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Synthesis of Novel Azetidines

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Synthesis of Novel Azetidines

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

Amber Nichole Thaxton

B.S. Clemson University, 2004
M.S. University of New Orleans, 2013

December 2013
For my family:
To my mom, Bee Thaxton, for everything she has done for me. I am extremely thankful for her constant support and reassurance.
To Teddy for his ability to make me smile especially when I am stressed.
To Robby who has my heart.
Acknowledgement

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Abstract

Azetidine is a four-membered nitrogen-containing heterocyclic ring that has recently received a great deal of attention as a molecular scaffold for the design and preparation of biologically active compounds. Structure-activity studies employing functionalized azetidines have led to the development of a variety of drug molecules and clinical candidates encompassing a broad spectrum of biological activities.

Herein, the synthesis of a novel series of 3-aryl-3-arylmethoxyazetidines is described. Selected 3-aryl-3-arylmethoxyazetidines were evaluated for their binding affinity to multiple monoaminergic transporters for the potential treatment of methamphetamine addiction. It was discovered that this scaffold exhibits high binding affinity (nM) for both the serotonin and dopamine transporters. In addition, a new method was developed for the synthesis of 3,3-diarylazetidines. This new approach provides a facile and efficient method to synthesize a variety of diaryl heterocycles including 3,3-diarylazetidines, 3,3-diarylpyrrolidines, and 4,4-diarylperidines in moderate to good yields.

Key Words: Azetidines, Methamphetamine addiction, Multi-targeted monoaminergic reuptake inhibitor, Diaryl heterocycle, Friedel-Crafts alkylation
Part I: Synthesis and Biological Evaluation of

3-Aryl-3-Arylmethoxy azetidines

Abstract

Methamphetamine (METH) is a highly addictive synthetic psychostimulant that targets monoaminergic transporters dopamine, serotonin, and norepinephrine located in the central nervous system. In an effort to find a single pharmacophore for the treatment of methamphetamine addiction, a series of novel of 3-aryl-3-arylmethoxyazetidine analogs as potential multi-targeted monoaminergic reuptake inhibitors have been synthesized and evaluated by in vivo studies. These analogs were found to be active (nM) for the serotonergic transporter and dopaminergic transporter in rat brain tissue. The aim of the project is to find a dually active compound at both the serotonin (SERT) and dopamine (DAT) transporters, which could be used in the field of psychotherapeutics. Binding studies for serotonergic and dopaminergic transporters were completed by competitive inhibition against $[^3\text{H}]$citalopram and $[^3\text{H}]$WIN 35,428, respectively, in rat brain tissue.

The scaffold proved to be highly selective for the serotonin receptor with $N$-methyl-3-phenyl-3-(3,4-dichlorophenylmethoxy)azetidine (31c) exhibiting high potency and
selectivity for the serotonin transporter over the dopamine transporter \( (K_i = 1.0 \text{ nM}, K_i = 1210 \text{ nM} \text{ respectively}) \). Analog \( N \)-methyl-3-(3,4-dichlorophenyl)-3-phenylmethoxyazetidine (31g) exhibited the highest dopamine binding affinity \( (K_i = 620 \text{ nM}) \) while maintaining good serotonin binding affinity \( (K_i = 23.2 \text{nM}) \) which offered a moderate serotoninergic/dopaminergic selectivity of 27. The 3-aryl-3-arylmethoxyazetidine scaffold proved to be a tunable template where minor changes in substitution on the aryl moieties as well as substitution at nitrogen on the azetidine ring can dramatically modify binding affinities and selectivity for multiple monoaminergic transporters.

Key Words: Azetidines, Methamphetamine addiction, Multi-targeted monoaminergic reuptake inhibitor.
Introduction

1.1 History of Methamphetamine

Methamphetamine, N-methyl-1-phenylpropan-2-amine (1), was originally synthesized by Japanese chemist and pharmacologist Nagia Nagayoshi during his studies on naturally occurring ephedrine (2).¹

Nagia was a well-respected chemist and member of the Meiji Japanese elite. He devoted most of his time to the chemical analysis of traditional Japanese and Chinese medicines utilizing the instruments and techniques of Western science. In 1885, Nagai isolated ephedrine from Ephedra sinica, a plant used for centuries in Chinese medicine. Ephedra, or ma huang as it is known in Chinese medicine, was typically brewed into teas and used for its effects of increased blood circulation, and reduction of coughs and fever.²
In July 1884, Sigmund Freud published his highly popular accolade to the wonders of cocaine, Über Coca. Cocaine exhibited effects profoundly more potent than its parent coca leaves, and chemists around the world were on the lookout for the next potential wonder drug.\(^3\) It is probable that Nagai hoped extracts from Ephedra would be the next big hit – and in many ways it was. Ephedrine was first synthesized in 1920, and the structure identified. It was during those synthetic trials that methamphetamine (METH) was created.\(^2\)

METH was introduced to the American market in 1932 by the company Smith Klein and French as the “Over-the-counter” (OTC) bronchodilator, Benzedrine, for the treatment of asthma. By 1937 the American Medical Association allowed for a tablet form of the drug to be prescribed for the treatment of narcolepsy.\(^4\) In both the tablet and inhaler form, Benzedrine was sold as the racemic mixture of methamphetamine.

During the United States federal government ban on the possession and distribution of alcohol (1920-1933), METH and other now controlled substances then found in OTC drugs thrived. The Benzedrine inhaler alone contained the equivalent of approximately 56 METH tablets and, was readily available to people even with no known illnesses. The start of the Great Depression (1929-1939) combined with prohibition had many Americans turning to medicinal sources for pleasure. It was reported that the nasal strips from the Benzedrine inhalers were removed and stirred in morning coffee to bring a small sense of happiness in the desolate times.\(^4\) During this time, “pep-pills,” such as Benzedrine, were legal and openly distributed everywhere from student unions to truck stops and few
thought much about the side effects and long term consequences of chronic methamphetamine use.⁴

The end to the Great Depression was greeted with the start of the second major world war. Though American prohibition was over, methamphetamine actually increased in popularity, which was aided, in part, by the United States government. Due to the short-term benefits of METH use, such as increased alertness and activity, increased aggression, and decreased appetite and fatigue, the United States military as well as the military forces of Germany, and Japan readily distributed METH to soldiers during the war. The US military alone circulated an estimated 200 million METH tablets to its troops.⁴ At the time, the toxicology and long-term effects of METH were not known.¹ In addition to METH distribution to soldiers, it has been established that Adolph Hitler was a strong advocate and frequent METH user. By October 1942 he received daily injections of increasing doses of a drug cocktail containing METH.⁴

After World War II, soldiers and civilians continued using methamphetamine. METH was available in an injectable form at the time, and became a unique recreational drug.¹ The impact of METH use can be seen in the work of many artists and writers of the day. This is most evident in Jack Kerouac’s novel On the Road. Kerouac claimed he wrote the novel on a 20 day Benzedrine high.⁴ His “free-form” literature became a hallmark of the entire Beatnik culture that reflected a free-form lifestyle of the more broadly based hippie movement in the 1960s and 1970s.⁴

By the mid 1960s it became increasingly difficult to get a prescription for injectable METH by simply claiming to be afflicted by any ailment. This is because physicians began
noticing negative side effects in long-term METH users, including an addiction pattern and a severe decline in dental health.\textsuperscript{4} In response to the lack of readily available METH prescriptions, clandestine labs illegally manufacturing METH began popping up around the San Francisco and San Diego areas of California.\textsuperscript{5} By 1968 an estimated 5-10 large scale labs and an unknown number of “mom and pop” operations were well established in the San Francisco Bay area.\textsuperscript{5} These labs were aided in transportation and distribution of METH by famous west coast motorcycle gangs such as the Hell’s Angels. METH was stored and transported in the crankcase of motorcycles, where it earned the street name “crank”.\textsuperscript{1}

In an effort to combat the addictive long-term effects of many drugs new legislation was generated. The 91\textsuperscript{st} congress passed the Comprehensive Drug Abuse Prevention and Control Act of 1970, which was signed into law by President Nixon. It was under this act that made the manufacturing, possession, distribution and importation of certain drugs illegal.\textsuperscript{6} Under new legislation, METH became a Schedule II drug and only legally available by prescription under extreme circumstance.\textsuperscript{6} This law only led to an increase in the number of clandestine labs and illegal production of METH.\textsuperscript{1}

In the 1980s the freebase smoke-able crystalline form of METH called “Ice” became popular due to its fast acting, and long lasting effects.\textsuperscript{1,4} “Ice” is said to provide a high lasting anywhere from eight to twenty-four hours, and the user is exceptionally violent, paranoid, and suffers from auditory and visual hallucinations.\textsuperscript{4} This may be due to Ice being the pure dextro enantiomer versus the enantiomeric mixtures seen in the liquid form. The dextro enantiomer is two to four times as stimulating as its levo counterpart, which is more commonly ingested nasally, orally or injected.\textsuperscript{4} The crystalline METH was imported from
Asia and Hawaii and quickly made its way east. In addition to being more potent than racemic METH, “Ice” was also very attractive because it was easy to transport, and had a new smoke-able form of ingestion. “Ice” quickly gained popularity with users and clandestine lab manufacturers and became the standard form of METH produced and used.

Though the Comprehensive Drug Abuse Prevention and Control Act of 1970 made the possession of intermediates and starting materials of METH illegal, new methods for production were created using common household ingredients. These methods were published in a 1987 book entitled Secrets of Methamphetamine Manufacture written under the pseudonym Uncle Fester.

From the late 1980’s to today, METH use has not been forgotten. With the booming US population METH use has spread. Today METH can be almost odorously synthesized in homes across America using a stovetop or even soda bottles. According to the United States Drug Enforcement Agency over 80% of clandestine lab seizures are METH labs due to the ease of methamphetamine synthesis. These issues brought forth the Methamphetamine Control Act of 1996, which controlled drug products containing the known METH starting materials ephedrine (2), pseudoephedrine (3) and phenyl-2-propanone (4). This law put a limit on the amount of OTC drugs containing these METH precursors one can purchase at a time.
A 2012 study completed by the National Survey on Drug Use and Health (NSDUH) found that over 12 million Americans have tried METH in their lifetime with 133,000 reported new users within that year. Methamphetamine is ranked second in popularity for abused substances among the United States youth falling well behind marijuana as the most popular abused substance. Though heavy METH use originated on the west coast, today, the highest concentration of METH users are in the Midwestern United States with the top five highest METH using states being Missouri, Kentucky, Indiana, Oklahoma, and Illinois.

METH is highly addictive, with an estimated 98% of first time triers become users after the first time. Even if they are not addicted after their first experience with METH an estimated 90% of users become abusers within one year of initial intake. Methamphetamine users become physically dependent on the drug, quickly developing a tolerance which forces the user to increase dosage to achieve the same effects.

METH abusers will do anything to get their next hit and according to law enforcement, METH is considered "a drug so harmful and damaging that it has been blamed for the destruction of the social fabric of many large areas across the United States". METH has long lasting psychological and physiological effects that are harmful to not only the user but also those around them. Crimes are increasing as a direct result of METH use.
Responding officials in Illinois say that 70% burglaries have increased because of METH use over the last year.11

A related survey conducted in Illinois found that METH is a key source of child abuse and neglect, and 40% of all child welfare officials reported increased out-of-home placements of children due to parental METH use over the past year. An approximate 59% of child welfare officials also reported that when parents are addicted to METH, it increases the difficulty of family reunification efforts.11

1.2 Effects of Meth

The short term effects of METH have been sought out by a variety of people from housewives, truck drivers, students and soldiers.1,4-5 Because METH is a powerful stimulant small doses can provide positive effects of increased wakefulness, increased physical activity, increased attention and decreased appetite, all coupled with euphoria and a boost in confidence. However the user could also experience increased respiration, rapid or irregular heartbeat and hyperthermia.4,6-7,12 However, it is the long-term effects that have the most damage on the body. Immediate euphoria upon administration leads to addiction. This addiction typically leads to a gradual dosage and/or frequency increase to create the same effect. Chronic METH abusers may develop difficulty feeling any pleasure other than that provided by the drug, thus fueling the abuse. In addition, chronic users may exhibit increased distractibility, memory loss, aggression or violent behavior, weight loss, and psychosis including paranoia, hallucinations, and repetitive motor activity.6,7,12
Withdrawal symptoms are not acute and may take upwards of 90 days to be expressed by an addicted individual. These symptoms can include depression, cravings, lack of energy and even suicidal thoughts. Research suggests that brain abnormalities similar to those seen in depression and/or anxiety patents can occur when a person discontinues METH use. METH abuse has an extremely high relapse rate of more than 90% of individuals returning to use.12

### 1.3 Monoamine Neurotransporters

There are three main monoamines found in the CNS: dopamine, serotonin, and norepinephrine. Dopamine (5) governs pleasure and reward systems, whereas serotonin (6) regulates well-being and happiness, and norepinephrine (7) modulates concentration and attention.7 These emotions are expressed when a high concentration of the monoamine is present at their respective transporter synaptic cleft. For example, reaching a personal goal would initiate release of dopamine and provide the pleasurable feeling of a job well done.4
Each of these monoamines is transmitted through the CNS by their respective neurotransmitters. These neurotransmitter systems belong to the sodium symporter (NSS) family of transporters which regulate monoamine concentrations at the neuronal synaptic cleft by carrying them across neuronal membranes into presynaptic nerve cells as seen in Figure 1.13-14

**Figure 1:** Transportation of dopamine at a dopamine transporter synaptic cleft

Together, monoamine transporters are responsible for mood modulation. Modifying the concentration of any of these monoamines can disrupt the delicate balance each of these systems play and drastically modify behaviors.
1.4 Effects of METH on Neurotransporters

The interaction of methamphetamine with the dopaminergic system is the most widely studied and well known. As seen in Figure 2, METH acts on this system in several ways to flood the synapse with high concentrations of dopamine, thus giving the user a rush of euphoria and an activation of the reward system.\textsuperscript{15} METH first permeates the dopamine containing axon of the neurotransmitter, binds to the stored dopamine containing vesicles forcing the release of excess dopamine into the synaptic cleft. It also competitively binds to the dopamine reuptake transporter and blocks the natural reuptake of dopamine. This creates a flood of dopamine at the synapse, which initiates the pleasurable sensation attributed to illicit drugs.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{METH_dopamine_transporter.png}
\caption{Effects of METH on dopamine transporter\textsuperscript{15}}
\end{figure}
Post-mortem studies of METH abusers have shown that dopamine levels in the striatum were severely depleted, indicating that METH can cause a release of dopamine large enough to completely exhaust stores in the tissue. There is also evidence of structural neuronal damage of long time METH users. Depleting stores of dopamine followed by neuronal damage may lead to decreased dopamine production.

A live study was completed which measured dopamine receptor levels, using a radioactive tag that binds to dopaminergic receptors in the brain. Subjects' brains were then imaged using a positron emission tomography (PET) scan that visualizes the radioactive tag and shows where it is bound to receptors. The strength of the signal indicates the concentration of receptors.

*Figure 3:* PET scan evaluating dopamine levels of a healthy brain and a brain of a METH abuser.
As seen in Figure 3, methamphetamine abusers had significantly lower levels of dopaminergic receptors than the control subjects. And the lower the number of dopaminergic receptors, the lower the metabolic activity in the orbitofrontal cortex. The blunted orbitofrontal cortex activity in these drug abusers reduces the ability of all other stimuli to trigger a reward response making ordinary stimuli not strong enough to activate the transporters.²⁰

Though the mode of action is not as well known, serotonin is also released and observed concentrations are elevated. Studies have shown significant loss of serotonin concentrations in the cerebral cortical and subcortical regions of the brain in chronic METH users. There is evidence that serotonin transporter function is rapidly impaired upon METH administration.²¹⁻²³ It was seen that multiple administrations of METH rapidly decreased serotonin transporter function in rat striatum and hippocampus. These injections rapidly decreased serotonin uptake without altering the binding of the serotonergic transporter ligand paroxetine.²⁴ This decrease in serotonin sinks the addict into a depression which is the number one cause of relapse in recovering addicts.¹²

The noradrenergic transporter, while less vulnerable than dopaminergic and serotonergic transporters, demonstrates significant METH induced effects. A decrease in norepinephrine transporter activity observed is a direct effect of dopamine and serotonin depletion due to high METH use. Abusers who demonstrate METH induced psychosis have been shown to exhibit elevated norepinephrine levels.²⁵
1.5 Methamphetamine vs Cocaine

Cocaine is a plant-derived drug found in the *Erythroxylon coca* bush. It is another widely abused psychostimulant that is active at the dopamine transporter. However, cocaine acts solely as a re-uptake inhibitor, which competitively binds to the transporter to block the re-uptake of naturally occurring dopamine, (Figure 4), thus elevating dopamine concentrations.\(^{26-27}\)

![Figure 4: Effect of cocaine on the dopamine transporter system\(^{27}\)](image)

In contrast to METH, the body quickly metabolizes cocaine. Cocaine exhibits a half-life of an hour, whereas METH has a half-life of 12 hours.
1.6 Attempted Methamphetamine Medications

Behavioral treatment programs have had some success in the treatment of methamphetamine addiction, however, many patients relapse even after several attempted treatments. Therefore, several pharmacotherapies have been attempted to compliment behavioral treatment programs.

The first pharmacotherapy program attempted utilized dextro-amphetamine. A preliminary study has demonstrated that a maintenance pharmacotherapy program of daily sustained-release dextro-amphetamine dispensed under pharmacist supervision is both feasible and safe. Clinical trial participants who received dextro-amphetamine in controlled conditions stayed in the program longer than those receiving a placebo. That coupled with a general decreases in methamphetamine use, degree of dependence and withdrawal symptom severity, provided preliminary evidence that this may be an efficacious treatment option for methamphetamine dependence. However, it due to the structural similarities between METH and dextro-amphetamine, medication self-administration would probably not be feasible. It is probable that the methamphetamine abuser would simply begin abusing dextro-amphetamine instead of METH.
Attempts at utilizing dopaminergic selective re-uptake inhibitor bupropion, and serotonin selective re-uptake inhibitor fluoxetine independently showed reduce cravings of METH and improve adherence to treatment. However, both had minimal effects at reducing overall METH dependence.\textsuperscript{29-30}

Fluoxetine is a serotonin selective re-uptake inhibitor (SSRI) synthesized by Eli Lilly Company. It is commonly used for the treatment of depression, obsessive-compulsive disorder and panic disorder. Fluoxetine has been on the United States market since December 1987, and is the third most prescribed SSRI after sertraline and citalopram.\textsuperscript{31} A Cochrane review concluded that fluoxetine at a dosage of 40 mg per day may have modest benefits in reducing short-term methamphetamine craving but does not reduce methamphetamine use or abuse.\textsuperscript{32}

Bupropion is an abnormal antidepressant because it exhibits stimulant properties.\textsuperscript{33} Bupropion is typically used for the treatment of depression and smoking cessation. The early clinical findings for the use of bupropion for methamphetamine addiction treatments were promising. For example, bupropion treatment (twice daily, 150 mg, sustained release) was well tolerated in patients that received intravenous METH infusions of 15 mg or 30 mg and by those abstaining from methamphetamine use. Additionally, bupropion reduced the subjective effects and cue-induced cravings of methamphetamine, and increased duration of abstinence in male participants classified as having “mild-to-moderate” methamphetamine dependence. \textit{In vivo} studies determined that acute administration of 30 and 60 mg/kg bupropion decreased intake of 0.025, 0.05, and 0.1 mg/kg/infusion of methamphetamine.\textsuperscript{33} However, bupropion (30 mg/kg) only momentarily reduced methamphetamine intake suggesting decreased effectiveness for
long-term administration as would be expected in an addict treatment plan.\textsuperscript{33}

\textbf{1.7 Dual Target Hypothesis}

It is evident that monoaminergic systems are responsible for modulation of METH-induced behaviors. However, dopaminergic and serotonergic selective medications have separately failed at reducing METH use among abusers.\textsuperscript{34-37} Available medications that have application to other abused substances such as cocaine fall short of being effective in treating the complex pharmacology of METH addiction. The failure of these drugs to be effective against METH is thought to be due to the limited scope of action: targeting single monoaminergic systems.

