCC (1.70 g, 7.89 mmol, 3 eq) was added to (4-fluorophenyl)(4-methoxyphenyl) methanol (0.61 g, 2.63 mmol, 1eq) dissolved in CH$_2$Cl$_2$ (40 mL) and allowed to stir under nitrogen overnight. The mixture was concentrated under reduced pressure and extracted using 30:70 ethyl acetate/ petroleum ether (3 x 100 mL each). The solution was filtered and concentrated under reduced pressure to afford (4-fluorophenyl)(4-methoxyphenyl)methanone (0.40 g, 66%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49-7.38 (m, 2H), 7.30- 7.23 (m, 2H), 7.18-7.10 (m, 2H), 7.03-6.93 (m, 2H), 3.81 (s, 3H).[29]

**(4-Chlorophenyl)(3,4-dichlorophenyl)methanone (33h).**

PCC (4.97 g, 0.023 mol, 1.25eq) was added to (4-chlorophenyl)(3,4-dichlorophenyl)methanol (2.21 g, 0.008 mol, 1eq) dissolved in CH_2Cl_2 (15 mL) and allowed to stir under nitrogen overnight. The mixture was concentrated under reduced pressure and extracted using 30:70 ethyl acetate/petroleum ether (3 x 100 mL each). The solution was filtered and concentrated under reduced pressure to afford (4-chlorophenyl)(3,4-dichlorophenyl)methanone (1.5 g, 68%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93-7.19 (m, 7H).[29]
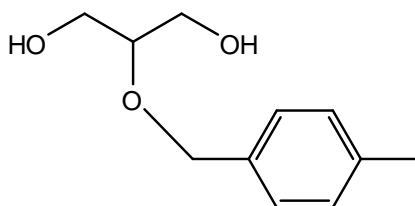
General Method E. 2-(4-Methylbenzyloxy)propane-1,3-diol (50a).

2-Phenyl-1,3-dioxan-5-ol (2.50 g, 0.014 mol) was dissolved in distilled THF (60 mL) and stirred for ten minutes. The mixture was placed in an ice bath and finely ground KOH (1.77 g, 0.032 mol) was added and allowed to react for ten minutes.

4-Methylbenzyl chloride (2.83 mL, 0.021 mol) was added via syringe at 0 ℃ and stirred overnight at room temperature. H$_2$O (30 mL) was added and the THF layer was concentrated under reduced pressure.   The solution was extracted with CH$_2$CL$_2$ (3 x 30 mL), dried over sodium sulfate and concentrated under reduced pressure.   The   dioxane   intermediate   product   was   precipitated   using ethanol/dichloromethane and evaporated to dryness. The dioxane intermediate was dissolved in THF (40 mL) and 10 % aq HCl (40 mL) and allowed to reflux for 2 hours.   The mixture was cooled to room temperature and poured over sodium carbonate (30 mL), followed by concentration of the THF layer.   The aqueous solution was extracted with CH$_2$Cl$_2$ (3 x 30 mL), dried over sodium sulfate and concentrated under reduced pressure. 2-(4-Methylbenzyloxy)propane-1,3-diol was precipitated using hexane and confirmed by NMR (2.6 g, 92%).   ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (d, J = 4 Hz, 2H), 7.18 (d, J = 4 Hz, 2H), 4.61 (s, 2H), 3.72 (d, J = 4 Hz, 4H), 3.61-3.52 (m, 1H), 2.36 (s, 3H).[35]
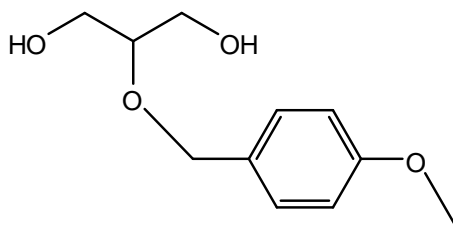
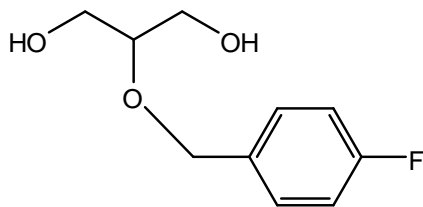**2-(4-Methoxybenzyloxy)propane-1,3-diol (50b).**

Synthesized using General Method E from 4-methoxybenzyl chloride and precipitated using methanol (2.6 g, 90%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, J = 4 Hz, 2H), 6.91 (d, J = 4 Hz, 2H), 4.60 (s, 2H), 3.81 (s, 3H), 3.62 (d, J = 4 Hz, 4H), 3.60-3.51 (m, 1H).
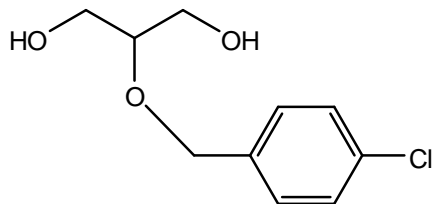
2-(4-Chlorobenzyloxy)propane-1,3-diol (50c).

Synthesized using General Method E from 4-chlorobenzyl chloride and precipitated using ethyl acetate/hexane (2.4 g, 84%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32-7.23 (m, 4H), 4.61 (s, 2H), 3.76 (d, J = 8 Hz, 4H), 3.61-3.50 (m, 1H).

2-(4-Fluorobenzyloxy)propane-1,3-diol (50d).

Synthesized using General Method E from 4-fluorobenzyl chloride and precipitated using methanol (2.3 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (d,

J = 8 Hz, 2H), 7.01 (d, J = 8 Hz, 2H), 4.59 (s, 2H), 3.71 (d, J = 8 Hz, 4H), 3.58-

3.50 (m, 1H).

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Vita

Kimari Slaughter was born in Baton Rouge, Louisiana. She received her Bachelor's degree in Chemistry from Xavier University of Louisiana in 2002. She joined the University of New Orleans chemistry graduate program to pursue a Masters in Organic Chemistry and became a member of Mark L. Trudell's research group in 2005. She is currently studying for the MCAT in preparation for medical school.