To date there is mounting evidence that in addition to dopaminergic systems, brain serotonergic systems also modulate responses in methamphetamine-induced behaviors.\textsuperscript{38-40} However, it has become evident that a single dopaminergic or serotonergic agent cannot adequately reduce the behavioral effects associated with psychostimulant abuse. Therefore, it has been suggested that a calibrated dual dopaminergic/serotonergic agent could be more effective.\textsuperscript{39-42}

A multi-targeted monoamine pharmacophore could be used to avoid psychotic effects and reduce reinforcing effects during METH detoxification. This theory is backed by several examples of weakened stimulant effects of dopaminergic agents by serotonergic activity, the most common being Fen-phen.\textsuperscript{42} Fen-phen was an anti-obesity treatment that
utilized two anorectics fenfluramine and phentermine. In this case, the stimulating effects of the dopaminergic/norepinephrine selective phentermine (8) are tempered by the serotonin releaser fenfluramine (9).42

![Chemical structures of phentermine (8) and fenfluramine (9)]

This model suggests that drug-induced dopamine and serotonin irregularities play a role in drug craving, withdrawal symptoms, and relapse.42-44 Therefore, it is postulated that a medication to restore dopaminergic and serotonergic levels should be able to treat dopamine and serotonin deficient stimulant abusers.

Previous studies of uptake inhibitor treatments for the treatment of the stimulant cocaine have utilized cocktails of dopaminergic selective and serotonergic selective inhibitors.45 This cocktail was given to rhesus monkeys and it was found that the combination was successful in preventing self-administration of cocaine. However, drug cocktails can be problematic due to pharmacokinetic differences between the medications. Formulating a single compound that could serve as a dual dopaminergic/serotonergic uptake inhibitor (DUI) or a dopaminergic/serotonergic/noradrenergic triple uptake inhibitor (TUI) could combat this issue and be used to restore monoaminergic levels and
reduce behavioral effects of METH.\textsuperscript{45}

Based on the pharmacological evidence available, it is clear that attenuation of dopaminergic, serotonergic and noradrenergic uptake can affect the behaviors associated with METH abuse and addiction. In addition, uptake inhibitors clearly offer a safer mechanism than releasing agents to attenuate METH activated monoaminergic systems. The failures of previous therapeutic approaches, we believe, has been due to the lack of a multi-target approach that addresses multiple transporter systems.

1.8 Triple Re-uptake Inhibitors in Clinical Trials

Currently there are multiple triple re-uptake inhibitors (TUIs) in clinical trials, none of which are explicitly intended for METH addiction. Euthymics Bioscience has two derivatives in clinical trials: Amitifadine® (10) and Nuerovance® (11).\textsuperscript{46-47} Amitifadine® has a 1:2:8 selectivity for SERT, NET and DAT respectively and is in clinical trials for major depression disorder (MDD).\textsuperscript{46,48-49} At the conclusion of its May 2013 trials a brief statement was made that Amitifadine® has shown “statistical significance for anti-depressant effects.”\textsuperscript{46} Nuerovance® is in clinical trials for adult attention deficit disorder (ADHD) and has a 1:6:14 SERT:DAT:NET selectivity ratio.\textsuperscript{47}
Due to relative novelty not much is known about the MDD medications from Lundbeck and Takeda, 12, or Glaxo-Smith Klein, 13. However, across each molecule similar motifs are seen.50-51 Each compound contains a heterocyclic amine, and an electron rich aromatic group. Amitifadine®, Nurovance® and 13 have a rigid carbocyclic system.

1.9 Ibudilast

MediciNova has a possible drug candidate for METH abuse, MN-166, which is currently in Phase II clinical trials.6,52,53 MN-166, dubbed Ibudilast, is the first non-opioid drug for the treatment of several pain indications and drug abuse treatment. Ibudilast (14) is a glial reducer that suppresses pro-inflammatory cytokines IL-1β, TNF-α, and IL-6. It has also been shown to be a functional antagonist that may contribute to its attenuation of neuroinflammation.52 While Ibudilast is a new molecular entity in the US it has been prescribed on the Japanese markets for more than 20 years for treatment of asthma.54
According to the MediciNova website, preclinical studies have shown that Ibudilast may prevent the activation of glial cells in the CNS that have been linked to drug dependence. In September 2012, University of California at Los Angeles's Department of Family Medicine/Center for Behavioral and Addiction Medicine, and MediciNova, announced approval for the commencement of Phase II clinical trials investigating the use of Ibudilast for the treatment of METH addiction. These trials, funded by the National Institute on Drug Abuse (NIDA), have had eleven reported volunteers to date which have passed safety tests and shown early signs of eased METH addiction. Clinical trials are scheduled to conclude July 2017.

1.10 Approach and Investigation of 3-Aryl-3-arylmethoxytropanes

Our approach to finding a pharmacophore for the treatment of METH addiction is innovative in that it seeks a single molecule to act as a re-uptake inhibitor at multiple neurotransmitters. This eliminates any issue of differentiated pharmacokinetics by multiple medications and is potentially less toxic than monoamine releasing agents. Our
efforts to develop a novel molecular scaffold began with the investigation of several classes of dopaminergic selective and serotonergic selective ligands.

In a search for stimulant abuse a variety of compounds have been evaluated as dopamine re-uptake inhibitors. WIN-35,065-2 (15), methylphenidates (16), mazindols (17), benztropines (18), and GBR analogs (19) are a representative collection of those compounds, which have a high affinity for the dopamine transporter.

In the search for a cocaine abuse drug, extensive studies were completed by the Clark group on the 3-phenyltropane scaffold. WIN-35,065-2 (IC$_{50} = 23$nM) was found to be
four times more potent than cocaine (IC$_{50}$ = 89nM) at the dopaminergic transporter. This provided a new scaffold for investigation at the dopamine transporter. Structure activity relationship studies on 3-phenyltropanes examined substitution at the 4-position of the aryl moiety. It was determined that this position plays a critical role in enhancing dopamine transporter affinity and substitution there resulted in analogs that exhibited high to moderate affinity ($K_i$ < 2 nM to 200nM) at the dopamine transporter. An interesting feature of these analogues was that they were much more selective for the serotonin transporter than the dopamine and norepinephrine transporters.

Substitutions at the 3-position of the aryl moiety of WIN 35,065-2 were also synthesized and analyzed for their binding affinities. However, it was determined 3-substitution does not affect the dopamine transporter binding affinity as significantly as substitution at the 4-position. Addition of halogens (F, Cl, Br, I), and phenyl groups at the 3-position only produced analogues which were only four to nine times more potent than cocaine. Disubstitution at the 3, 4-positions on the aryl provided some of the most potent 3-phenyltropanes to date. Combinations of -chloro, -fluoro, -bromo, or -iodo substituents at the 3,4-positions of the phenyl group provided compounds with subnanomolar affinities at the dopamine transporter ($K_i$ < 2nM).

Although halogens are well tolerated at the dopamine transporter, there is a limited tolerance for the hydroxyl group. Monohydroxyl substitution on the phenyl at 3- and 4-positions displayed dopamine transporter binding affinities around $K_i$ = 12 nM whereas the 3,4-dihydroxy analog was found to be 113-fold less potent at the dopamine transporter. The catechol derivative was prepared to determine if the aryl group of phenyltropanes interacted with the dopamine transporter in a similar manner as the 3, 4-dihydroxylphenyl
group of dopamine. The low binding affinity of the dihydroxy-substituted tropane suggests that dopamine does not occupy the same binding site on the dopamine transporter as the 3-phenyltropanes.

A series of 2β-derivatives were synthesized and found, to have highly increased dopaminergic potency. Although in general, these compounds displayed high potencies and selectivities for the dopamine transporter, some compounds appear to have unique pharmacological profiles in vivo. Heterocyclic 2β-derivatives do not produce locomotor stimulation in mice despite having potent IC₅₀ values at the dopamine transporter. This trend has also been observed for other classes of dopamine transporter uptake inhibitors and requires further investigation.67

Exchanging the methyl group on the tropane nitrogen with alkyl, allyl and even phenylpropyl substitutions showed little effect on dopamine transporter binding affinity.68-70 N-Substituted derivatives retained high affinity at the dopamine transporter and even analogues with bulky groups were well tolerated.68-69

A large number of 3-phenyltropanes have been synthesized and analyzed for the purpose of selectively modulating the dopamine transporter for potential medications. Analogues have been developed with high affinity for all three transporters and many of these have been evaluated in locomotor activity and cocaine discrimination studies. Almost all the compounds investigated show reduction of cocaine self-administration in both rat and monkey models and some analogues are in clinical or advanced preclinical studies for treating cocaine addiction.71-73
Serotonin selective re-uptake inhibitors (SSRIs) are commonly used medications. SSRIs are generally prescribed for treatment of depression under trade names of Paxil® (23) and Prozac® (20). The compounds below are illustrations of known SSRIs.

Meperidine (22) is an atypical μ-opioid receptor agonist. Chronic use can produce central nervous system stimulant effects of hyperflexia and increased susceptibility to startle. These effects are generally specific to meperidine and are typically not observed with other μ-opioid receptor agonists such as morphine. Meperidine shares numerous
structural features with the 3-phenyltropane analogs. The piperidine ring is a common ring structure in both meperidine and the 3-phenyltropane. N-methyl substitution occurs in meperidine as well. The phenyl ring attached to the 3-position on the tropanes ring of the WIN 35065-2 is equivalent to the phenyl on the 4-position of the piperidine ring of meperidine. These common structural features between meperidine and cocaine congeners, such as WIN 35065-2, combined with the unique pharmacological profile of meperidine suggested that the non-opioid actions of meperidine could be due to a cocaine-like pharmacological action.

Given the similar structural characteristics of 3-phenyltropane and meperidine it was of interest to explore the possibility of merging the two pharmacophores to develop a class of monoamine transporter ligands that would have a unique profile of multiple transporter affinity as seen in Figure 5. To this end, the 3α-arylmethoxy-3β-aryltropane pharmacophore (25) was envisaged.

Figure 5: Approach to Pharmacophore Scaffold
Pharmacophore 25 was designed not only to incorporate the main skeletal features of the dopamine transporter selective 3-phenyltropane and the serotonin transporter selective meperidine, but the arylmethoxy moiety common to many of the prototypical serotonin selective re-uptake inhibitors (SSRIs) and serotonin-norepinephrine selective re-uptake inhibitors (SNRIs) was also envisaged to be an important structural feature for molecular recognition at monoamine transporters.\textsuperscript{57}

Analogs of 3-methoxy-3-arylmethoxytopanes were synthesized and a structure-activity relationship (SAR) was completed. These analogs were shown to possess nanomolar (nM) affinity for both dopaminergic and serotonergic transporters but were generally selective for the serotonin transporter. Table 1 shows binding affinities for 3-aryl-3-arylmethoxytopane analogs. The most potent serotonin transporter and dopamine transporter analog of the series was 25e with $K_i = 0.061\text{nM}$, and $K_i = 16\text{nM}$ respectively.\textsuperscript{78}
<table>
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<tr>
<th>Cpd</th>
<th>Code</th>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>DAT (K_i, nM)</th>
<th>SERT (K_i, nM)</th>
<th>NET (K_i, nM)</th>
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<tr>
<td>25a</td>
<td>HK2-151</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>117 ± 19</td>
<td>247 ± 27</td>
<td>NT</td>
</tr>
<tr>
<td>25b</td>
<td>HK3-27</td>
<td>CH3</td>
<td>H</td>
<td>H</td>
<td>95 ± 21</td>
<td>141 ± 7.0</td>
<td>446 ± 57</td>
</tr>
<tr>
<td>25c</td>
<td>HK6-63</td>
<td>H</td>
<td>H</td>
<td>F</td>
<td>2,137 ± 252</td>
<td>17 ± 6.0</td>
<td>NT</td>
</tr>
<tr>
<td>25d</td>
<td>HK3-77</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>22 ± 8</td>
<td>6.1 ± 0.5</td>
<td>101 ± 0</td>
</tr>
<tr>
<td>25e</td>
<td>HK3-45</td>
<td>H</td>
<td>H</td>
<td>3,4-Cl2</td>
<td>16 ± 1</td>
<td>0.061 ± 0.024</td>
<td>996 ± 53</td>
</tr>
<tr>
<td>25f</td>
<td>HK3-87</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>172 ± 70</td>
<td>65 ± 25</td>
<td>1,718 ± 18</td>
</tr>
<tr>
<td>25g</td>
<td>HK3-19</td>
<td>H</td>
<td>F</td>
<td>F</td>
<td>105 ± 1</td>
<td>7.9 ± 3.7</td>
<td>1,443 ± 5</td>
</tr>
<tr>
<td>25h</td>
<td>HK3-35</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>63 ± 7</td>
<td>0.10 ± 0.02</td>
<td>2,370 ± 367</td>
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<tr>
<td>25i</td>
<td>HK3-119</td>
<td>H</td>
<td>3,4-Cl2</td>
<td>H</td>
<td>716 ± 52</td>
<td>62 ± 15</td>
<td>1,232 ± 438</td>
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<tr>
<td>25j</td>
<td>HK3-49</td>
<td>H</td>
<td>3,4-Cl2</td>
<td>3,4-Cl2</td>
<td>2,930 ± 70</td>
<td>4.7 ± 0.3</td>
<td>2,552 ± 326</td>
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<tr>
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<td>HK3-31</td>
<td>CH3</td>
<td>CF3</td>
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<td>3,761 ± 632</td>
<td>7.4 ± 3.2</td>
<td>11,721 ± 3247</td>
</tr>
</tbody>
</table>

*a* All compounds were tested as the oxalate salts. *b* All values are the mean ± SEM of three experiments performed in triplicate.

It is evident from Table 1 that changing substituents on aryl rings of the 3-aryl-3-arylmethoxytropane scaffold can readily modify dopaminergic, serotonergic and noradrenergic binding affinity.78 Because the 3-aryl-3-arylmethoxytropane derivatives seen have exhibited high binding affinity and selectivity for the serotonin transporter, structural modifications seen in Figure 6 indicates enhanced affinities for dopaminergic and noradrenergic transporters.78
**Figure 6:** Modification areas for increased binding affinities

### 1.11 Design Strategy for Novel 3-aryl-3-arylmethoxyazetidines

It was discovered however that the 3-aryl-3-arylmethoxytropane scaffold had a high clogP, which could indicate that it is too lipophilic and could have poor bioavailability. It was envisaged that a less lipophilic scaffold could produce compounds with improved bioavailability and the azetidine derivative (26) was identified as a viable target scaffold.77 The azetidine scaffold allows for lower molecular weight and less lipophilic (cLogP) analogs.
Lipophilicity values for un-substituted free-base for 3-phenyl-3-phenylmethoxytropane and 3-phenyl-3-phenylmethoxyazetidine were calculated using software from Collaborative Drug Discovery, Inc., and were found to be 3.67 and 3.02 respectively. These values increase for varying substitution on the α-aryl, β-aryl, and substitution at the amine.\textsuperscript{77}

The azetidine scaffold was validated computationally by the superposition of the un-substituted 3-phenyl-3-phenylmethoxytropane (25) and 3-phenyl-3-phenylmethoxazetidine (26) seen in Figure 7.\textsuperscript{77} This demonstrates that the azetidine scaffold allows for favorable alignment of the major structural elements of the two compounds.
The retrosynthetic analysis for the synthesis of 3-aryl-3-arylmethoxyazetidines is outlined in **Scheme 1**. The synthesis was envisaged to start from the commercially available 1-Boc-3-azetidinone (27). The addition of the aryl group can be completed using lithium reagents and halogenated aryls to form the tertiary alcohol (28). 1-Boc-3-aryl-3-arylmethoxyazetine (29) could be achieved via ether synthesis. The carbonyl protective group can then either be removed under acidic conditions for formation of the secondary amine (30) or reduced with lithium aluminum hydride to form $N$-methyl-3-aryl-3-arylmethoxyazetidine (31).
Scheme 1: Retrosynthetic analysis for the preparation of 3-aryl-3-arylmethoxyazetidines

It has been established by the previously reported tropane structure-activity relationship studies that chloro and fluoro substitution on both the aryl and arylmethoxy substituents increased dopamine and norepinephrine transporter binding affinity. Methyl substitution on the amine, similar to that seen in both cocaine and methamphetamine, have markedly increased dopaminergic-binding affinity. In accordance with this data, substitution of chloro, fluoro and trifluoromethane at various positions on the aryl moieties on the azetidine scaffold can be examined for binding affinities at multiple monoaminergic systems.\textsuperscript{78-79}
Results and Discussion

2.1 Synthesis of 3-Aryl-3-arylmethoxyazetidine and N-Methyl-3-aryl-3-arylmethoxyazetidine

Due to the fragile nature of the azetidine ring, there were many obstacles encountered during development of synthesis. Several variations were attempted for each step of the full synthesis to determine the highest yielding results.

2.1.1 Synthesis of N-Boc-3-aryl-3-azetidinol

The first step of the synthetic approach was to convert commercially available reagents N-Boc-3-azetidinone (27) into N-Boc-3-phenyl-3-azetidinol (32). This was completed by reacting N-Boc-3-azetidinone with 1.8M phenyllithium in tetrahydrofuran (THF) solution at -78 ⁰C overnight. Various equivalents of phenyl lithium solution were added to optimize yields. The reaction was also attempted in two different solvent systems, dichloromethane and tetrahydrofuran. It was discovered that three equivalents of lithium reagent and tetrahydrofuran as the solvent system gave the highest yielding reactions of 94%.
Reactions with less than three equivalents of lithium reagent produced products in poor yield (26-31%), while reactions utilizing dichloromethane as a solvent system decomposed completely. Reacting $N$-Boc-3-azetidinone with higher than three equivalents of phenyl lithium solution did neither improve nor hinder results (four equivalents yielded 80% product), but due to the expense of the chemical, using the reagent in excess of three equivalents was not warranted.

Substituted $N$-Boc-3-aryl-3-azetidinols were synthesized in a similar fashion using the same solvent system and lithium reagent equivalencies as seen above. However, substituted aryls were first reacted with 2M butyllithium solution in hexanes before $N$-Boc-3-azetidinone was added. This allowed for formation of an aryllithium intermediate (33), which then would react with $N$-Boc-3-azetidinone.
Scheme 3: Formation of substituted N-Boc-3-aryl-3-azetidinols

With this synthesis, a variety of substituted 3-aryl-azetidinol analogs could be synthesized. Compounds 34a-h were synthesized using the optimized reaction conditions.

Figure 8: N-Boc-3-aryl-3-azetidinol derivatives
2.1.2 Synthesis of \textit{N-Boc-3-aryl-3-arylmethoxyazetidine}

Benzylation of the tertiary azetidinol (28) was also attempted under a variety of reaction conditions. First by reacting \textit{N-boc-3-aryl-3-azetidinol} with 1.5 equivalents of 60\% sodium hydride in \textit{N,N-Dimethylformamide} followed by 5 equivalents of halogenated benzyl bromide under inert conditions.\textsuperscript{83} However, the results varied from 10-75\% yield. When a catalytic amount of sodium iodide was added to the reaction, a slight increase in percent yield (from 10\% to 35\%) was seen.

\begin{center}
\begin{tikzpicture}
    \node (start) at (0,0) {28};
    \node (end) at (3,0) {29};
    \draw[->] (start) -- node[above] {1.)NaH, DMF} node[below] {0\degree C} (end);
    \node at (1.5,0.2) {10-75\%};
    \node[above] at (1.5,0.5) {\textit{X}};
    \node[above] at (1.5,-0.5) {\textit{Y}};
    \node[above] at (0.5,0.5) {\textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O}};
    \node[above] at (3.5,0.5) {\textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C} \textit{O} \textit{N} \textit{O} \textit{C}};
    \node[above] at (2.5,0) {\textit{Br}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 4:} Attempted formation of \textit{N-Boc-3-aryl-3-arylmethoxyazetidine}

Another issue seen with this procedure was that not all of the starting material was reacting. This created a need for column chromatography. This was completed using 30\% ethyl acetate/hexanes. However, decomposition of the intended product occurred while on the column. Assuming that the column was too acidic, 1\% \textit{NH}_4\textit{OH} was added to the solvent.
system. This worked for both the benzyloxy and 3,4-dichlorobezylxyloxy compounds but some decomposition was still seen for the 4-chlorobenzyloxy series.

Therefore, a simpler two-phase reaction was implemented. 1-Boc-3-phenyl-3-azetidinol and a catalytic amount of tetrabutylammonium bromide were dissolved in dichloromethane and freshly prepared 4N sodium hydroxide solution. The corresponding benzyl bromide was added and the reaction refluxed at 35 °C overnight.

\[ \text{Scheme 5: Formation of } N\text{-Boc-3-aryl-3-arylmethoxyazetidine} \]

Once a procedure was determined optimization of the reagents was completed. It was determined that three equivalents of benzylbromide was sufficient for complete conversion of \( N\text{-Boc-3-aryl-3-azetidinol} \) to \( N\text{-Boc-3-aryl-3-arylmethoxyazetidine} \).

This procedure was mild, with quantitative results after column chromatography. Side products of this reaction identified by \(^1\text{H} \) NMR were excess benzyl bromide and
corresponding benzyl alcohol. With no unreacted azetidinol observed, the need for column chromatography was eliminated. All azetidinols were reacted with benzylbromide to give compounds 35a-h seen in Figure 9.

![Chemical structures](image)

**Figure 9:** 3-Aryl-3-phenylmethoxy analogs

Substitution on benzylbromide in the form of 4-halo or 3,4-dihalobenzylbromide allows for numerous analogs to be synthesized. Compounds 36a-m (Figure 10) were synthesized using 4-choro, 4-fluoro 2-fluoro or 4-trifluoromethane benzylbromide. Compounds 37a-n (Figure 11) were synthesized 3,4-dichloro, 3,4-difluoro, 2,4-bis(trifluoromethane) or 3,5-bis(trifluoromethane).
Figure 10: Substituted benzyl ether azetidine analogs
Figure 11: Di-substituted benzyl ether azetidine analogs
2.1.3 Optimization for Formation of N-Methyl Azetidine

Only one procedure for this reaction was implemented with good results. Utilizing lithium aluminum hydride (LAH) for the reduction of the Boc carbonyl to a methyl group is standard. Work-ups when handling lithium aluminum hydride, however, can be problematic and therefore two different work-ups were attempted. The traditional Fieser work-up and a work up employing Glauber’s salt were completed. The Fieser work up was completed by cooling the reaction to 0°C then slowly adding X mL deionized water, X mL 15% NaOH, three times X mL deionized water in successive order where X is the grams of lithium aluminum hydride used.81

Glauber’s salt (Na₂SO₄ • H₂O) is made by recrystallization of anhydrous sodium sulfate in deionized water. For use of Glauber’s salt the reaction was also cooled to 0°C and
Glauber’s salt was slowly added until release of hydrogen is complete. This addition could take upwards of 2 hours to complete. Though the Glauber's salt work-up takes longer to complete, formation of product was double in comparison to the traditional Fieser work-up, 30% to 15% yield comparatively.

Each $N$-Boc-3-aryl-3-arylmethoxazetidine compound 35a-h, 36a-j, and 37a-n were reduced using LAH followed by work-up with Glauber's salt to yield $N$-methyl-3-aryl-3-arylmethoxazetidine compounds 31a-ii in 4-66% yield.
2.1.4 Optimization of Formation of 3-Aryl-3-arylmethoxyazetidine

Removal of the Boc group was the trickiest part of the synthesis. Several methods were attempted before a high yielding reproducible procedure was achieved. The first attempt was completed by using 50% trifluoroacetic acid and 50% dichloromethane. However, in this case the azetidine decomposed. This procedure was repeated multiple times using shorter reaction times and lower reaction temperatures. However, the same results were observed, and no azetidine was isolated.
A milder procedure using bismuth trichloride was attempted to remove the Boc protecting group. \(N\)-Boc-3-phenyl-3-phenylmethoxyazetidine was dissolved in 50:1 acetonitrile/water and \(\text{BiCl}_3\) was added.\(^{84}\) The reaction was heated to 55°C under nitrogen and stirred for 1 hour before a second dose of \(\text{BiCl}_3\) was added. The mixture was then stirred at 55°C overnight. After column chromatography using 25:5:70 EtoAc:NH\(_4\)OH:Hexanes the intended product was identified by \(^1\)H NMR.\(^{84}\) This reaction went to completion for small reactions, under 50 mg, with 20-25% yield. However, larger reactions needed longer run times, in excess of 48 hours, for the reaction to go to completion and the percent yield was lowered to 9%. With a minimum of 50 mg of final product needed for characterization and biological testing this reaction was deemed unfeasible due to length of run time and poor yield.
The best method found, using 2M hydrochloric acid in ethyl acetate, is a modification of a synthesis by Gibson et al. In each deprotection the acid solution was freshly made (no more than 5 days old) *in situ* by adding 95% ethanol (1.5 equivalents) and acetyl chloride (1 equivalent) to dry ethyl acetate under nitrogen. The reaction was stirred at 0°C for 2 hours and the solution was stored in the refrigerator for up to five days. Adding an excess of the prepared acid solution to *N*-boc-3-aryl-3-arylmethoxyazetidine afforded the product as a hydrochloric salt in good yield within three hours. This method gave the best results (65% yield) while eliminating the need for more steps to make a solid as would have been necessary for the other attempted deprotections.
Scheme 9: Deprotection of N-Boc using 2M HCl/EtOAc

Each N-Boc-3-aryl-3-arylmethoxazetidine compound 35a-h, 36a-j, and 37a-n were deprotected using excess 2M HCl/EtOAc to yield 3-aryl-3-arylmethoxazetidine compounds 30a-ii in 8-69% yield.
2.1.5 Forward Synthesis and Crystallographic Representation

The overall forward synthesis for the preparation of 3-aryl-3-arylmethoxyazetidine is seen in Scheme 10 combining the above optimized reactions.

Scheme 10: Synthetic route for the synthesis of 3-aryl-3-arylmethoxyazetidine and N-methyl-3-aryl-3-arylmethoxyazetidine analogs
Crystallographic data for 3-phenyl-3-phenylmethoxyazetidine (30a) was obtained to confirm the structure (Figure 12). The structure was confirmed unequivocally and the synthetic scheme was validated. 

Figure 12: X-ray structure of 3-phenyl-3-phenylmethoxyazetidine (30a) provided courtesy of Prof. Edwin Stevens.
2.2 Binding Affinity

Drugs were evaluated for their potency by the value of their binding affinity to their respective transporter. This was completed by competitive inhibition against a known radiolabeled ligand. These ligands characteristically have high binding affinity for the targeted transporter. Binding studies completed for our synthesized molecules utilized \([^3H]\text{WIN-35,428 (26)}\) and \([^3H]\text{citalopram (21)}\) for respective dopamine and serotonin transporters.

Binding values are typically expressed in terms of IC_{50} or \(K_i\). IC_{50} is the concentration at which the compound is needed to displace 50% of the bound radiolabeled ligand. \(K_i\) is the inhibition constant and is directly related to IC_{50} by the Chen-Pursoff equation.\(^{86}\)

\[
K_i = \frac{IC_{50}}{[^3H]/K_d + 1}
\]
$[^3]H$ is the concentration of radiolabeled ligand use and $K_d$ is the previously determined dissociation constant of the radiolabeled ligand. Several factors effect the IC$_{50}$ value including the type and amount of radiolabeled ligand used, the state of the tissue used, the incubation time, buffer and protein content. Due to the variety of factors $K_i$ offers a better comparison of data because it takes into account $[^3]H$ and $K_d$. $K_i$ is also normally reported as an average over multiple trials to eliminate outlying data.$^{86}$

### 2.3 Binding Affinities of 3-Aryl-3-arylmethoxyazetidine and N-Methyl-3-aryl-3-arylmethoxy Analogs

Each final compound was characterized either has a hydrochloric salt or in the case of non-salt formation the product was freebased and the oxalate salt was formed. Salts were evaluated for biological binding affinity at multiple monoaminergic transporters.

The transporter binding affinities were determined for some of the 3-aryl-3-arylmethoxyazetidine (30a-i) and N-methyl-3-aryl-3-arylmethoxyazetidine (31a-i) analogs and are presented in Table 2. The binding affinity values were obtained by the ability of the tested compounds to displace bound radiolabeled ligands from rat caudate tissue. The $K_i$ values reported in Table 2 are the inhibition constants derived from the unlabeled ligands. The binding affinities of the novel azetidine analogs were determined at the dopamine and serotonin transporters by the inhibition of $[^3]H$WIN–35,428 and $[^3]H$citalopram, respectively.$^{77}$
Table 2: Monoamine transporter affinity and selectivity

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<th>X</th>
<th>Y</th>
<th>R</th>
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<th>DAT $K_i$ (nM)$^b$</th>
<th>DAT/SERT</th>
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<td></td>
<td></td>
<td></td>
<td>32 ± 5</td>
<td>388 ± 211</td>
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<td>H</td>
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<td>H</td>
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<td>73.0 ± 9.4</td>
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$^a$Compounds tested as hydrochloric salt unless otherwise noted.
$^b$All values are mean ± SEM of three experiments performed.
$^c$Compound tested as oxalate salt.

In general compounds with $N$-methyl substitutions were found to have higher binding affinity at both dopaminergic and serotonergic systems and the corresponding unsubstituted analogs. The outliers with this conclusion are 31b, 31e, and 31h. Both 30e and 30h show a two times higher binding affinity for serotonin for the $N$-H versus its $N$-methyl substituted counterpart, while 31b has a slightly lower dopamine binding affinity than 31b.$^{77}$
The dichloro substituted analogs 30e and 30h were the most potent azetidines at SERT having binding affinities of $K_i = 3.5\text{nM}$ and $K_i = 2.9\text{nM}$ respectively. All compounds demonstrate a higher selectivity for the serotonergic system over the dopaminergic system exhibiting nanomolar affinity for serotonin and micromolar affinity for dopamine. 3,4-dichloronated analog 31c demonstrated the highest serotonin selectivity (1210 SERT/DAT) as well as binding affinity at serotonin ($K_i = 1.0\text{nM}$).\textsuperscript{77}

Binding studies revealed that compounds with the 3,4-dichlorophenyl group attached as the 3-aryl substituent had increased dopaminergic binding affinity and a decreased serotonin selectivity. If the 3-arylmethoxy moiety contained a chloro substituent then the dopamine binding affinity decreased and the serotonin affinity dominated. Conversely, if the 3-arylmethoxy ligand contained the 3,4-dichloro substituent then the analog exhibited high serotonergic affinity. When both aryl groups contained 3,4-dichloro substituents little improvement of serotonin affinity or selectivity was seen.\textsuperscript{77}

Of the 3-aryl-3-arylmethoxyazetidines tested, compound 31g proved to be most similar to a dual re-uptake inhibitor. $N$-methyl-3-(3,4-dichlorophenyl)-3-phenylazetidine exhibited a profile that closely approached that of a DUI with a DAT/SERT selectivity of 27 while maintaining nanomolar affinity for both transporters. Although 31g was serotonin selective, the moderate dopamine affinity is promising.\textsuperscript{77}

These trends were consistent with those seen in the 3-aryl-3-arylmethoxytropane series. It is clear from the preliminary binding affinity data that substitution on the aryl rings might lead to a potent DAT/SERT dual re-uptake inhibitor for METH addiction.\textsuperscript{77}
Following trends of the synthesized tropanes numerous analogs were also synthesized for biological trends. Table 3 lists synthesized compounds 30j-ii and 31j-ii, which are awaiting biological testing of dopaminergic and serotonergic binding affinities. 77

Table 3: Synthesized compounds

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Conclusion

A novel series of N-methyl and N-H 3-aryl-3-arylmethoxyazetidine analogs were synthesized and evaluated at dopamine and serotonin transporter ligands. The \textit{in vitro} binding affinity for the dopamine and serotonin transporters were determined by competitive inhibition against radiolabeled ligands [\textsuperscript{3}H]WIN-35,428 and [\textsuperscript{3}H]citalopram respectively in rat brain tissue. The results of the binding study clearly demonstrate that the tested 3-aryl-3-arylmethoxyazetidine analogs were selective for the serotonin over the dopaminergic system. The N-methyl compounds (31) were generally found to exhibit a higher binding affinity and potency than their N-H companions (30). N-methyl-3-(3,4-dichlorophenyl)-3-phenylmethoxyazetidine (31c) had the highest potency and selectivity for serotonin of the tested series with a binding affinity of $K_i = 1.0\text{nM}$, and a serotonin dopamine ratio of 1210.

It was analog 31g, N-methyl-3-(3,4-dichlorophenyl)-3-phenylazetidine, that was shown to be most similar to a dual re-uptake inhibitor with a dopamine/serotonin selectivity of 27 and nanomolar affinity at both dopamine and serotonin receptors $K_i = 620\text{nM}$ and $K_i = 23\text{nM}$ respectively. Overall, this initial investigation suggested that the chloro-subsituted aryl rings are a key structural feature for improved serotonin and dopamine binding affinity.

Though structurally similar to its predecessor 3-aryl-3-arylmethoxytropane, the 3-aryl-3-arylmethoxyazetidine analogs display vastly different binding affinities to both the dopaminergic and serotonergic systems. While both follow a similar trend, it appears the decreased bioavailability of the azetidine system contributes to decreased potency at both
serotonergic and dopaminergic transporters. Because the 3-aryl-3-arylmethoxyazetidine analogs still demonstrated nanomolar affinity for both dopamine and serotonin it is still a viable scaffold for further testing.

The remaining compounds synthesized in this study are in various stages of biological evaluation. The potency and selectivity that will be determined for these compounds will provide direction for further studies with this novel 3-aryl-3-arylmethoxyazetidine scaffold.
Experimental Section

General Information

Chemicals were purchased from Sigma-Aldrich Chemical Co., Oakwood Products Inc., and VWR International LLC and used as received or otherwise noted. Anhydrous solvents were purchased from EMD Millipore and were used under nitrogen without any further purification. Chromatography refers to column chromatography on silica gel (Silica Gel 60Å, 230-400 mesh). Reported melting points are uncorrected. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in DMSO-d$_6$. $^1$H NMR chemical shifts are reported as $\delta$ values (ppm) relative to tetramethylsilane. $^{13}$C NMR chemical shifts are reported as $\delta$ values (ppm) relative to DMSO-d$_6$ (39.5 ppm). Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

Solvent acronyms – Tetrahydrofuran (THF), Dichloromethane (DCM), Deionized water (DI).

General Procedure A: Preparation of 1-Boc-3-arylazetidin-3-ols (34b-h)

Halogenated bromobenzene (3 equiv.) was dissolved in anhydrous THF and cooled to -78 °C for 10 minutes. n-butyllithium (2.5M, 3 equiv.) was added and the reaction stirred for 1 hour under nitrogen. 1-Boc-3-azetidinone (1 equiv.) was dissolved in anhydrous THF, and added via syringe to the reaction. The mixture was stirred overnight to room
temperature. The reaction was quenched with 10% NH₄Cl, extracted with diethyl ether (3 x 15 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 34b-h.

**General Procedure B: Preparation 3-Aryl-3-arylmethoxyazetidine hydrochloride**

The azetidinols (34a-h) (1 equiv.) and tetrabutylammonium bromide (25 mg) were dissolved in DCM and freshly prepared 4N NaOH (5 mL DCM:6 mL NaOH per 0.1g of azetidinol). The corresponding benzyl bromide was added (3 equiv.) and the reaction was heated to 35 °C overnight. The reaction was extracted with DCM (3 x 15 mL), washed with brine, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was dried on high vacuum for 1h then placed under nitrogen. Excess 2M HCl/EtOAc was added and the mixture was stirred at room temperature for 3-6h. The white precipitant was filtered and triturated in diethyl ether to afford the 3-aryl-3-arylmethoxyazetidines, 30a, 30d-z, 30bb-ii as hydrochloric salts.
General Procedure C: Preparation of N-methyl-3-aryl-3-arylmethoxyazetidine

The azetidinols (34a-h) (1 equiv.) and tetrabutylammonium bromide (25 mg) were dissolved in DCM and freshly prepared 4N NaOH (5 mL DCM: 6 mL NaOH per 0.1 g of azetidinol). The corresponding benzyl bromide was added (3 equiv.) and the reaction was heated to 35 °C overnight. The reaction was extracted with DCM, washed with brine, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. Crude benzyl ether derivatives were placed on high vacuum for 1h then placed under nitrogen. THF (10 mL) was added and the reaction cooled to 0 °C. Lithium aluminum hydride (LAH) in THF (1M, 5 equiv.) was slowly added and the reaction was refluxed at 65 °C for 14h. The reaction was cooled to 0 °C, quenched with Glauber's salt and stirred for an additional hour. The aluminum salts were filtered and the filtrate was concentrated under reduced pressure. Excess 2M HCl/EtOAc was added and the mixture stirred under nitrogen for 2h. The solvent was removed under reduced pressure, and the residue was triturated in diethyl ether to afford the pure N-methyl azetidines, 31a-j, 31m-n, 31p, 31u, 31w, 31bb-cc, and 31ff as the hydrochloric salts.

General Procedure D: Formation of Oxalic Salts

In the event that the hydrochloric salts were not formed in either General Procedures B or C, the crude 1-methyl-3-aryl-4arylmethoxyazetidine or 3-aryl-3-arylmethoxyazetidine was dissolved in DCM (10 mL). Saturated NaHCO₃ solution (10 mL),
and a minimal amount of NH₄OH to achieve a pH of 11 was added. The mixture was then extracted with DCM (3 x 15 mL), washed with brine (15 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the remaining oil was dissolved in a minimal amount of diethyl ether. Oxalic acid (1.1 equiv.) was separately dissolved in a minimal amount of diethyl ether then slowly pipetted into the azetidine solution. The oxalate salts were immediately formed and collected by vacuum filtration.

1-Boc-3-phenyl-3-azetidinol (34a)

1-Boc-3-azetidinone (1 equiv) was dissolved in anhydrous THF under nitrogen, and cooled to -78 °C for 10 minutes. Phenyllithium (2M in THF, 3 equiv.) was slowly added and the mixture allowed to warm to room temperature over night. The reaction was quenched with 30 mL 10% NH₄Cl solution. The aqueous layer was extracted with Et₂O (3 x 15 mL), washed with brine (15 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purified by column chromatography (30% EtOAc / Hexanes) to afford the product (34a) as a pale yellow solid (94%). MP 85.3-87.8 °C; ¹H NMR (400MHz, CDCl₃): δ 7.49(d, J = 8 Hz, 2H), 7.42-7.38(m, 2H), 7.33-7.30(m, 1H), 4.27(d, J = 9.2 Hz, 2H), 4.16(d, J = 9.2 Hz, 2H), 1.46(s, 9H).
1-Boc-3-(4-chlorophenyl)-3-azetidinol (34b)

General Procedure A. The azetidinol was obtained as a pale yellow solid (86%) mp 139.0-140.6 °C; $^1$H NMR (400MHz, CDCl$_3$): δ 7.4-7.38(m, 2H), 7.28(d, $J$ = 8.8 Hz, 2H), 4.63(s, 1H), 4.13-4.05(m, 4H), 1.39(s, 9H).

1-Boc-3-(3,4-dichlorophenyl)-azetidinol (34c)

General Procedure A. The azetidinol was obtained as a colorless oil (91%) $^1$H NMR (400MHz, CDCl$_3$): δ 7.60(d, $J$ = 2.0 Hz, 1H), 7.41(d, $J$ = 8.4 Hz, 1H), 7.33-7.30(m, 1H), 4.56(s, 1H), 4.12(dd, $J$ = 9.2 Hz, $J$ = 21.6 Hz, 4H), 1.42(s, 9H).

1-Boc-3-(4-fluorophenyl)-3-azetidinol (34d)

General Procedure A. The azetidinol was obtained as a pale yellow solid (64%); mp 90.8 - 92.8 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.46 – 7.34 (m, 2H), 7.04 – 6.88 (m, 2H), 4.81 (s, 1H), 4.08 (t, $J$ = 5.8 Hz, 4H), 1.44 – 1.31 (m, 9H).

1-Boc-3-(3,4-difluorophenyl)-3-azetidinol (34e)

General Procedure A. The azetidinol was obtained as a yellow oil (31%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.20 – 7.03 (m, 3H), 4.40 (d, $J$ = 9.6 Hz, 2H), 4.15 (d, $J$ = 9.2 Hz, 2H), 1.42 (s, 9H).
1-Boc-3-(4-(trifluoromethyl)phenyl)-3-azetidinol (34f)

General Procedure A. The azetidinol was obtained as a white solid (42%); mp 147.0-147.8 oC; 1H NMR (400 MHz, CDCl3) δ 7.63 (d, J = 4.6 Hz, 4H), 4.18 (s, 4H), 1.43 (s, 9H).

1-Boc-3-(2,4-bis(trifluoromethyl)phenyl)-3-azetidinol (34g)

General Procedure A. The azetidinol was obtained as a dark orange solid (46%); mp 133.3-135.2 oC; 1H NMR (400 MHz, CDCl3) δ 7.98 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 4.48 (d, J = 9.7 Hz, 2H), 4.22 (d, J = 9.8 Hz, 2H), 3.19 (s, 1H), 1.44 (s, 9H).

1-Boc-3-(3,5-bis(trifluoromethyl)phenyl)-3-azetidinol (34h)

General Procedure A. The azetidinol was obtained as a dark orange solid (69%); mp 119.5-119.9 oC; 1H NMR (400 MHz, CDCl3) δ 8.01 (s, 2H), 7.84 (s, 1H), 4.22 (s, 4H), 3.10 (s, 1H), 1.48 (s, 9H).

3-Phenyl-3-phenylmethoxyazetidine hydrochloride (30a, ANT-35)

General Procedure B. The azetidine was obtained as a white solid (35%); mp 153.3-155.2 oC; 1H NMR (400 MHz, DMSO-d6): δ 7.49-7.48(m, 4H), 7.27-7.31(m, 6H), 4.37(d, J = 11.6 Hz, 2H), 4.26 (d, J = 11.6 Hz, 2H), 4.12(s, 2H); 13C NMR (100 MHz, DMSO-d6): δ 138.4, 138.0,
129.4, 128.9, 128.3, 127.1, 79.0, 66.1, 55.7. Anal. Calcd. for C\textsubscript{16}H\textsubscript{17}NO\textsubscript{•}HCl: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.42; H, 6.59; N, 5.15.

3-Phenyl-3-(4-chlorophenyl)methoxyazetidine oxalate (30b, ANT-74)

General Procedures B and D. The azetidine was obtained as a white solid (22%); mp 207.3-208.9 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-\textsubscript{d}\textsubscript{6}): \(\delta\) 7.48-7.30(m, 9H), 4.42-4.31(m, 4H), 4.10(s, 2H); \textsuperscript{13}C NMR (100 MHz, DMSO-\textsubscript{d}\textsubscript{6}): \(\delta\) 162.9, 138.3, 137.1, 134.6, 132.7, 131.1, 130.1, 129.4, 129.3, 128.8, 127.2, 77.2, 65.3, 62.7, 57.9. Anal. Calcd. for C\textsubscript{16}H\textsubscript{16}ClNO\textsubscript{•}C\textsubscript{2}H\textsubscript{2}O\textsubscript{4}: C, 59.43; H, 4.99; N, 3.85. Found: C, 59.11; H, 5.17; N, 3.62.

3-Phenyl-3-(3,4-dichlorophenyl)methoxyazetidine oxalate (30c, ANT-57)

General Procedures B and D. The azetidine was obtained as a white solid (29%); mp 179.3-181.4 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-\textsubscript{d}\textsubscript{6}): \(\delta\) 7.62-7.92(m, 8H), 4.43(d, \(J = 11.2\) Hz, 2H), 4.31(d, \(J = 11.2\) Hz, 2H), 4.16(s, 2H); \textsuperscript{13}C NMR (100 MHz, DMSO-\textsubscript{d}\textsubscript{6}): \(\delta\) 163.3, 139.6, 139.2, 131.0, 130.6, 129.8, 129.4, 129.3, 129.1, 128.3, 127.1, 77.3, 64.6, 63.3, 58.6. Anal. Calcd. for C\textsubscript{16}H\textsubscript{15}Cl\textsubscript{2}NO\textsubscript{•}C\textsubscript{2}H\textsubscript{2}O\textsubscript{4}•H\textsubscript{2}O: C, 41.83; H, 4.39; N, 2.44. Found: C, 41.77; H, 4.30; N, 2.21.
3-(4-Chlorophenyl)-3-phenylmethoxyazetidine hydrochloride (30d, ANT-129)

General Procedures B. The azetidine was obtained as a white solid (41%); mp 210.3-211.2°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.56-7.51 (m, 4H), 7.31-7.23 (m, 5H), 4.34 (d, \(J = 12.0\) Hz, 2H), 4.22 (d, \(J = 12.0\) Hz, 2H), 4.14 (s, 2H); \(^1^3\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 137.9, 137.5, 134.1, 19.4, 129.2, 128.8, 128.3, 128.3, 78.4, 66.1, 55.4. Anal. Calcd. for C\(_{16}\)H\(_{16}\)ClNO•HCl: C, 61.95; H, 5.52; N, 4.52. Found: C, 61.28; H, 5.76; N, 4.46.

3-(4-Chlorophenyl)-3-(4-chlorophenyl)methoxyazetidine hydrochloride (30e, ANT-87)

General Procedure B. The azetidine was obtained as a white solid (44%); mp 171.5-173.4°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.53 (t, \(J = 10.4\) Hz, 4H), 7.39-7.33 (m, 4H), 4.35 (d, \(J = 11.6\) Hz, 2H), 4.25 (d, \(J = 11.2\) Hz, 2H), 4.14 (s, 2H); \(^1^3\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 155.3, 137.4, 137.0, 134.2, 132.8, 130.1, 129.4, 129.2, 128.8, 78.6, 65.3, 55.6. Anal. Calcd. for C\(_{16}\)H\(_{15}\)Cl\(_2\)NO•HCl: C, 55.76; H, 4.68; N, 4.06. Found: C, 55.4; H, 4.87; N, 3.91.

3-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)methoxyazetidine hydrochloride (30f, ANT-92)

General Procedure B. The azetidine was obtained as a white solid (65%); mp 197.7-199.4°C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.63 (s, 1H), 7.58-7.49 (m, 5H), 7.31 (d, \(J = 8.4\) Hz 1H), 4.35 (d, \(J = 11.6\) Hz, 2H), 4.26 (d, \(J = 11.6\) Hz, 2H), 4.16 (s, 2H); \(^1^3\)C NMR (100 MHz, DMSO-
d_6): \( \delta 139.3, 137.2, 134.3, 131.6, 131.0, 130.7, 130.1, 129.4, 129.2, 128.4, 78.8, 64.7, 55.5 \).

Anal. Calcd. for C_{16}H_{14}Cl_3NO•HCl: C, 50.69; H, 3.99; N, 3.69. Found: C, 50.11; H, 3.97; N, 3.54.

**3-(3,4-Dichlorophenyl)-3-phenylmethoxyazetidine hydrochloride (30g, ANT-110)**

General Procedure B. The azetidine was obtained as a white solid (46%); mp 184.6-186.1 °C; \(^1\)H NMR (400 MHz, DMSO-d_6): \( \delta 7.79(s, 1H), 7.28(s, 5H), 7.70(s, 1H), 7.48(s, 1H), 4.50-4.11(m, 6H); \(^{13}\)C NMR (100 MHz, DMSO-d_6): \( \delta 139.6, 137.7, 132.2, 131.6, 129.6, 128.9, 128.4, 127.7, 78.1, 66.4, 55.4 \). Anal. Calcd. for C_{16}H_{15}Cl_2NO•HCl•H_2O: C, 52.99; H, 5.00; N, 3.86. Found: C, 52.89 H, 5.23; N, 3.82.

**3-(3,4-Dichlorophenyl)-3-(4-chlorophenyl)methoxyazetidine hydrochloride (30h, ANT-126)**

General Procedure B. The azetidine was obtained as a white solid (28%); mp 148.2-149.8 °C; \(^1\)H NMR (400 MHz, DMSO-d_6): \( \delta 7.81(s, 1H), 7.72(d, J = 8.4 Hz, 1H), 7.48 (dd, J = 6.0 Hz, J = 2.4 Hz, 1H), 7.33(s, 4H), 4.38(d, J = 12.0 Hz, 2H), 4.25(d, J = 12.0 Hz, 2H), 4.18(s, 2H); \(^{13}\)C NMR (100 MHz, DMSO-d_6): \( \delta 139.4, 136.9, 132.9, 132.2, 131.6, 130.1, 129.6, 128.8, 127.6, 78.3, 65.5, 55.9, 55.4 \). Anal. Calcd. for C_{16}H_{14}Cl_3NO•HCl•H_2O: C, 48.39; H, 4.31; N, 3.51. Found: C, 48.17 H, 4.26; N, 3.51.
3-(3,4-Dichlorophenyl)-3-(3,4-dichlorophenyl)methoxyazetidine hydrochloride (30i, ANT-108).

General Procedure B. The azetidine was obtained as a white solid (62%); mp 196.7-197.6 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.79(s, 1H), 7.71(d, \(J = 8.4\) Hz, 1H), 7.61 (s, 1H), 7.55(d, \(J = 8.4\) Hz, 1H), 7.47(d, \(J = 8.0\) Hz, 1H), 7.31(d, \(J = 8.4\) Hz, 1H), 4.38 (d, \(J = \)12.0 Hz, 2H), 4.26 (d, \(J = 11.6\) Hz, 2H), 4.20(s, 2H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 139.2, 139.1, 131.6, 131.5, 130.9, 130.7, 130.1, 129.6, 128.5, 127.6, 78.4, 64.9, 55.3. Anal. Calcd. for C\(_{16}\)H\(_{13}\)Cl\(_4\)NO•HCl: C, 46.47; H, 3.41; N, 3.39. Found: C, 46.18 H, 3.58; N, 3.34.

3-Phenyl-3-(4-fluorophenyl)methoxyazetidine hydrochloride (30j, ANT-159)

General Procedure B. The azetidine was obtained as a pale yellow solid (25%); mp 157.8-159.3 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.54 – 7.32 (m, 7H), 7.14 (t, \(J = 8.9\) Hz, 2H), 4.35 (d, \(J = 11.8\) Hz, 2H), 4.25 (d, \(J = 11.8\) Hz, 2H), 4.12 (s, 2H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 163.5, 161.1, 138.5, 134.3, 130.5, 130.4, 129.5, 127.1, 115.8, 115.6, 79.0, 75.8, 65.4, 55.5. Anal. Calcd. for C\(_{16}\)H\(_{16}\)NOF•HCl: C, 65.42; H, 5.83; N, 4.77. Found: C, 65.22; H, 5.94; N, 4.66.

3-Phenyl-3-(2-fluorophenyl)methoxyazetidine hydrochloride (30k, ANT-140)

General Procedure B. The azetidine was obtained as a white solid (24%); mp 160.0-162.1 °C; \(^1\)H NMR (400 MHz, D\(_2\)O) \(\delta\) 7.39 – 7.26 (m, 5H), 7.20 (dd, \(J = 15.3\) Hz, \(J = 7.5\) Hz, 1H), 7.08 (dd, \(J = 8.2\) Hz, \(J = 6.7\) Hz, 1H), 7.04 – 6.87 (m, 2H), 4.45 (d, \(J = 12.3\) Hz, 2H), 4.25 (d, \(J = 12.3\) Hz, 2H), 4.09 (d, \(J = 12.3\) Hz, 2H).
2H), 4.02 (s, 2H). $^{13}$C NMR (100 MHz, D$_2$O) $\delta$ 162.2, 159.8, 136.3, 123.2, 115.6, 115.4, 79.2, 60.8, 60.7, 55.8, 23.3, 19.3, 13.00. Anal. Calcd. for C$_{16}$H$_{16}$NO$_2$•HCl: C, 65.42; H, 5.83; N, 4.77. Found: C, 65.39; H, 5.8; N, 4.72.

**3-Phenyl-3-(3,4-difluorophenyl)methoxyazetidine hydrochloride (30l, ANT-141)**

General Procedure B. The azetidine was obtained as a white solid (24%); mp 105.4-108.3 $^\circ$C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.46 (t, $J = 8.2$ Hz, 5H), 7.42 (d, $J = 5.2$ Hz, 1H), 7.39 – 7.31 (m, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 4.38 (d, $J = 12.0$ Hz, 2H), 4.27 (d, $J = 12.0$ Hz, 2H), 4.12 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 191.2, 155.3, 138.2, 129.6, 129.5, 127.1, 125.0, 118.0, 117.8, 117.4, 117.3, 79.3, 64.9. Anal. Calcd. for C$_{16}$H$_{15}$F$_2$NO•HCl: C, 61.49; H, 5.17; N, 4.49. Found: C, 61.29; H, 5.5; N, 4.22.

**3-(4-Fluorophenyl)-3-phenylmethoxyazetidine hydrochloride (30m, ANT-148)**

General Procedure B. The azetidine was obtained as a white solid (32%); mp 184.7-186.4 $^\circ$C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.62 – 7.54 (m, 2H), 7.35 – 7.23 (m, 7H), 4.34 (d, $J = 11.6$ Hz, 2H), 4.25 (d, $J = 11.5$ Hz, 2H), 4.14 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 164.0, 161.6, 138.0, 135.0, 129.6, 129.6, 128.9, 128.4, 128.3, 116.4, 116.2, 78.5, 75.8, 66.1, 55.5. Anal. Calcd. for C$_{16}$H$_{16}$FNO•HCl: C, 65.44; H, 5.83; N, 4.77. Found: C, 65.72; H, 6.04; N, 4.56.
3-(4-Fluorophenyl)-3-(2-fluorophenyl)methoxyazetidine hydrochloride (30o, ANT-160)

General Procedure B. The azetidine was obtained as a white solid (25%); mp 154.3-156.2 °C; 1H NMR (400 MHz, DMSO-d$_6$) δ 7.57 (dd, $J = 7.3$ Hz, $J = 5.5$ Hz, 2H), 7.49 (t, $J = 7.2$ Hz, 1H), 7.32 (dd, $J = 17.5$ Hz, $J = 8.7$ Hz, 3H), 7.22 - 7.09 (m, 2H), 4.34 (d, $J = 11.2$ Hz, 2H), 4.25 (d, $J = 11.0$ Hz, 2H), 4.18 (s, 2H). 13C NMR (100 MHz, DMSO-d$_6$) δ 164.0, 161.9, 161.6, 159.5, 134.7, 131.2, 130.7, 129.7, 129.6, 124.8, 116.4, 116.1, 115.9, 115.7, 78.6, 60.1, 55.5 Anal. Calcd. for C$_{16}$H$_{15}$F$_2$NO•HCl: C, 61.64; H, 5.17; N, 4.49. Found: C, 61.55; H, 5.23; N, 4.33.

3-(4-Fluorophenyl)-3-(4-fluorophenyl)methoxyazetidine hydrochloride (30n, ANT-149)

General Procedure B. The azetidine was obtained as a white solid (46%); mp 174.5-176.1 °C; 1H NMR (400 MHz, DMSO-d$_6$) δ 7.61 – 7.52 (m, 2H), 7.34 – 7.114 (m, 2H), 7.13 (dd, $J = 12.3$ Hz, $J = 5.4$ Hz, 2H), 4.34 (d, $J = 11.3$ Hz, 2H), 4.25 (d, $J = 11.3$ Hz, 2H), 4.12 (s, 2H). 13C NMR (100 MHz, DMSO-d$_6$) δ 164.0, 163.5, 161.6, 161.1, 134.9, 134.3, 134.3, 130.5, 129.5, 116.2, 115.6, 78.6, 65.4, 55.5. Anal. Calcd. for C$_{16}$H$_{15}$F$_2$NO•HCl: C, 61.64; H, 5.17; N, 4.49. Found: C, 61.42; H, 5.24; N, 4.36.

3-(4-Fluorophenyl)-3-(3,4-difluorophenyl)methoxyazetidine hydrochloride (30p, ANT-161)

General Procedure B. The azetidine was obtained as a lime green solid (31%); mp 182.2-184.3 °C; 1H NMR (400 MHz, DMSO-d$_6$) δ 9.80 (s, 2H), 7.60 – 7.42 (m, 3H), 7.33 – 7.28 (m,
3H), 7.17 (s, 1H), 4.35 (d, J = 11.4 Hz, 2H), 4.26 (d, J = 11.4 Hz, 2H), 4.14 (s, 2H). 13C NMR (100 MHz, DMSO-d_6) δ 164.1, 161.6, 136.0, 134.7, 129.6, 129.6, 125.0, 118.0, 117.8, 117.5, 117.3, 116.4, 116.2, 78.8, 64.9, 55.5. Anal. Calcd. for C_{16}H_{14}F_{3}NO•HCl: C, 58.28; H, 4.59; N, 4.25. Found: C, 58.22; H, 4.64; N, 4.66.

3-(3,4-Difluorophenyl)-3-phenylmethoxyazetidine hydrochloride (30q, ANT-212)

General Procedure B. The azetidine was obtained as a white solid (44%); mp 185.2-186.0 °C; 1H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 9.71 (s, 1H) 7.69 (dd, J = 13.6 Hz, J = 5.6 Hz, 1H), 7.56 (dt, J = 19.2 Hz, 5.5 Hz, 1H), 7.40 (d, J = 7.6, 1H), 7.33-7.27 (m, 5H), 4.36 (d, J = 11.2, 2H), 4.25 (d, J = 12.2 Hz, 2H), 4.19 (s, 2H). 13C NMR (100 MHz, DMSO-d_6) δ 155.3, 151.3, 148.9, 137.9, 136.6, 128.9, 128.4, 124.5, 118.5, 117.0, 78.2, 66.3, 55.4. Anal. Calcd. for C_{16}H_{15}F_{2}NO•HCl: C, 61.64; H, 5.17; N, 4.49. Found: C, 61.39; H, 5.32; N, 4.37.

3-(3,4-Difluorophenyl)-3-(4-fluorophenyl)methoxyazetidine hydrochloride (30r, ANT-170)

General Procedure B. The azetidine was obtained as a white solid (26%); mp 202.8-204.0 °C; 1H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 2H), 7.53 (dd, J = 7.5 Hz, J = 2.7 Hz, 1H), 7.42 - 7.30 (m, 4H), 7.13 (dd, J = 12.3 Hz, J = 5.4 Hz, 2H), 4.48 (d, J = 12.0 Hz, 2H), 4.31 (d, J = 12.3 Hz, 2H), 4.21 (s, 2H). 13C NMR (100 MHz, DMSO-d_6) δ 161.1, 134.1, 130.6, 130.5, 125.7, 125.1, 119.4, 119.3, 115.3, 115.5, 76.9, 65.7, 55.4. Anal. Calcd. for C_{16}H_{17}F_{3}NO•HCl•½ H_2O: C, 56.72; H, 4.46; N, 4.13. Found: C, 56.89; H, 4.57; N, 4.00.
3-(3,4-Difluorophenyl)-3-(2-fluorophenyl) methoxyazetidine hydrochloride (30s, ANT-171)

General Procedure B. The azetidine was obtained as a white solid (4%); mp 185.9-187.7 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.83 (s, 2H), 7.53 (dd, $J = 17.4$ Hz, $J = 8.5$ Hz, 1H), 7.47 – 7.37 
(m, 2H), 7.37 – 7.28 (m, 2H), 7.13 (dt, $J = 14.7$ Hz, 8.0 Hz, 2H), 4.48 (d, $J = 12.1$ Hz, 2H), 4.31 
(d, $J = 12.3$ Hz, 2H), 4.27 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 161.9, 159.5, 131.3, 130.8, 
127.4, 125.6, 125.2, 125.0, 124.7, 124.6, 119.5, 119.3, 115.9, 115.7, 76.9, 60.4, 55.20. Anal. 
Calcd. for C$_{16}$H$_{14}$F$_3$NO•HCl: C, 58.28; H, 4.59; N, 4.25. Found: C, 57.91; H, 4.77; N, 4.13.

3-(3,4-Difluorophenyl)-3-(3,4-difluorophenyl)methoxyazetidine hydrochloride (30t, 
ANT-172)

General Procedure B. The azetidine was obtained as a yellow/green solid (26%); mp 164.7- 
166.9 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.84 (s, 2H), 7.52 – 7.42 (m, 2H), 7.32 (s, 3H), 7.14 
(s, 1H), 4.47 (d, $J = 9.7$ Hz, 2H), 4.31 (d, $J = 10.2$ Hz, 2H), 4.22 (s, 2H). $^{13}$C NMR (100 MHz, 
DMSO-d$_6$) δ 151.7, 149.3, 135.7, 127.4, 127.3, 125.1, 119.5, 119.3, 117.9, 117.7, 117.5, 117.4, 
77.0, 65.2, 58.2, 55.2. Anal. Calcd. for C$_{16}$H$_{13}$F$_4$NO•HCl: C, 55.26; H, 4.06; N, 4.03. Found: C, 
54.93; H, 4.18; N, 3.88.
3-Phenyl-3-(4-(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30u, ANT-219)

General Procedure B. The azetidine was obtained as a white solid (20%); mp 166.8-169.4 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 9.81 (s, 2H), 7.67 (d, \(J = 8.2\) Hz, 2H), 7.56 (d, \(J = 8.1\) Hz, 2H), 7.53 - 7.39 (m, 5H), 4.37 (d, \(J = 11.8\) Hz, 2H), 4.28 (d, \(J = 11.8\) Hz, 4H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 143.0, 138.4, 129.5, 129.5, 128.7, 127.1, 125.7, 125.7, 95.7, 79.2, 75.8, 65.3, 55.5, 16.1. Anal. Calcd. for C\(_{17}\)H\(_{16}\)F\(_3\)NO•HCl: C, 59.39; H, 4.89; N, 4.07. Found: C, 59.14; H, 5.22; N, 3.89.

3-Phenyl-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30v, ANT-220)

General Procedure B. The azetidine was obtained as a white solid (41%); mp 170.2-137.1 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 9.92 (s, 2H), 8.19 (d, \(J = 8.2\) Hz, 1H), 8.07 (d, \(J = 8.2\) Hz, 1H), 7.91 (s, 1H), 7.48 - 7.40 (m, 5H), 4.46 - 4.29 (m, 6H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 141.3, 137.8, 131.9, 130.2, 129.7, 129.4, 129.2, 127.7, 127.4, 127.1, 125.3, 123.1, 122.5, 79.5, 75.8, 61.8, 55.3. Anal. Calcd. for C\(_{18}\)H\(_{15}\)F\(_6\)NO•HCl: C, 52.5; H, 3.92; N, 3.4. Found: C, 52.37; H, 3.9; N, 3.21.
3-Phenyl-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30w, ANT-221)

General Procedure B. The azetidine was obtained as a white solid (28%); mp 136.4-139.2 °C; 1H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 9.66 (s, 1H), 8.02 – 7.96 (m, 3H), 7.56 – 7.30 (m, 5H), 4.50 – 4.26 (m, 6H). 13C NMR (100 MHz, DMSO-d_6) δ 155.3, 141.8, 138.1, 130.9, 130.6, 130.2, 129.6, 129.4, 128.8, 127.2, 125.3, 122.6, 121.8, 79.5, 75.8, 64.7, 55.4. Anal. Calcd. for C_{18}H_{15}F_6NO•HCl: C, 52.5; H, 3.9; N, 3.4. Found: C, 52.17; H, 4.07; N, 3.12.

3-(4-(Trifluoromethyl)phenyl)-3-phenylmethoxyazetidine hydrochloride (30x, ANT-188)

General Procedure B. The azetidine was obtained as a white solid (30%); mp 209.7-210.8 °C; 1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 2H), 7.84 – 7.79 (m, 4H), 7.29 (dt, J = 12.2 Hz, 7.0 Hz, 5H), 4.38 – 4.28 (m, 4H), 4.18 (s, 2H). 13C NMR (100 MHz, DMSO-d_6) δ 143.3, 137.9, 130.0, 129.6, 128.9, 128.4, 128.3, 128.2, 126.3, 126.3, 126.1, 123.4, 78.5, 75.8, 66.3, 55.1. Anal. Calcd. for C_{17}H_{16}F_3NO•HCl: C, 59.39; H, 4.98; N, 4.07. Found: C, 59.12; H, 5; N, 3.88.

3-(4-(Trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30y, ANT-311)

General Procedure B. The azetidine was obtained as a white solid (21%); mp 106.7-107.8 °C; 1H NMR (400 MHz, DMSO-d_6) δ 10.15 – 10.12 (m, 1H), 9.85 (s, 1H), 7.92 – 7.71 (m, 4H),
7.65 – 7.57 (m, 4H), 4.60 – 4.24 (m, 6H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 193.3, 166.8, 147.7, 143.0, 131.3, 130.7, 130.1, 129.8, 129.0, 128.7, 128.2, 127.00, 126.3, 125.6, 78.8, 72.7, 65.6, 59.7, 55.2.

3-(4-(Trifluoromethyl)phenyl)-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30z, ANT-191)

General Procedure B. The azetidine was obtained as a white solid (33%); mp 214.5-215.7 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.66 (s, 2H), 8.03 (s, 2H), 7.97 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 4.48 – 4.34 (m, 6H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 142.6, 141.6, 130.9, 130.5, 130.2, 129.8, 129.5, 129.0, 128.3, 126.3, 125.3, 122.6, 121.9, 79.1, 64.9, 55.3. Anal. Calcd. for C$_{19}$H$_{14}$F$_6$NO•HCl•H$_2$O: C, 45.75; H, 3.29; N, 2.54. Found: C, 45.79; H, 3.52; N, 2.76.

3-(4-(Trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (30aa, ANT-190)

General Procedures B and D. The azetidine was obtained as a white solid (33%); mp 164.6-166.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.15 – 7.99 (m, 2H), 7.93 (s, 2H), 7.88 – 7.69 (m, 3H), 4.55 – 4.32 (m, 2H), 4.01 (s, 1H), 3.81 (d, $J = 8.0$ Hz, 1H), 3.63 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 162.7, 145.8, 142.2, 141.7, 140.9, 130.2, 129.7, 129.3, 128.3, 127.6, 126.2, 125.3, 123.3, 122.6, 79.3, 77.4, 64.6, 62.2, 58.5, 55.5. Anal. Calcd. for C$_{19}$H$_{14}$F$_9$NO•C$_2$H$_2$O$_4$•1H$_2$O: C, 45.75; H, 3.29; N, 2.54. Found: C, 45.7; H, 3.31; N, 2.49.
3-(2,4-Bis(trifluoromethyl)phenyl)-3-phenylmethoxyazetidine hydrochloride (30bb, ANT-262)

General Procedure B. The azetidine was obtained as a pale yellow solid (29%); mp 187.2-188.5 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 9.93 (s, 2H), 8.18 (s, 1H), 8.09-8.03 (m, 1H), 7.27 (s, 5H), 4.56 - 4.30 (m, 4H), 4.08 (s, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 139.8, 137.5, 132.5, 131.2, 130.9, 130.2, 128.8, 128.5, 128.4, 125.7, 125.1, 122.4, 79.2, 66.6, 55.0.

3-(2,4-Bis(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30cc, ANT-263)

General Procedure B. The azetidine was obtained as a white solid (38%); mp 183.6-185.3 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 10.19 – 9.88 (m, 2H), 8.16 – 8.04 (m, 3H), 7.58 – 7.52 (m, 4H), 4.82 – 3.96 (m, 6H). ¹³C NMR (100 MHz, DMSO-d₆) δ 142.4, 139.6, 132.6, 131.3, 130.9, 130.3, 128.9, 126.2, 125.6, 125.1, 123.5, 122.3, 79.3, 65.8, 55.0.

3-(2,4-Bis(trifluoromethyl)phenyl)-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30dd, ANT-288)

General Procedure B. The product was obtained as a white solid (26%); mp 191.8-192.7 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 9.99 (s, 2H), 8.23 (d, J = 7.9 Hz, 2H), 8.07 (d, J = 8.8 Hz, 3H), 7.86 (s, 1H), 4.65 (d, J = 12.2 Hz, 2H), 4.37 (d, J = 17.1 Hz, 4H). ¹³C NMR (100 MHz, DMSO-d₆) δ 140.6, 139.0, 132.6, 132.0, 131.5, 131.1, 130.1, 129.6, 129.3, 128.8, 128.5, 127.7, 127.3, 125.5, 122.9, 79.7, 62.0, 54.8.
**3-(2,4-Bis(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30ee, ANT-265)**

General Procedure B. The product was obtained as a white solid (8%); mp 207.2-208.5 °C;

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.82 (s, 2H), 8.20 (d, $J$ = 8.1 Hz, 1H), 8.09 (s, 1H), 7.99 (t, $J$ = 10.4 Hz, 4H), 4.63 (d, $J$ = 12.2 Hz, 2H), 4.38 (d, $J$ = 13.5 Hz, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 141.2, 139.4, 132.5, 131.3, 130.8, 130.5, 130.3, 130.0, 128.7, 128.4, 125.6, 125.3, 125.0, 122.6, 122.4, 121.9, 79.6, 65.0, 55.0.

**3-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylmethoxyazetidine hydrochloride (30ff, ANT-249)**

General Procedure B. The product was obtained as a green solid (47%); mp 141.8-144.1 °C;

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 10.12 – 9.66 (m, 2H), 8.22- 8.13 (m, 2H), 8.01 – 7.94 (m, 2H), 7.43 – 7.36 (m, 2H), 7.17 (s, 2H), 4.69 – 4.01 (m, 6H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 167.8, 164.9, 146.4, 134.9, 133.4, 131.3, 130.3, 130.0, 128.7, 128.2, 128.0, 127.2, 123.1, 78.2, 67.0, 59.5, 55.5. Anal. Calcd. for C$_{18}$H$_{15}$F$_6$NO•HCl: C, 52.5; H, 3.92; N, 3.4. Found: C, 52.33; H, 4.11; N, 3.17.
3-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30gg, ANT-235)

General Procedure B. The product was obtained as a white solid (64%); mp 176.6-178.3 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.90 (s, 2H), 8.20 – 8.09 (m, 3H), 7.61 – 7.50 (m, 4H), 4.66 – 4.16 (m, 6H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 142.7, 141.9, 131.5, 131.1, 128.7, 128.6, 126.1, 125.6, 125.2, 123.3, 122.5, 78.6, 75.8, 65.9, 55.2.

3-(3,5-Bis(trifluoromethyl)phenyl)-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30hh, ANT-250)

General Procedure B. The product was obtained as a white solid (46%); mp 155.8-157.2 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.89 (s, 2H), 8.26 – 7.95 (m, 5H), 7.84 (s, 1H), 4.60 – 4.26 (m, 6H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 141.0, 140.7, 132.5, 131.7, 130.7, 129.7, 129.4, 128.7, 127.9, 127.6, 125.1, 123.3, 123.0, 122.3, 78.9, 62.4, 55.0.

3-(3,5-Bis(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (30ii, ANT-236)

General Procedure B. The product was obtained as a white solid (40%); mp 183.1-183.4 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 10.10 - 9.71 (m, 2H), 8.16 (s, 2H), 8.02 (s, 1H), 7.87 (s, 3H), 4.61 – 4.46 (m, 4H), 4.38 (d, $J = 11.2$ Hz, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 141.7, 141.67, 131.4, 131.1, 130.9, 130.5, 128.7, 125.2, 125.1, 123.3, 122.5, 122.4, 121.7, 78.9, 75.8, 65.3,
N-Methyl-3-phenyl-3-phenylmethoxyazetidine hydrochloride (31a, ANT-47)

General Procedure C. The product was obtained as a white solid (38%); mp 164.8-166.6 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.51-7.42 (m, 5H), 7.31-7.24 (m, 5H), 4.45 (s, 4H), 4.12 (s, 2H), 2.89 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 137.8, 129.5, 129.4, 128.8, 128.4, 128.3, 127.2, 66.2, 64.3. Anal. Calcd. for C$_{17}$H$_{19}$NO•HCl: C, 70.44; H, 6.97; N, 4.83. Found: C, 69.09; H, 7.02; N, 4.80.

N-Methyl-3-phenyl-3-(4-chlorophenyl)methoxyazetidine hydrochloride (31b, ANT-73)

General Procedure C. The product was obtained as a pale yellow solid (18%); mp 165.3-168.9 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.47-7.32 (m, 9H), 4.65-4.39 (m, 4H), 4.14 (s, 2H), 2.85 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 137.0, 132.8, 130.3, 129.6, 129.4, 128.8, 128.4, 127.2, 65.4, 64.2. Anal. Calcd. for C$_{17}$H$_{18}$ClNO•HCl: C, 62.97; H, 5.91; N, 4.32. Found: C, 62.88; H, 5.72; N, 4.09.
**N-Methyl-3-phenyl-3-(3,4-dichlorophenyl)methoxyazetidine hydrochloride (31c, ANT-72)**

General Procedure C. The product was obtained as a white solid (19%); mp 191.8-194.1 °C; \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.58-7.29 (m, 8H), 4.47 (s, 4H), 4.15 (s, 2H); 2.89 (s, 3H); \(^1^3^C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 131.0, 130.7, 130.2, 130.2, 129.7, 129.5, 128.5, 128.5, 127.2, 64.8, 64.5. Anal. Calcd. for C\(_{17}\)H\(_{17}\)Cl\(_2\)NO•HCl: C, 56.92; H, 5.06; N, 3.90. Found: C, 56.00; H, 5.50; N, 3.60.

**N-Methyl-3-(4-Chlorophenyl-3-phenylmethoxyazetidine hydrochloride (31d, ANT-85)**

General Procedure C. The product was obtained as a pale yellow solid (44%); mp 176.6-178.6 °C; \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.56-7.47 (m, 4H), 7.32-7.28 (m, 5H), 4.43 (s, 4H), 4.14 (s, 2H), 2.88 (s, 3H); \(^1^3^C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 137.8, 137.0, 134.2, 129.5, 129.4, 128.8, 128.5, 128.3, 127.2, 66.3, 64.8. Anal. Calcd. for C\(_{17}\)H\(_{18}\)ClNO•HCl: C, 62.97; H, 5.91; N, 4.32. Found: C, 62.84; H, 6.02; N, 4.29.

**N-Methyl-3-(4-chlorophenyl)-3-(4-chlorophenyl)methoxyazetidine hydrochloride (31e, ANT-84)**

General Procedure C. The product was obtained as a pale green solid (24%); mp 185.7-189.4 °C; \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.56-7.50 (m, 4H), 7.37-7.30 (m, 4H), 4.43 (s, 4H), 4.14 (s, 2H), 2.88 (s, 3H); \(^1^3^C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 136.9, 134.3, 132.9, 130.2, 129.4,
128.8, 95.6, 65.5, 64.4. Anal. Calcd. for C$_{17}$H$_{17}$Cl$_2$NO•HCl: C, 54.20; H, 5.35; N, 3.72. Found: C, 54.36; H, 5.16; N, 3.88.

**N-Methyl-3-(4-chlorophenyl)-3-(3,4-dichlorophenyl)methoxyazetidine hydrochloride (31f, ANT-125)**

General Procedure C. The product was obtained as a white solid (33%); mp 169.1-170.2 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.68-7.30 (m, 7H), 4.63-4.36 (m, 4H), 4.15 (s, 2H), 2.84 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): 139.0, 136.7, 134.3, 131.5, 130.9, 130.7, 130.2, 139.4, 128.6, 128.2, 64.9, 64.0. Anal. Calcd. for C$_{17}$H$_{16}$Cl$_3$NO•HCl: C, 51.94; H, 4.36; N, 3.56. Found: C, 51.47; H, 4.77; N, 3.49.

**N-Methyl-3-(3,4-dichlorophenyl)-3-phenylmethoxyazetidine hydrochloride (31g, ANT-133)**

General Procedure C. The product was obtained as a white solid (28%); mp 180.9-182.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.58-7.49 (m, 3H), 7.32-7.26 (m, 5H), 4.45 (s, 4H), 4.17-4.13 (m, 2H), 2.88 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 137.7, 134.2, 131.4, 129.5, 129.4, 128.8, 128.5, 128.3, 127.3, 75.7, 66.4, 64.1. Anal. Calcd. for C$_{17}$H$_{17}$Cl$_2$NO•HCl: C, 56.92; H, 5.06; N, 3.90. Found: C, 56.83 H, 5.19; N, 3.77.
**N-Methyl-3-(3,4-dichlorophenyl)-3-(4-chlorophenyl)methoxyazetidine hydrochloride (31h, ANT-124)**

General Procedure C. The product was obtained as a white solid (23%); mp 160.7-162.8 °C; 

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.51-7.35 (m, 7H), 4.67-4.14 (m, 4H), 4.14 (s, 2H), 2.88 (d, $J = 5.0$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 136.8, 134.2, 132.8, 131.4, 130.2, 129.6, 129.4, 128.8. Anal. Calcd. for C$_{17}$H$_{16}$Cl$_3$NO•HCl•EtOAc: C, 52.41; H, 5.24; N, 2.91. Found: C, 52.41 H, 5.35; N, 3.61.

**N-Methyl-3-(3,4-dichlorophenyl)-3-(3,4-dichlorophenyl)methoxyazetidine hydrochloride (31i, ANT-106)**

General Procedure C. The product was obtained as a white solid (57%); mp 176.2-178.9 °C; 

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.13-7.31 (m, 6H), 4.51 (m, 4H), 4.19 (s, 2H), 2.86 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 136.4, 135.9, 134.4, 134.0, 133.0, 132.6, 131.7, 130.9, 129.6, 128.7, 127.9, 127.0, 126.6, 126.0, 65.7, 64.6, 43.9. Anal. Calcd. for C$_{17}$H$_{15}$Cl$_4$NO•HCl: C, 47.75; H, 3.77; N, 3.28. Found: C, 47.50 H, 3.94; N, 3.18.

**N-Methyl-3-phenyl-3-(4-fluorophenyl)methoxyazetidine hydrochloride (31j, ANT-199)**

General Procedure C. The product was obtained as a white solid (42%); mp 177.8-180.3 °C; 

$^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.55 – 7.31 (m, 7H), 7.13 (t, $J = 8.7$, 2H), 4.65 – 4.13 (m, 4H), 4.13 (s, 2H), 2.89 (d, $J = 30.8$, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 163.5, 161.1, 157.0,
134.2, 130.7, 130.6, 129.5, 129.5, 127.2, 115.8, 115.6, 115.4, 77.6, 65.5, 64.0. Anal. Calcd. for C_{17}H_{18}NO_{13}F\cdot C_2H_2O_4: C, 63.15; H, 5.85; N, 3.88. Found: C, 63%; H, 5.89; N, 3.67.

**N-Methyl-3-phenyl-3-(2-fluorophenyl)methoxyazetidine oxalate (31k, ANT-138)**

General Procedures C and D. The product was obtained as a tan solid (20%); mp 149.0-152.8 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.61 – 7.29 (m, 7H), 7.22 – 7.07 (m, 2H), 4.49 – 4.18 (m, 4H), 4.18 (s, 2H), 2.90 (d, $J$ = 9.8 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 137.9, 131.3, 130.6, 129.6, 129.4, 127.2, 125.1, 124.8, 115.6, 115.6, 77.5, 64.3, 60.07, 55.9. Anal. Calcd. for C$_{17}$H$_{18}$NO$\cdot$C$_2$H$_2$O$_4$: C, 63.15; H, 5.85; N, 3.88. Found: C, 63; H, 5.89; N, 3.67.

**N-Methyl-3-phenyl-3-(3,4-difluorophenyl)methoxyazetidine oxalate (31l, ANT-139)**

General Procedures C and D. The product was obtained as a tan solid (21%); mp 124.1-126.9 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.38 (d, $J$ = 7.4 Hz, 12H), 4.37 – 3.91 (m, 6H), 2.92 (s, 2H), 1.96 (d, $J$ = 1.0 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 171.1, 164.2, 142.4, 137.7, 129.6, 129.4, 129.0, 128.6, 127.3, 126.1, 71.2, 68.7, 65.3, 64.4, 64.0, 42.2, 25.4. Anal. Calcd. for C$_{17}$H$_{17}$F$_2$NO$\cdot$C$_2$H$_2$O$_4$: C, 60.16; H, 5.05; N, 3.69. Found: C, 60.12; H, 5.14; N, 3.57.

**N-Methyl-3-(4-fluorophenyl)-3-phenylmethoxyazetidine hydrochloride (31m, ANT-158)**

General Procedure C. The product was obtained as a white solid (24%); mp 197.3-197.6 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.54 (s, 2H), 7.34 – 7.26 (m, 7H), 4.43 (s, 4H), 4.13 (s, 2H),
2.88 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.1, 161.6, 137.9, 134.5, 129.8, 129.7, 128.9, 128.5, 128.3, 116.4, 116.1, 76.7, 66.2, 64.2. Anal. Calcd. for C$_{17}$H$_{18}$FNO•HCl: C, 65.42; H, 5.83; N, 4.77. Found: C, 65.05; H, 6.00; N, 4.51.

**N-Methyl-3-(4-fluorophenyl)-3-(4-fluorophenyl)methoxyazetidine oxalate (31o, ANT-156)**

General Procedures C and D. The product was obtained as a tan solid (23%); mp 112.3-114.7 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.52 (dd, $J = 16.7$ Hz, $J = 11.9$ Hz, 4H), 7.37 – 7.14 (m, 4H), 4.18 (s, 4H), 4.18 (s, 2H), 2.85 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.3, 161.6, 134.3, 131.3, 130.7, 129.8, 129.7, 129.4, 127.2, 125.1, 116.3, 116.1, 115.9, 115.7, 77.1, 68.7, 64.4, 60.1. Anal. Calcd. for C$_{17}$H$_{17}$F$_2$NO•C$_2$H$_2$O$_4$: C, 60.16; H, 5.05; N, 3.69. Found: C, 59.99; H, 5.20; N, 3.50.

**N-Methyl-3-(4-fluorophenyl)-3-(4-fluorophenyl)methoxyazetidine hydrochloride (31n, ANT-147)**

General Procedure C. The product was obtained as a tan solid (19%); mp 173.4-177.0 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.74 – 7.00 (m, 8H), 4.75 – 4.16 (m, 6H), 4.11 (s, 2H), 2.83 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.1, 163.5, 161.6, 161.1, 155.3, 134.2, 130.7, 130.66, 129.8, 116.4, 116.2, 115.7, 65.5, 64.2. Anal. Calcd. for C$_{17}$H$_{17}$F$_2$NO•HCl: C, 62.67; H, 5.57; N, 4.30. Found: C, 62.72; H, 5.64; N, 4.56.
**N-Methyl-3-(4-fluorophenyl)-3-(3,4-difluorophenyl)methoxyazetidine hydrochloride (31p, ANT-157)**

General Procedure C. The product was obtained as a pale green solid (26%); mp 186.0-187.0 °C; \(^1^H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.57 – 7.48 (m, 4H), 7.38 – 7.30 (m, 3H), 7.17 (s, 1H), 4.52 – 4.16 (m, 4H), 4.15 (d, J = 13.6, 2H), 2.85 (s, 3H). \(^1^3^C\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 164.1, 161.6, 150.6, 135.8, 134.3, 129.7, 125.1, 117.7, 116.4, 116.2, 101.2, 95.7, 75.8, 65.0, 64.1. Anal. Calcd. for C\(_{17}\)H\(_{16}\)F\(_3\)NO•HCl: C, 59.39; H, 4.98; N, 4.07. Found: C, 59.15; H, 5.01; N, 3.99.

**N-Methyl-3-(3,4-difluorophenyl)-3-phenylmethoxyazetidine oxalate (31q, ANT-173)**

General Procedures C and D. The product was obtained as a tan solid (4%); mp 110.0-111.4 °C; \(^1^H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.53 – 7.27 (m, 8H), 4.56 – 4.25 (m, 4H), 2.94 (s, 2H), 2.49 (s, 3H). \(^1^3^C\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 164.1, 137.8, 129.0, 128.5, 128.4, 125.8, 125.4, 124.6, 66.7, 66.6, 66.5, 64.7, 64.6, 55.9, 51.0, 49.9, 49.6. Anal. Calcd. for C\(_{17}\)H\(_{17}\)F\(_2\)NO•C\(_2\)H\(_2\)O\(_4\)•H\(_2\)O: C, 57.43; H, 5.33; N, 3.5. Found: C, 57.55; H, 5.44; N, 3.41.

**N-Methyl-3-(3,4-difluorophenyl)-3-(4-fluorophenyl)methoxyazetidine oxalate (31r, ANT-174)**

General Procedures C and D. The product was obtained as a white solid (12%); mp 133.4-135.2 °C; \(^1^H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.53 (s, 1H), 7.33 (s, 4H), 7.12 (s, 2H), 4.55-4.23
(m, 6H), 2.90 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.2, 163.5, 161.1, 134.0, 130.7, 130.6, 125.8, 125.2, 119.4, 119.2, 115.8, 115.6, 75.0, 65.8, 64.2. Anal. Calcd. for C$_{17}$H$_{16}$F$_3$NO•C$_2$H$_2$O$_4$•1½H$_2$O: C, 53.79; H, 4.96; N, 3.30. Found: C, 53.55; H, 4.76; N, 3.40.

*N-Methyl-3-(3,4-difluorophenyl)-3-(2-fluorophenyl)methoxyazetidine oxalate (31s, ANT-175)*

General Procedures C and D. The product was obtained as a white solid (11%); mp 128.4-131.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.52-7.12 (m, 7H), 4.88 – 3.96 (m, 6H), 2.90 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.3, 131.2, 130.8, 127.2, 125.7, 125.3, 125.1, 124.7, 119.4, 119.3, 115.9, 115.7, 75.1, 64.0, 60.4. Anal. Calcd. for C$_{17}$H$_{16}$F$_3$NO•C$_2$H$_2$O$_4$ : C, 57.43; H, 4.57; N, 3.53. Found: C, 57.15; H, 4.77; N, 3.30.

*N-Methyl-3-(3,4-difluorophenyl)-3-(3,4-difluorophenyl)methoxyazetidine oxalate (31t, ANT-176)*

General Procedures C and D. The product was obtained as a tan solid (17%); mp 137.6-140.7 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.53 (s, 1H), 7.39 – 7.16 (m, 5H), 4.57 – 4.24 (m, 6H), 2.90 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 163.7, 148.6, 135.6, 127.1, 125.8, 125.2, 119.4, 119.3, 118.0, 117.8, 117.6, 117.4, 75.1, 65.3, 64.2. Anal. Calcd. for C$_{17}$H$_{15}$F$_4$NO•C$_2$H$_2$O$_4$•1½H$_2$O: C, 53.79; H, 4.96; N, 3.30. Found: C, 53.89; H, 4.30; N, 3.26.
**N-Methyl-3-phenyl-3-(4-(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (31u, ANT-225)**

General Procedure C. The product was obtained as a white solid (28%); mp 131.3-134.0 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.96 – 6.72 (m, 9H), 4.46 (s, 2H), 4.32 – 4.16 (m, 2H), 3.43 (s, 2H), 2.89 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 142.9, 137.8, 129.6, 129.5, 128.9, 128.9, 128.6, 128.5, 127.2, 126.1, 125.6, 115.5, 75.8, 74.8, 68.9, 65.4, 64.0. Anal. Calcd. for C$_{18}$H$_{18}$F$_3$NO•HCl: C, 60.42; H, 5.35; N, 3.91. Found: C, 60.11; H, 5.54; N, 3.78.

**N-Methyl-3-phenyl-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31v, ANT-217)**

General Procedures C and D. The product was obtained as a white solid (33%); mp 116.9-117.7 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.46 (s, 8H), 4.54 – 4.26 (m, 6H), 2.95 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 170.9, 163.6, 129.7, 129.5, 129.4, 127.3, 125.9, 125.7, 75.80, 73.6, 66.8, 65.2, 64.6, 62.1, 58.4, 42.8. Anal. Calcd. for C$_{19}$H$_{16}$F$_6$NO•C$_2$H$_2$O$_4$: C, 52.62; H, 4; N, 2.92. Found: C, 5.44; H, 4.11; N, 2.88.

**N-Methyl-3-phenyl-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine hydrochloride (31w, ANT-218)**

General Procedure C. The product was obtained as a white solid (23%); mp 173.5-175.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.94 – 7.11 (m, 8H), 4.79 – 4.06 (m, 6H), 2.86 (s, 3H). $^{13}$C
NMR (100 MHz, DMSO-d$_6$) $\delta$ 170.9, 141.7, 140.1, 139.9, 139.4, 137.8, 130.4, 129.6, 129.4, 126.3, 122.0, 116.9, 115.8, 114.6, 112.2, 75.8, 65.2, 64.0, 21.5. Anal. Calcd. for C$_{19}$H$_{17}$F$_6$NO•HCl: C, 53.59; H, 4.26; N, 3.29. Found: C, 53.41; H, 4.31; N, 3.20.

$N$-Methyl-3-(4-trifluoromethyl)phenyl-3-phenylmethoxyazetidine oxalate (31x, ANT-184)

General Procedures C and D. The product was obtained as a white solid (22%); mp 130.1-132.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.66 (s, 2H), 7.94 - 7.14 (m, 9H), 4.46 - 4.14 (m, 6H), 2.90 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 171.0, 163.3, 137.8, 129.0, 128.1, 128.5, 128.3, 127.9, 127.4, 126.8, 126.4, 115.3, 66.4, 65.7, 64.2, 56.0, 42.3. Anal. Calcd. for C$_{18}$H$_{18}$F$_3$NO•C$_2$H$_2$O$_4$: C, 58.39; H, 4.90; N, 3.40. Found: C, 58.03; H, 5.11; N, 3.35.

$N$-Methyl-3-(4-trifluoromethyl)phenyl-3-(4-(trifluoromethyl)phenyl)methoxyazetidine oxalate (31y, ANT-185)

General Procedures C and D. The product was obtained as a white solid (19%); mp 183.4-184.8 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.06 - 7.46 (m, 8H), 4.44 - 4.17 (m, 6H), 2.85 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 165.1, 142.9, 128.8, 128.6, 128.2, 127.8, 127.1, 126.8, 126.3, 125.7, 123.6, 77.1, 68.6, 65.7, 64.1, 42.6. Anal. Calcd. for C$_{19}$H$_{17}$F$_6$NO•C$_2$H$_2$O$_4$: C, 52.62; H, 4; N, 2.92. Found: C, 52.22; H, 4.3; N, 2.75.
**N-Methyl-3-(4-trifluromethyl)phenyl-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31z, ANT-187)**

General Procedures C and D. The product was obtained as a white solid (34%); mp 182.9-183.3 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 – 7.40 (m, 7H), 4.46 – 4.241 (m, 6H), 2.86 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 165.0, 142.7, 140.0, 139.8, 133.0, 131.8, 129.7, 128.9, 128.3, 127.2, 126.3, 125.3, 124.3, 123.3, 122.3, 77.3, 65.3, 64.1, 42.6  Anal. Calcd. for C₂₀H₁₆F₉NO•C₂H₂O₄•H₂O: C, 46.74; H, 3.51; N, 2.48. Found: C, 46.55; H, 3.65; N, 2.24.

**N-Methyl-3-(4-trifluromethyl)phenyl-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31aa, ANT-186)**

General Procedures C and D. The product was obtained as a white solid (30%); mp 114.6-118.5 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 – 7.50 (m, 7H), 4.66 – 4.16 (m, 6H), 2.90 (s, 3H). ¹³C NMR (100 MHz, DMSO-d₆) δ 172.7, 163.7, 142.1, 132.7, 131.6, 128.4, 127.2, 126.3, 123.4, 123.1, 115.6, 68.5, 63.94, 56.0, 42.3. Anal. Calcd. for C₂₀H₁₆F₉NO•C₂H₂O₄•H₂O: C, 46.74; H, 3.57; N, 2.48. Found: C, 46.69; H, 3.55; N, 2.44.

**N-Methyl-3-(2,4-bis(trifluoromethyl)phenyl)-3-phenylmethoxyazetidine hydrochloride (31bb, ANT-258)**

General Procedure C. The product was obtained as a brown solid (35%); mp 156.0-157.2 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (m, 5H), 7.26 (s, 3H), 5.38 – 3.63 (m, 6H), 2.91 (s,
$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 165.3, 139.8, 137.7, 133.5, 131.2, 130.2, 128.9, 128.6, 128.1, 126.3, 125.4, 123.9, 114.4, 112.0, 110.0, 77.5, 67.0, 63.9, 42.3.

*N-Methyl-3-(2,4-bis(trifluromethyl)phenyl)-3-(4-trifluoromethyl)phenylmethoxyazetidine hydrochloride (31cc, ANT-259)*

General Procedure C. The product was obtained as a yellow solid (23%); mp 167.9-169.4 oC; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.51 (dt, $J$ = 4.2 Hz, $J$ = 2.3 Hz, 3H), 7.42 – 7.34 (m, 4H), 4.28 – 4.12 (m, 6H), 1.98 (dd, $J$ = 13.2 Hz, $J$ = 2.7 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.3, 138.2, 129.3, 128.6, 126.3, 101.5, 69.3, 65.7, 43.3, 43.2, 29.9, 29.2, 29.1, 26.0, 25.6.

*N-Methyl-3-(2,4-bis(trifluromethyl)phenyl)-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31dd, ANT-286)*

General Procedures C and D. The product was obtained as a brown solid (18%); mp oC; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.92 – 6.98 (m, 6H), 4.58 – 4.29 (m, 3H), 2.90 (s, 2H), 2.28 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.9, 141.3, 139.4, 138.9, 137.0, 132.7, 131.4, 130.3, 129.0, 128.6, 127.3, 126.7, 125.3, 123.1, 64.4, 21.3, 19.2.
**N-Methyl-3-(2,4-bis(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl) methoxyazetidine oxalate (31ee, ANT-287)**

General Procedures C and D. The product was obtained as a yellow solid (24%); mp °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.92 (tt, $J = 23.0$ Hz, 11.5 Hz, 3H), 7.61 - 7.33 (m, 1H), 7.31 - 6.90 (m, 2H), 4.45 (m, 6H), 2.89 (s, 3H). 
$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 172.7, 164.7, 141.8, 139.4, 132.6, 130.4, 128.9, 128.5, 126.7, 125.3, 122.6, 121.7, 78.7, 64.9, 64.4, 64.0, 55.9.

**N-Methyl-3-(3,5-bis(trifluoromethyl)phenyl)-3-phenylmethoxyazetidine hydrochloride (31ff, ANT-247)**

General Procedure C. The product was obtained as a tan solid (36%); mp 161.2-163.6 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.88 – 6.90 (m, 8H), 4.88 – 4.02 (m, 6H), 2.91 (s, 3H). 
$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 172.6, 170.9, 145.7, 140.5, 137.8, 132.1, 128.8, 128.5, 128.3, 127.2, 126.6, 126.1, 123.8, 123.4, 115.5, 77.3, 66.5, 63.9, 62.6. Anal. Calcd. for C$_{19}$H$_{17}$F$_6$NO•HCl•1½ H$_2$O: C, 50.39; H, 3.79; N, 3.09. Found: C, 50.68; H, 3.99; N, 2.6.

**N-Methyl-3-(3,5-bis(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)methoxyazetidine oxalate (31gg, ANT-238)**

General Procedures C and D. The product was obtained as a white solid (46%); mp 157.3-160.0 °C; 
$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.81 – 7.45 (m, 7H), 4.41 (d, $J = 95.6$, 6H), 2.91 (s, 3H). 
$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.5, 161.9, 137.9, 131.3, 130.7, 129.6, 129.4, 129.0,
N-Methyl-3-(3,5-bis(trifluromethyl)phenyl)-3-(2,4-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31hh, ANT-248)

General Procedures C and D. The product was obtained as a yellow solid (66%); mp 106.4-108.1 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.23 – 6.78 (m, 6H), 4.64 – 3.96 (m, 4H), 2.30 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 165.2, 132.7, 132.0, 131.1, 130.9, 126.6, 126.3, 125.6, 123.8, 115.6, 68.7, 65.1, 64.3, 21.5, 21.2, 21.1. Anal. Calcd. for C\(_{20}\)H\(_{16}\)F\(_9\)NO\(\cdot\)C\(_2\)H\(_2\)O\(_4\): C, 47.29; H, 3.02; N, 2.63. Found: C, 47.01; H, 3.22; N, 2.47.

N-Methyl-3-(3,5-bis(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)methoxyazetidine oxalate (31ii, ANT-239)

General Procedures C and D. The product was obtained as a off white solid (37%); mp 125.6-128.4 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.20 – 6.90 (m, 6H), 4.74 – 4.11 (m, 6H), 2.90 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 170.9, 164.0, 138.4, 132.1, 130.9, 130.5, 129.4, 128.8, 127.2, 126.7, 126.4, 125.3, 123.9, 122.4, 121.9, 121.2, 114.5, 77.3, 63.9, 21.3. Anal. Calcd. for C\(_{21}\)H\(_{15}\)F\(_{12}\)NO\(\cdot\)C\(_2\)H\(_2\)O\(_4\)\(\cdot\)1H\(_2\)O: C, 43.61; H, 3.02; N, 2.21. Found: C, 43.33; H, 3.02; N, 2.01.
Part II: Synthesis of 3,3-Diaryl Azetidines

Abstract

Diaryl heterocycles are known to have an important in place in pharmaceuticals. Many diaryl heterocycles are commercially used and studied for a variety of diseases and disorders. Traditional syntheses of diaryl heterocycles are accomplished in three to eight steps involving either time consuming steps or complication cyclizations from expensive starting materials. The novel synthesis described completes formation of 3,3-diarylazetidines, 3,3-diarylpyrrolidines, and 4,4-diarylpiperidines in two steps from the respective N-Boc-ketones in moderate to good yield. These diarylation syntheses have been accomplished in both symmetrical and asymmetrical aryl additions.

Key Words: Diaryl heterocycles, Friedel-Crafts Alkylation, Azetidine, Pyrrolidine, Piperidine
Introduction

Nitrogen containing ring systems are widely used throughout medicinal chemistry in everything from illicit drugs to penicillin. Molecules such as 3,3-diaryloxindoles in particular exhibit antibacterial, antiprotozoal and antiinflammatory activities. 3,3-diphenyl derivatives of succinimides and hydantoins display anticonvulsant activity. In all cases the 3,3-diaryl analogs are shown to be more biologically important. The synthesis of 3,3-diphenylpyrrolidines known in literature include those starting from diarylacetonitrile (39), 4-phenoxy, benzophenone (38), 4-bromo-2,2-diphenylbutylamine hydrochloride (40), or 4-amino-3,3-diphenylbutan-1-ol hydrochloride (41).87-91

![Chemical Structures](#)
4.1 Pharmaceutical Examples of Diaryl Heterocycles

There are several examples of diaryl heterocyclic systems both in drug discovery and on the market. 3,3-Diaryloxindoles (42 and 43) have been used as laxatives, the β-lactam azetidine (44) is known to have sedative and hypnotic effects. The imidizolidine (45) is currently on the market and used as an anticonvulsant and azepane (46) analogs are patented as having serotonin effects. Synthesis of these diaryl heterocyclic compounds, however, is highly involved and either takes multiple time consuming steps or starts from expensive starting materials.
4.2.1 Synthesis of 3,3-Diarylpyrrolidine from Benzophenone

Starting from benzophenone, 3,3-diphenylpyrrolidine was synthesized in seven steps. The condensation of benzophenone was completed using cyanoacetate under Knoevenagel conditions then converted to 2,2-diphenylsuccinic acid via the dicyanoester (49). Diphenylsuccinic acid was cyclized to the anhydride using acetyl chloride and subsequent treatment with benzylamine gave the succinimic acid (52). It was then recylized by refluxing in acetic anhydride and then reduced using sodiumborohydride to afford 3,3-diphenylpyrrolidine (54).

As exhibited in Scheme 11 this complex synthesis is completed in seven steps, and three recrystallizations that proved to be very timely and gave an overall 58% yield. While employing very inexpensive reagents, the reaction takes upwards of 131 hours to complete, which is excessive in terms of pharmaceutical development for both academia and industry alike.
4.2.2 Synthesis of 3,3-Diarylpyrrolidine from Diphenylbutylamine

Scheme 12 details the synthetic route for the synthesis of 3,3-diarylpyrrolidine using diphenylbutylamine as an intermediate. Reacting 3,3-diphenyl-5-methyl-2-furanone-imine (55) with ethylmagnesium bromide followed by treatment of and ice cold ammonium chloride solution afforded 2,5-dimethyl-3,3-diphenyltetrahydrofuran-2-amine (56). The 2-amino tetrahydrofuran was then reduced with lithium aluminum hydride producing 6-ethoxy-4,4-diphenylhexan-3-amine (57). The hydrochloride then underwent pyrolysis to give the cyclized 3,3-diarylpyrrolidine (58).

While this synthesis is completed in three steps with only three recrystallizations, the 3,3-diphenyl-5-methyl-2-furanone-imine starting material is a very expensive. At
$100 for 50mg this route is not feasible for extensive studies. Commercial sources, also, do not sell substituted diaryl-furanone-imines therefore only the formation of 3,3-diphenyl analogs can be synthesized from commercially available materials. This significantly diminishes the range of possible pharmacophores. In order to synthesize an analog with substitution on the aryls, the substituted furanone-imine starting material would need to be synthesized which would increase reaction length, time, and materials needed.

### 4.2.3 Synthesis of 3,3-Diarylpyrrolidine from Diphenylacetonitrile

Synthesis of 3,3-diphenylpyrrolidine from diphenylacetonitrile can be completed in three steps with three recrystallizations. The intermediate carbethoxylalkyl-phenylacetonitrile (60) was synthesized by the alkylation of diphenylacetonitrile with carbethoxybromide and sodium amide. These esters were then hydrogenated with Raney nickel to form 3,3-diarylpyrrolidinone (61), which was then reduced with lithium aluminum hydride to produce 3,3-diarylpyrrolidine (54).
Of the three syntheses seen thus far, **Scheme 13** is the first to depict the ability to form heterocycles of various sizes. By simply changing the alkylbormide used, the ring system can be expanded or contracted from the pyrrolidine depicted above. This reaction also uses inexpensive reagents and produces 3,3-diarylpyrrolidine in good yield.\(^{88}\) While diphenylacetonitrile is moderately priced and commercially available, that is not the case for substituted diarylacetonitriles. Typical commercial chemical retailers such as Sigma-Aldrich or Acros Organics do not carry any substituted diarylacetonitriles in their inventory. Therefore, similar to reactions from furanone-imine as the starting material, the synthesis of a substituted diarylacetonitrile would first have to be completed.

### 4.2.4 Synthesis of 4,4-Diarylpiperidines from 4-Piperidinone

Recently, Klump reported that \(N\)-substituted-4,4-diarylpiperidines can be synthesized from \(N\)-substituted-4-piperidinone using an excess of triflic acid.\(^{93}\) This work was expanded to include syntheses starting from tropanones and quinuelidones. These compounds were synthesized in one step as seen in **Scheme 14.**\(^{93}\)

![Scheme 14: Synthesis of 4,4-diphenylpiperidine from 4-piperidinone](image)
Table 4: Results of Diaryl Formation

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>62a</td>
<td>63a</td>
<td>99%</td>
</tr>
<tr>
<td>62b</td>
<td>63b</td>
<td>99%</td>
</tr>
<tr>
<td>64</td>
<td>65</td>
<td>80%</td>
</tr>
<tr>
<td>66a</td>
<td>67a</td>
<td>85%</td>
</tr>
<tr>
<td>66b</td>
<td>67b</td>
<td>Not Provided</td>
</tr>
</tbody>
</table>

Each Starting material was reacted with 6 equiv. of TfOH and excess benzene or chlorobenzene.

Table 4 provides percent yields for the formation of diaryl products. As seen in the table, each of these products was produced in good to excellent yield when reacted with six equivalents of triflic acid and excess benzene. *N*-substituted piperidines were produced in quantitative yield for the formation of 4,4-diphenylpiperidine, 63a and 63b. Moderate yields were seen for the formation of *N*-methyl-4,4-diphenyl-tropane, 67a and *N*-ethyl-3,3-diphenylpiperidine, 65.93
Klump also attempted synthesis of an asymmetrical 4,4-diaryl-piperidinone, as seen in Scheme 15. Unfortunately, multiple products were seen. When reacting intermediate 68 with 6 equivalents of triflic acid and chlorobenzene products 63a, 69, and 70 were seen in a ratio of 1.0:9.3:12.2. Therefore, synthesis of asymmetrical heterocycles using this method is not viable.

Scheme 15: Attempted formation of asymmetrical piperidine

4.3 New Methodology

After examining formation of 3,3-diarylpyrrolidines from benzophenone, diphenylbutylamine, diphenylacetonitrile, and piperidinone it is evident that a novel facile synthesis of substituted diarylhetocyclic systems is needed. All of the previously reported syntheses also either ignore or were unsuccessful as isolating in good yield asymmetrically substituted aryl moieties.

It was recently determined that a diarylated piperidine could be synthesized using aluminum chloride via Scheme 16. This synthesis gives the diarylation formation in one
step from 4-(4-bromophenyl)4-piperidinol. It provides the ability for substituted aryl moieties as well as an asymmetrical system. However, the patent that described this work as an intermediate only provided the single example and did not evaluate the scope and versatility of this methodology.\textsuperscript{94}

Taking into account the previously reported optimized experimental method for formation of $N$-Boc-3-aryl-3-azetidinol, it was envisaged that asymmetrical diarylation could be achieved for four, five, and six membered heterocycles in two steps from the Boc-protected ketone. Examining the same methodology in a tropanol system was also thought to be attractive for purposes of biological evaluation at various monoamine transporters. It was also assumed that Boc deprotection would easily be achieved in the same arylation step utilizing aluminum chloride. The retrosynthetic approach for the formation of 3,3-diarylazetidine is seen in \textbf{Figure 13}. 
Figure 13: Retrosynthetic approach to the formation of 3,3-diarylazetidines
Results and Discussion

The reported 4,4-diarylpiperidine was a robustly stable compound. It was of interest to see if similar methodologies could be employed on azetidine, pyrrolidine and tropane scaffolds. The ability to easily synthesize various diaryl heterocyclic ring systems quickly would aid in determination of pharmacophore scaffolds and drug discovery.

5.1 Proposed Mechanism of Formation of 3,3-Diarylheterocycles

The novel synthesis of 3,3-diarylheterocycles utilizes aluminum chloride as its major reagent. Aluminum chloride is known as a Lewis acid and is typically used in Friedel-Crafts alkylation reactions. It was postulated that in our reaction, aluminum chloride first would remove the protecting group by coordinating to the carbamate oxygen atoms to form the intermediate seen in Scheme 17. This intermediate then breaks down to form isobutene and carbon dioxide.

Scheme 17: Proposed Boc deprotection using AlCl₃
The reaction then undergoes a Friedel-Crafts alkylation. Aluminum chloride acts as an electron lone pair acceptor and forms AlCl₃OH as well as a strong electrophilic carbocation on the ring structure as seen in Scheme 18.

![Scheme 18: Proposed Friedel-Crafts Alkylation](image)

**5.2 Synthesis of Symmetrical and Asymmetrical 3,3-Diarylazetidines**

Synthesis of 3,3-diaryl azetidine analogs was completed in two steps with moderate to good yield. As seen in Scheme 19 the N-Boc-3-aryl-azetidinol intermediate 28 was synthesized under previously reported conditions by reacting N-Boc-3-azetidinone 27 with butyllithium and the intended arylbromide. Column chromatography was utilized before
moving onto the next step of the synthesis. The N-Boc-3-aryl-azetidinol 28 was then treated with aluminum chloride and the desired benzene derivative to achieve 3,3-diarylazetidine (73). This reaction took place in two hours at 0°C. The Boc protecting group was removed during this reaction as well, which allowed the crude mixture to be freebased and the product to be isolated as the oxalate salt. Formation of the final product as the oxalate salt eliminated the need for an additional purification step.

Scheme 19: Synthesis of 3,3-Diarylazetidine oxalate

As seen in Table 5, symmetrical and asymmetrical diaryl substitution on the azetidine ring system was completed in good yield (53-84%). Aryl electron withdrawing and donating substituents were tolerated by the reaction conditions. A slight increase in percent yield was seen when adding chlorobenzene to the azetidine system. The exception is compound 73n, which had the highest observed yield at 84%. Adding fluorobenzene to the system produced lower yields (53-60%). In the case of activating groups on the aryl ring, toluene was added in higher yield than methoxybenzene, 62-84% yield and 62-73% yield, respectively.
Table 5: Percent Yield for 3,3-Diarylazetidine

<table>
<thead>
<tr>
<th>Compound</th>
<th>Experiment</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>73a</td>
<td>ANT - 243</td>
<td>H</td>
<td>H</td>
<td>71%</td>
</tr>
<tr>
<td>73b</td>
<td>ANT - 267</td>
<td>H</td>
<td>Cl</td>
<td>80%</td>
</tr>
<tr>
<td>73c</td>
<td>ANT - 268</td>
<td>H</td>
<td>F</td>
<td>60%</td>
</tr>
<tr>
<td>73d</td>
<td>ANT - 330</td>
<td>H</td>
<td>CH₃</td>
<td>71%</td>
</tr>
<tr>
<td>73e</td>
<td>ANT - 331</td>
<td>H</td>
<td>OMe</td>
<td>62%</td>
</tr>
<tr>
<td>73f</td>
<td>ANT - 289</td>
<td>Cl</td>
<td>H</td>
<td>69%</td>
</tr>
<tr>
<td>73g</td>
<td>ANT - 290</td>
<td>Cl</td>
<td>Cl</td>
<td>81%</td>
</tr>
<tr>
<td>73h</td>
<td>ANT - 318</td>
<td>Cl</td>
<td>F</td>
<td>53%</td>
</tr>
<tr>
<td>73i</td>
<td>ANT - 291</td>
<td>Cl</td>
<td>CH₃</td>
<td>62%</td>
</tr>
<tr>
<td>73j</td>
<td>ANT - 319</td>
<td>Cl</td>
<td>OMe</td>
<td>63%</td>
</tr>
<tr>
<td>73k</td>
<td>ANT - 332</td>
<td>F</td>
<td>H</td>
<td>63%</td>
</tr>
<tr>
<td>73l</td>
<td>ANT - 333</td>
<td>F</td>
<td>Cl</td>
<td>74%</td>
</tr>
<tr>
<td>73m</td>
<td>ANT - 293</td>
<td>F</td>
<td>F</td>
<td>59%</td>
</tr>
<tr>
<td>73n</td>
<td>ANT - 313</td>
<td>F</td>
<td>CH₃</td>
<td>84%</td>
</tr>
<tr>
<td>73o</td>
<td>ANT - 334</td>
<td>F</td>
<td>OMe</td>
<td>73%</td>
</tr>
</tbody>
</table>

5.3 Synthesis of 4,4-Diarylpiperidine, 3,3-Diarylpyrrolidine, and 4,4-Diaryltropane

4,4-diarylpiperidine was synthesized in the same manner as 3,3-diaryl azetidines, depicted in Scheme 20. Commercially available N-Boc-4-piperidinone (76) was reacted with butyllithium and bromobenzene to form N-Boc-4-phenyl-piperidinol (77). The tertiary alcohol intermediate was purified by column chromatography and then reacted with aluminum chloride and the corresponding benzene to form 4,4-diarylpiperidine analogs (78). The crude mixture was freebased and the product isolated as an oxalate salt.
Scheme 20: Synthesis of 4,4-Diarylpyrrolidine

\[ \begin{array}{c}
\text{76} \\
\text{77} \\
\text{78}
\end{array} \]

*N-Boc-3-pyrrolidinone (80)* is not commercially available due to rapid decomposition. Therefore, *N*-Boc-3-pyrrolidinol was oxidized using Dess-Martin reagent to form *N*-Boc-3-pyrrolidinone (80), which was then reacted with butyllithium and bromobenzene to form *N*-Boc-3-phenyl-3-pyrrolidinol (81). Purification was completed by column chromatography and pure 81 underwent the established Friedel-Crafts alkylation, and formation of the oxalate salt to generate 3,3-diarylpyrrolidine analogs (82) as seen in Scheme 21.
Scheme 21: Formation of 3,3-Diarylpyrrolidine

*N*-Boc-nortropinone is commercially available however, due to its exorbitant price, *N*-ethoxycarbonyl-nortropinone (84) was synthesized instead by treating nortropinone (83) with ethylchloroformate under basic conditions. The protected tropinone was purified and then reacted under the established conditions to form 4,4-diaryl tropane analogs as represented in Scheme 22.
Table 6 shows the yields for reacting \( N \)-Boc-4-phenyl-piperidinol (77), \( N \)-Boc-3-phenyl-3-pyrrolidinol (81) and \( N \)-ethoxycarbonyl-4-phenyl-4-tropanol (85) were reacted with benzene, chlorobenzene, methoxybenzene and toluene.
Table 6: Percent Yields for Diarylation of Piperidine, Pyrrolidine, and Tropane analogs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Experiment</th>
<th>Ring System</th>
<th>X</th>
<th>Y</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>78a</td>
<td>ANT - 312</td>
<td>Piperidine</td>
<td>H</td>
<td>H</td>
<td>51%</td>
</tr>
<tr>
<td>78b</td>
<td>ANT - 320</td>
<td>Piperidine</td>
<td>H</td>
<td>Cl</td>
<td>60%</td>
</tr>
<tr>
<td>78c</td>
<td>ANT - 329</td>
<td>Piperidine</td>
<td>H</td>
<td>OMe</td>
<td>72%</td>
</tr>
<tr>
<td>78d</td>
<td>ANT - 321</td>
<td>Piperidine</td>
<td>H</td>
<td>CH₃</td>
<td>79%</td>
</tr>
<tr>
<td>82a</td>
<td>ANT - 339</td>
<td>Pyrrolidine</td>
<td>H</td>
<td>H</td>
<td>44%</td>
</tr>
<tr>
<td>82b</td>
<td>ANT - 340</td>
<td>Pyrrolidine</td>
<td>H</td>
<td>Cl</td>
<td>46%</td>
</tr>
<tr>
<td>82c</td>
<td>ANT - 341</td>
<td>Pyrrolidine</td>
<td>H</td>
<td>OMe</td>
<td>41%</td>
</tr>
<tr>
<td>82d</td>
<td>ANT - 342</td>
<td>Pyrrolidine</td>
<td>H</td>
<td>CH₃</td>
<td>54%</td>
</tr>
<tr>
<td>86a</td>
<td>ANT - 325</td>
<td>Tropane</td>
<td>H</td>
<td>H</td>
<td>6%</td>
</tr>
<tr>
<td>86b</td>
<td>ANT - 326</td>
<td>Tropane</td>
<td>H</td>
<td>Cl</td>
<td>12%</td>
</tr>
<tr>
<td>86c</td>
<td>ANT - 327</td>
<td>Tropane</td>
<td>H</td>
<td>OMe</td>
<td>NP</td>
</tr>
<tr>
<td>86d</td>
<td>ANT - 328</td>
<td>Tropane</td>
<td>H</td>
<td>CH₃</td>
<td>11%</td>
</tr>
</tbody>
</table>

Both 4,4-diarylpiperidine (78) analogs demonstrate similar results to that seen in the azetidine series. Moderate to good yields were seen for the formation of 4,4-diarylpiperidine analogs with 51-79% yield. The addition of toluene and methoxybenzene had the highest percent yields seen for the piperidine analogs (79% yield, 72% yield), which was to be expected, since toluene and methoxybenzene are mildly electron rich they facilitate electrophilic addition to the heterocyclic scaffolds.

The 3,3-diarylpyrrolidine analogs (82) were synthesized in moderate yield, 41-54%. Analog 3-phenyl-3-(p-methylphenyl)pyrrolidine (82d) had the highest yield at 54% while 3-phenyl-3-(p-methoxyphenyl)pyrrolidine (82c) had the lowest yield at 41%.
Tropane analogs (86) displayed very poor yields, with 4-phenyl-4(p-methoxyphenyl)tropanes (86c) having no product formation at all. These results were somewhat expected. It is probable that deprotection occurs first leaving the free amine. The formation of the carbocation at the 4 position leaves the opportunity for the free amine to attack and form a tricyclic system (88) as seen in Figure 14. This tricyclic system leaves no room for aryl addition. Though the tricycle, 88, was not isolated and identified as a side product, this isomer is known to occur in literature when a free amine and carbocation at C-4 are present in the tropane system.95

Figure 14: Formation of tricyclic tropanes cation
Conclusions

A novel two-step synthesis for the formation of 3,3-diaryl heterocycles been established. Diaryl heterocyclic formation can be achieved via a Friedel-Crafts alkylation from 3-aryl-azetidinol, 3-aryl-3-pyrollidinol, and 4-aryl-4-piperidinol. This synthesis is facile and efficient for the formation of both symmetrical and asymmetrical aryl substituents. Formation of 3,3-diarylazetine, 4,4-diarylpiperidine analogs were synthesized in moderate to good yields, 53-84%. Azetidine analog 73n, 3-fluorophenyl-3-(methylphenyl)azetidine had the highest yield at 84%. Of the piperidine series, 78d 4-phenyl-4-(methylphenyl)piperidine had the highest yield at 79% yield. The 3,3-diarylpyrrolidine analogs were synthesized in moderate yields, 41-54% with 3-phenyl-3-(methylphenyl)pyrrolidine (82d) having the highest percent yield. Scope and versatility of this synthetic scheme is limited to date. Further evaluation including heterocyclic addition as well as a variety of substituted aryl addition, should be completed.
Experimental

General Information

Chemicals were purchased from Sigma-Aldrich Chemical Co., Oakwood Products Inc., and VWR International LLC and used as received or otherwise noted. Anhydrous solvents were purchased from EMD Millipore and were used under nitrogen without any further purification. Chromatography refers to column chromatography on silica gel (Silica Gel 60Å, 230-400 mesh). Reported melting points are uncorrected. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in DMSO-D$_6$. $^1$H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. $^{13}$C NMR chemical shifts are reported as δ values (ppm) relative to DMSO-D$_6$ (39.5 ppm).

Solvent acronyms – Tetrahydrofuran (THF), Dichloromethane (DCM), Deionized water (DI).

Preparation of N-Ethoxycarbonyl-nortropinone (84)

3-Tropinone (1 equiv.), potassium carbonate (0.05 equiv.) and ethylchloroformate (5 equiv.) were dissolved in dry toluene (15 mL) and the mixture heated to 110 °C overnight. The solvent was removed under reduced pressure and the oil partitioned between DCM and DI (15 mL each). The aqueous layer was extracted with DCM (3 x 10 mL), washed with brine (2 x 10 mL) and dried over anhydrous sodium sulfate. The solvent was
removed under reduced pressure and the oil purified by column chromatography (30% ethyl acetate:hexanes) to afford 84 as a colorless oil (57%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 – 4.02 (m, 2H), 4.00 – 3.93 (m, 1H), 2.53 (s, 2H), 2.27 – 2.15 (m, 2H), 1.96 (d, $J$ = 3.0 Hz, 2H), 1.90 – 1.88 (m, 1H), 1.55 (d, $J$ = 6.9 Hz, 2H), 1.20 – 1.12 (m, 3H).

Preparation of N-Ethoxycarbonyl-4-phenyl-4-tropanol (85)

Bromobenzene (3 equiv.) was dissolved in anhydrous THF and cooled to -78 °C for 10 minutes. $n$-butyllithium (2.5M, 3 equiv.) was added and the reaction stirred for 1 hour under nitrogen. N-Ethoxycarbonyl-4-phenyl-4-tropanol (1 equiv.) was dissolved in anhydrous THF, and added via syringe to the reaction. The mixture was stirred overnight to room temperature. The reaction was quenched with 10% NH$_4$Cl, extracted with diethyl ether (3 x 15 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 85 as a white solid (57%); mp 90.7 - 92.4 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.34 (m, 2H), 7.28 (dd, $J$ = 10.5 Hz, $J$ = 4.9 Hz, 2H), 7.17 (dd, $J$ = 8.1 Hz, 6.4, 1H), 4.33 (s, 2H), 4.15 – 4.06 (m, 2H), 2.44 – 2.17 (m, 4H), 1.95 – 1.77 (m, 4H), 1.25 (d, $J$ = 7.1 Hz, 3H).

Preparation of N-Boc-3-pyrrolidinone (80)

$N$-Boc-3-pyrrolidinol (79) (1 equiv.) and Dess-martin reagent (3 equiv.) was dissolved in 15 mL DCM. The reaction was stirred at room temperature for 3 hours. The
reaction was quenched with 15mL of DI, then extracted with DCM (3 x 10 mL), washed with brine (2 x 10 mL) and dried over anhydrous sodium sulfate. The clear oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 80 as a colorless oil (72%). 1H NMR (400 MHz, CDCl₃) δ 3.63 (dd, $J = 14.7$ Hz, $J = 6.7$ Hz, 4H), 2.46 (t, $J = 7.8$ Hz, 2H), 1.35 (s, 9H).

**Preparation of N-Boc-3-phenyl-3-pyrrolidinol (81)**

Bromobenzene (3 equiv.) was dissolved in anhydrous THF and cooled to -78 °C for 10 minutes. n-butyllithium (2.5M, 3 equiv.) was added and the reaction stirred for 1 hour under nitrogen. N-Boc-3-pyrrolidinone (80) (1 equiv.) was dissolved in anhydrous THF, and added via syringe to the reaction. The mixture was stirred overnight to room temperature. The reaction was quenched with 10% NH₄Cl, extracted with diethyl ether (3 x 15 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 81 as a white solid (30%); mp 133.3 - 134.8 °C; 1H NMR (400 MHz, CDCl₃) δ 7.48 (d, $J = 6.6$ Hz, 2H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.31 (ddd, $J = 7.3$ Hz, $J = 3.7$ Hz, $J = 1.2$ Hz, 1H), 3.81 – 3.53 (m, 4H), 2.41 – 2.11 (m, 2H), 2.03 (d, $J = 3.4$ Hz, 1H), 1.47 (d, $J = 8.4$ Hz, 9H).
**Preparation of N-Boc-4-phenyl-4-piperidinol (77)**

Bromobenzene (3 equiv.) was dissolved in anhydrous THF and cooled to -78 °C for 10 minutes. n-butyllithium (2.5M, 3 equiv.) was added and the reaction stirred for 1 hour under nitrogen. N-Boc-3-pyrrolidinone (1 equiv.) was dissolved in anhydrous THF, and added via syringe to the reaction. The mixture was stirred overnight to room temperature. The reaction was quenched with 10% NH₄Cl, extracted with diethyl ether (3 x 15 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 77 as a white solid (30%); mp 110.2 - 111.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 7.1 Hz, 1H), 3.96 (s, 2H), 3.21 (s, 2H), 1.93 (s, 2H), 1.69 (d, J= 12.6 Hz, 2H), 1.44 (s, 9H).

**General Procedure A: Preparation of 1-Boc-3-arylazetidin-3-ols (34)**

Halogenated bromobenzene (3 equiv.) was dissolved in anhydrous THF and cooled to -78 °C for 10 minutes. n-butyllithium (2.5M, 3 equiv.) was added and the reaction stirred for 1 hour under nitrogen. 1-Boc-3-azetidinone (27) (1 equiv.) was dissolved in anhydrous THF, and added via syringe to the reaction. The mixture was stirred overnight to room temperature. The reaction was quenched with 10% NH₄Cl, extracted with diethyl ether (3 x 15 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% ethyl acetate:hexanes) to afford 34a, 34b, and 34d.
**1-Boc-3-phenyl-3-azetidinol (34a)**

General Procedure A. The azetidinol was obtained as a pale yellow solid (94%); mp 85.3-87.8 °C; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.49(d, $J = 8$, 2H), 7.42-7.38(m, 2H), 7.33-7.30(m, 1H), 4.27(d, $J = 9.2$ Hz, 2H), 4.16(d, $J = 9.2$ Hz, 2H), 1.46(s, 9H).

**1-Boc-3-(4-chlorophenyl)-3-azetidinol (31b)**

General Procedure A. The azetidinol was obtained as a pale yellow solid (86%) mp 139.0-140.6 °C; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.4-7.38(m, 2H), 7.28(d, $J = 8.8$ Hz, 2H), 4.63(s, 1H), 4.13-4.05(m, 4H), 1.39(s, 9H).

**1-Boc-3-(4-fluorophenyl)-3-azetidinol (31d)**

General Procedure A. The azetidinol was obtained as a pale yellow solid (64%); mp 90.8 - 92.8 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 – 7.34 (m, 2H), 7.04 – 6.88 (m, 2H), 4.81 (s, 1H), 4.08(t, $J = 5.8$ Hz, 4H), 1.44 – 1.31 (m, 9H).

**General Procedure B: Formation of 3-Phenyl-3-aryl-heterocycles**

Aluminum chloride (3.5 equiv.) placed in an ice bath and suspended in benzene (1.5 mL). $N$-protected-aryl-heterocycle secondary alcohols ($28$, $77$, $81$ or $85$) were separately dissolved in benzene (1.5mL) and added to the suspended aluminum chloride. The mixture
was stirred at 0 °C under argon for 2 hours. The reaction was then quenched with 0.1g of ice and allowed to stir for 30 minutes. Saturated sodium bicarbonate (3mL) was then added to the mixture followed by ammonium hydroxide to achieve a pH of 11. The mixture was then extracted with DCM (3 x 5 mL), washed with brine (2 x 5 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The mixture was then re-dissolved in a minimal amount of diethyl ether, and in a separate container oxalic acid (1.1 equiv.) is dissolved in a minimal amount if diethyl ether. The dissolved oxalic acid was then added drop-wise to the reaction mixture. The oxalate salts (73a, 74f, 73k, 78a, 82a, and 86a) were immediately formed and collected by vacuum filtration.

3,3-Diphenylazetidine oxalate salt (73a, ANT-243)

General Procedure B. The azetidine was obtained as a white solid; mp 230.5-232.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.69 (s, 2H), 7.44 (d, $J$ = 7.2 Hz, 4H), 7.34 (t, $J$ = 6.9 Hz, 4H), 7.22 (t, $J$ = 6.6 Hz, 2H), 4.58 (s, 4H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 146.0, 129.4, 127.5, 126.5, 115.6, 75.8, 57.2, 55.9, 48.9.

3-Phenyl-3-(4-chlorophenyl)-azetidine oxalate salt (73f, ANT-289)

General Procedure B. The azetidine was obtained as a white solid; mp 214.6-217.6 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.51 - 7.26 (m, 8H), 7.24 (t, $J$ = 6.6, 1H), 4.58 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 145.6, 144.9, 132.3, 129.5, 129.3, 128.6, 127.6, 126.5, 57.0, 48.6.
### 3-Phenyl-3-(4-fluorophenyl)-azetidine oxalate salt (73k, ANT-332)

General Procedure B. The azetidine was obtained as a white solid; mp 164.2-166.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 7.51 – 7.40 (m, 4H), 7.35 (t, $J$ = 7.5 Hz, 2H), 7.20 (dt, $J$ = 17.5 Hz, $J$ = 7.9 Hz, 3H), 4.61 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 164.4, 162.8, 160.4, 145.9, 142.2, 142.2, 129.4, 128.8, 128.7, 127.5, 126.5, 126.2, 116.2, 116.0, 57.3, 48.7, 31.7.

### 3,3-Diphenylpiperidine oxalate salt (78a, ANT-312)

General Procedure B. The piperidine was obtained as a white solid; mp 110.2 – 111.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.94 (s, 1H), 7.32 (dt, $J$ = 15.3 Hz, $J$ = 7.8 Hz, 8H), 7.17 (t, $J$ = 6.8 Hz, 2H), 2.97 (s, 4H), 2.60 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 129.4, 127.0, 126.9, 55.9, 43.9, 41.3, 32.1.

### 3,3-Diphenylpyrrolidine oxalate salt (82a, ANT-339)

General Procedure B. The pyrrolidine was obtained as a white solid; mp 86.9 – 87.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.52 (s, 1H), 7.43 – 7.35 (m, 2H), 7.30 (t, $J$ = 7.1 Hz, 4H), 7.19 (dd, $J$ = 7.9 Hz, $J$ = 6.8 Hz, 4H), 3.93 (s, 2H), 3.16 (t, $J$ = 6.7, 2H), 2.70 (t, $J$ = 6.9, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 205.1, 204.8, 166.9, 163.2, 144.6, 129.3, 127.4, 127.2, 55.1, 53.7, 44.2, 36.0.
**3,3-Diphenyltropane oxalate salt (86a, ANT-325)**

General Procedure B. The tropane was obtained as a white solid; mp 113.1-115.3 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.33 – 7.24 (m, 8H), 7.18 (td, $J$ = 5.9 Hz, $J$ = 2.9 Hz, 2H), 1.98 (s, 9H), 1.76 (d, $J$ = 11.1 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.6, 144.8, 129.1, 127.8, 127.2, 115.6, 114.4, 55.1, 54.3, 46.4, 36.2, 33.5, 27.6, 26.5.

**General Procedure C: Formation of p-substituted Phenyl-aryl-heterocycle oxalate salt**

Aluminum chloride (3.5 equiv.) placed in an ice bath and suspended in substituted-benzene (1.5 mL). $N$-protected-aryl-heterocycle secondary alcohols (28, 77, 81 or 85) were separately dissolved in substituted-benzene (1.5mL) and added to the suspended aluminum chloride. The mixture was stirred at 0 °C under argon for 2 hours. The reaction was then quenched with 0.1g of ice and allowed to stir for 30 minutes. Saturated sodium bicarbonate (3mL) was then added to the mixture followed by ammonium hydroxide to achieve a pH of 11. The mixture was then extracted with DCM (3 x 5 mL), washed with brine (2 x 5 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The mixture was then re-dissolved in a minimal amount of diethyl ether, and in a separate container oxalic acid (1.1 equiv.) is dissolved in a minimal amount if diethyl ether. The dissolved oxalic acid was then added drop-wise to the reaction mixture.
The oxalate salts (73b-e, 74g-j, 73l-o, 78b-d, 82b-d, and 86b-d) were immediately formed and collected by vacuum filtration.

3-(4-Chlorophenyl)-3-phenyl-azetidine oxalate salt (73b, ANT-267)

General Procedure C. The azetidine was obtained as a white solid; mp 210.4-212.1 °C; \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) δ 9.81 (s, 2H), 7.54 – 7.32 (m, 8H), 7.24 (t, \(J = 7.0\) Hz, 1H), 4.58 (s, 4H); \(^{13}\)C NMR (100 MHz, DMSO-\(\text{d}_6\)) δ 145.6, 144.9, 132.3, 129.5, 129.3, 128.6, 127.6, 126.5, 57.0, 48.6.

3-(4-Fluorophenyl)-3-phenyl-azetidine oxalate salt (73c, ANT-268)

General Procedure C. The azetidine was obtained as a white solid; mp 221.4-223.8 °C; \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) δ 9.84 (s, 2H), 7.55 – 7.41 (m, 4H), 7.35 (t, \(J = 7.2\) Hz, 2H), 7.22 (dt, \(J = 17.1\) Hz, 7.6 Hz, 3H), 4.76 – 4.44 (m, 4H). \(^{13}\)C NMR (100 MHz, DMSO-\(\text{d}_6\)) δ 162.8, 160.4, 145.9, 142.2, 129.4, 128.8, 128.8, 127.6, 116.2, 116.0, 75.8, 57.2, 56.2, 48.5, 46.2.

3-(4-Methylphenyl)-3-phenyl-azetidine oxalate salt (73d, ANT-330)

General Procedure C. The product was obtained as a white solid; mp 185.6-187.6 °C; \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) δ 7.40 (d, \(J = 7.8\) Hz, 11H), 7.36 – 7.27 (m, 4H), 7.21 (t, \(J = 7.2\) Hz, 1H), 7.14 (d, \(J = 7.9\) Hz, 2H), 4.58 (s, 4H), 2.23 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-\(\text{d}_6\)) δ 165.3, 146.2, 143.1, 136.7, 129.9, 129.3, 127.4, 126.4, 115.6, 57.3, 48.9, 21.1.
3-(4-Methoxyphenyl)-3-phenyl-azetidine oxalate salt (73e, ANT-331)

General Procedure C. The azetidine was obtained as a white solid; mp 160.0-162.8 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.40 – 7.21 (m, 7H), 6.89 (d, $J = 8.6$ Hz, 2H), 4.64 – 4.52 (m, 4H), 3.70 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 165.1, 158.6, 146.4, 137.9, 127.8, 127.3, 126.8, 126.4, 121.4, 116.5, 114.7, 57.3, 56.6, 55.9, 55.8, 48.6, 31.3.

3-(4-Chlorophenyl)-3-(4-chlorophenyl)-azetidine oxalate salt (73g, ANT-290)

General Procedure C. The azetidine was obtained as a white solid; mp 219.6-221.1 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.63 (s, 1H), 7.47 (d, $J = 8.1$ Hz, 4H), 7.41 (d, $J = 7.9$ Hz, 4H), 4.54 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 144.5, 135.5, 132.4, 129.4, 129.4, 128.6, 56.9, 48.3.

3-(4-Fluorophenyl)-3-(4-chlorophenyl)-azetidine oxalate salt (73h, ANT-318)

General Procedure C. The azetidine was obtained as a white solid; mp 170.9-172.9 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.49 – 7.41 (m, 6H), 7.18 (t, $J = 8.8$ Hz, 2H), 4.72 – 4.48 (m, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 165.4, 162.9, 160.5, 144.8, 141.8, 135.5, 132.3, 129.3, 128.8, 128.7, 128.6, 116.3, 116.1, 99.0, 90.2, 57.1, 48.4.

3-(4-Methylphenyl)-3-(4-chlorophenyl)-azetidine oxalate salt (73i, ANT-291)

General Procedure C. The azetidine was obtained as a white solid; mp 203.4-204.6 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.65 (s, 1H), 7.42 (dd, $J = 20.8$ Hz, $J = 7.4$ Hz, 4H), 7.29 (d, $J = 7.1$ Hz,
2H), 7.15 (d, J = 7.0 Hz, 2H), 4.54 (s, 4H), 2.23 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 145.1, 142.6, 136.9, 132.2, 130.0, 129.2, 128.6, 126.4, 57.1, 48.3, 21.2.

**3-(4-Methoxyphenyl)-3-(4-chlorophenyl)-azetidine oxalate salt (73j, ANT-319)**

General Procedure C. The azetidine was obtained as a white solid; mp 155.7-159.8 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.41 (q, J = 8.7 Hz, 4H), 7.32 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.55 (s, 4H), 3.70 (d, J = 3.9 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 165.5, 158.8, 145.3, 137.5, 132.1, 129.2, 128.9, 128.5, 127.8, 114.8, 99.0, 94.6, 85.9, 75.8, 57.2, 55.8, 48.3.

**3-(4-Chlorophenyl)-3-(4-fluorophenyl)-azetidine oxalate salt (73l, ANT-333)**

General Procedure C. The azetidine was obtained as a white solid; mp 166.1-168.2 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.52 – 7.44 (m, 4H), 7.40 (d, J = 8.6 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 4.58 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 165.4, 162.9, 160.4, 144.9, 141.8, 132.3, 129.3, 128.8, 128.7, 128.6, 116.3, 116.1, 95.7, 75.8, 57.0, 48.4.

**3-(4-Fluorophenyl)-3-(4-fluorophenyl)-azetidine oxalate salt (73m, ANT-293)**

General Procedure C. The azetidine was obtained as a white solid; mp 212.9-214.4 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.52 (s, 1H), 7.48 (dd, J = 8.3 Hz, J = 5.6 Hz, 4H), 7.19 (t, J = 8.8 Hz, 4H), 4.55 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 162.9, 160.4, 155.4, 142.1, 128.8, 128.7, 116.3, 116.1, 57.3, 48.1.
3-(4-Methylphenyl)-3-(4-fluorophenyl)-azetidine oxalate salt (73n, ANT-313)

General Procedure C. The azetidine was obtained as a white solid; mp 161.4-163.3 °C; \(^1H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.46 (dd, \(J = 8.4\) Hz, \(J = 5.4\) Hz, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H), 7.21 – 7.12 (m, 4H), 4.53 (s, 4H), 2.23 (s, 3H). \(^{13}C\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 160.4, 142.9, 142.4, 136.8, 129.9, 128.8, 128.7, 126.4, 116.2, 115.9, 115., 57.2, 48.2, 21.2.

3-(4-Methoxyphenyl)-3-(4-fluorophenyl)-azetidine oxalate salt (73o, ANT-334)

General Procedure C. The azetidine was obtained as a white solid; mp 150.6-151.8 °C; \(^1H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.43 (dt, \(J = 12.4\) Hz, \(J = 6.2\) Hz, 2H), 7.32 (d, \(J = 8.7\) Hz, 2H), 7.17 (t, \(J = 8.8\) Hz, 2H), 6.90 (d, \(J = 8.6\) Hz, 2H), 4.68 – 4.44 (m, 4H), 3.71 (s, 3H). \(^{13}C\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 165.2, 158.7, 142.5, 137.8, 128.7, 128.6, 127.8, 116.1, 115.9, 114.8, 99.0, 65.6, 57.4, 55.8, 48.2, 31.4.

3-(4-Chlorophenyl)-3-phenyl-piperidine oxalate salt (78b, ANT-320)

General Procedure C. The piperidine was obtained as a white solid; mp 112.0 – 113.7 °C; \(^1H\) NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.60 – 7.04 (m, 9H), 2.98 (s, 2H), 2.54 – 2.38 (m, 6H). \(^{13}C\) NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 172.0, 164.8, 162.9, 150.0, 129.3, 123.9, 122.2, 120.7, 115.6, 90.2, 75.8, 70.2, 25.1.
**3-(4-Methoxyphenyl)-3-phenyl-piperidine oxalate salt (78c, ANT-329)**

General Procedure C. The piperidine was obtained as a white solid; mp 171.8-173.3 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 9.20 (s, 1H), 7.34 – 7.12 (m, 7H), 6.86 (d, \(J = 8.5\) Hz, 2H), 3.80 – 3.61 (m, 3H), 2.98 (s, 4H), 2.54 - 2.48 (m, 4H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 165.0, 158.1, 129.3, 128.3, 126.9, 126.7, 116.6, 114.7, 55.7, 43.3, 41.3, 32.5.

**3-(4-Methylphenyl)-3-phenyl-piperidine oxalate salt (78d, ANT-321)**

General Procedure C. The piperidine was obtained as a white solid; mp 120.1-121.5 °C; \(^1\)H NMR (400 MHz, DMSO-D\(_6\)) \(\delta\) 9.00 (s, 1H), 7.22 - 6.96 (m, 9H), 2.98 (s, 2H), 2.53 (d, \(J = 3.6\) Hz, 4H), 2.25 (s, 3H), 2.21 (s, 2H). \(^{13}\)C NMR (100 MHz, DMSO-D\(_6\)) \(\delta\) 164.2, 155.4, 138.4, 123.0, 129.8, 129.3, 127.5, 126.9, 124.1, 115.6, 44.2, 43.4, 41.3, 32.3, 30.2, 21.9, 21.1.

**3-(4-Chlorophenyl)-3-phenyl-pyrrolidine oxalate salt (82b, ANT-340)**

General Procedure C. The pyrrolidine was obtained as a white solid; mp 126.5 - 128.0 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta\) 7.41 – 7.06 (m, 9H), 4.47 - 4.14 (m, 1H), 3.85 - 3.79 (m, 1H), 3.56 – 3.29 (m, 1H), 2.72 – 2.56 (m, 1H), 2.34 – 2.08 (m, 1H), 1.68 (s, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta\) 196.3, 165.1, 165.1, 155.4, 130.4, 128.9, 128.4, 127.8, 116.6, 115.5, 115.6, 76.4, 75.8.
3-(4-Methoxyphenyl)-3-phenyl-pyrrolidine oxalate salt (82c, ANT-341)

General Procedure C. The pyrrolidine was obtained as a white solid; mp 115.1 – 118.8 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta 9.64\) (s, 1H), 7.38 – 7.20 (m, 7H), 6.89 – 6.79 (m, 2H), 3.90 - 3.81 (m, 2H), 3.66 (s, 4H), 3.12 (s, 2H), 2.75 – 2.56 (m, 2H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta 175.3, 172.1, 142.5, 140.2, 137.5, 129.2, 128.4, 127.1, 114.5, 113.2, 111.4, 110.2, 110.0, 75.8, 55.7.

3-(4-Methylphenyl)-3-phenyl-pyrrolidine oxalate salt (82d, ANT-342)

General Procedure C. The pyrrolidine was obtained as a white solid; mp 133.5 – 135.2 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta 9.58\) (s, 1H), 7.38 (t, \(J = 8.3\), 1H), 7.31 – 7.26 (m, 2H), 7.16 (d, \(J = 6.3\) Hz, 4H), 7.10 (d, \(J = 7.5\), 1H), 7.00 (s, 1H), 3.89 (d, \(J = 11.2\) Hz, 2H), 3.14 (s, 2H), 2.67 (dd, \(J = 15.3\) Hz, 7.1 Hz, 2H), 2.24 (d, \(J = 1.7\) Hz, 3H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta 163.5, 135.5, 129.8, 129.2, 127.7, 127.0, 124.2, 95.7, 94.5, 90.2, 44.1, 36.1, 21.8, 21.1.

3-(4-Chlorophenyl)-3-phenyl-tropane oxalate salt (86b, ANT-326)

General Procedure C. The tropane was obtained as an orange oil; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta 9.04\) (s, 1H), 7.92 – 6.96 (m, 9H), 1.98 - 1.94 (m, 8H), 1.76 (d, \(J = 8.1\) Hz, 2H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta 164.6, 144.7, 131.0, 129.2, 129.1, 128.6, 127.9, 127.7, 127.2, 115.6, 55.9, 55.2, 36.2, 33.4, 26.5.
3-(4-Methylphenyl)-3-phenyl-tropane oxalate salt (86d, ANT-328)

General Procedure C. The tropane was obtained as a white solid; mp 132.3-133.8 °C; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \(\delta 8.67\) (s, 1H), 7.33 – 6.99 (m, 9H), 3.07 (d, \(J = 6.0\) Hz, 3H), 2.04 – 1.88 (m, 8H), 1.80 - 1.77 (m, 2H). \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \(\delta 162.1, 131.7, 131.6, 131.1, 129.7, 129.2, 128.7, 128.6, 127.7, 127.3, 127.2, 114.4, 55.3, 30.2.\)
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95 Kaur, H. Synthesis and Evaluation of Novel Tropanone Compounds as Potential
Appendix I

List of abbreviations

METH – Methamphetamine
DAT – Dopamine transporter
SERT – Serotonin transporter
NET – Norepinephrine transporter
IC$_{50}$ – Half maximal inhibitory concentration
$K_i$ – Inhibition constant
SSRI – Serotonin selective re-uptake inhibitor
SNRI – Serotonin/Norepinephrine re-uptake inhibitor
cLogP – Calculated lipophilicity
EtOAc – Ethyl acetate
DI – Deionized water
DCM – dichloromethane
NH$_4$Cl – Ammonium chloride
THF – Tetrahydrofuran
LAH – Lithium aluminum hydride
TFA – Trifluoroacetic acid
### Table 1: Crystal data and structure refinement for ANT-35.

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Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for ANT-1. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for ANT-1.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for ANT-1. The anisotropic displacement factor exponent takes the form: -2π² \[ h^2 a^\ast 2 U^{11} + \ldots \]

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<th></th>
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<th>U^{22}</th>
<th>U^{33}</th>
<th>U^{23}</th>
<th>U^{13}</th>
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Table 5. Hydrogen coordinates ($x$ x $10^4$) and isotropic displacement parameters ($Å^2 x 10^{-3}$) for ANT-1.

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<th>z</th>
<th>U(eq)</th>
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Table 6. Torsion angles [°] for ANT-1.

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Symmetry transformations used to generate equivalent atoms:
Table 7. Hydrogen bonds for ANT-1 [Å and °].

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<th>d(H...A)</th>
<th>d(D...A)</th>
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</table>

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,z+1/2
Vita

The author was born in Charleston, West Virginia on August 24, 1986. She graduated from Myrtle Beach High School in Myrtle Beach, South Carolina in 2004. She received a Bachelors of Science in Chemistry from Clemson University in Clemson, South Carolina in 2008. In the fall of 2009, she came to the University of New Orleans. She completed the requirements for the degree of Doctor of Philosophy in Organic Chemistry in December 2013 under the supervision of Professor Mark L. Trudell.