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# Synthesis and Biological Evaluation of N-heterocycles for Activity on Monoamine Transporters and Exploration of Iridium Chemistry for Synthesis of Medicinally Important Molecules

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# Synthesis and Biological Evaluation of N-Heterocycles for Activity on Monoamine Transporters and Exploration of Iridium Chemistry for Synthesis of Medicinally Important Molecules

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CHAPTER 1

## Abstract

The focus of these studies was directed towards the synthesis of novel N-heterocyclic compounds and pharmacological evaluation of these compounds for activity at monoamine transporters. A series of novel piperidine and pyrrolidine analogues were prepared from commercially available starting material with a three and four step synthetic method, respectively. A variety of substituents on the aromatic ring were incorporated to achieve a diverse library of compounds. The preliminary binding studies of piperidine molecules showed strong affinity towards serotonin transporters and moderate affinity towards dopamine transporters. The focus of further studies was directed towards utilization of iridium catalysis for the development of new synthetic methods for biologically important molecules. This research has led to the development of a new synthetic strategy for the construction of nicotine and its analogues. In addition, the iridium catalysis was also used for alkylation of amides with primary and secondary alcohols under microwave conditions.

Key words: Dopamine, Serotonin, Methamphetamine, Cocaine, Iridium, *N*-Heterocyclization, Catalysis, Microwave, Nicotine, N-Alkylation

# Chapter 1: Design, synthesis and evaluation of novel piperidine derivatives for monoamine transporter affinity

## 1.1. Abstract

In an effort to search for potential therapeutic agents for methamphetamine addiction, a novel class of compounds was synthesized and evaluated for *in vitro* dopamine and serotonin transporter affinities. These unique 4β-aryl-4α-arylmethoxypiperidine analogues incorporated the structure of previously designed dual monoamine transporter selective 3β-aryl-3α-arylmethoxytropane and serotonin selective meperidine derivatives.

The short three step methodology was developed for the synthesis of the target compounds. To study the effect of substitution of aryl group on dopamine and serotonin affinity, we substituted various derivatives with electron-donating, electron-withdrawing and halogen groups on the aryl ring. All the compounds were tested for affinity for dopamine and serotonin transporters by ability of these compounds to displace natural radiolabeled ligands from the transporters.

## 1.2. Introduction

### Psychostimulants

Cocaine **(1)** and amphetamines are the most common illicit stimulants among drug abused individuals. According to data from the 2012 National Survey on Drug Use and Health (NSDUH), over 12 million people (4.7 percent of the population) have tried methamphetamine at least once. NSDUH also reports that approximately 1.2 million people used methamphetamine in the year leading up to the survey. The number of people who abused methamphetamine for the first time in the past year has increased by 62% from 2008 to 2009.[1] Since then, there has been

little deviation from this level of psychostimulant abuse. The U.S. Department of Justice's National Drug Threat Assessment continues to report that total 82% of state and local agencies in the Western states perceive methamphetamine and cocaine as their greatest drug threat (**Figure 1.1**).[2]

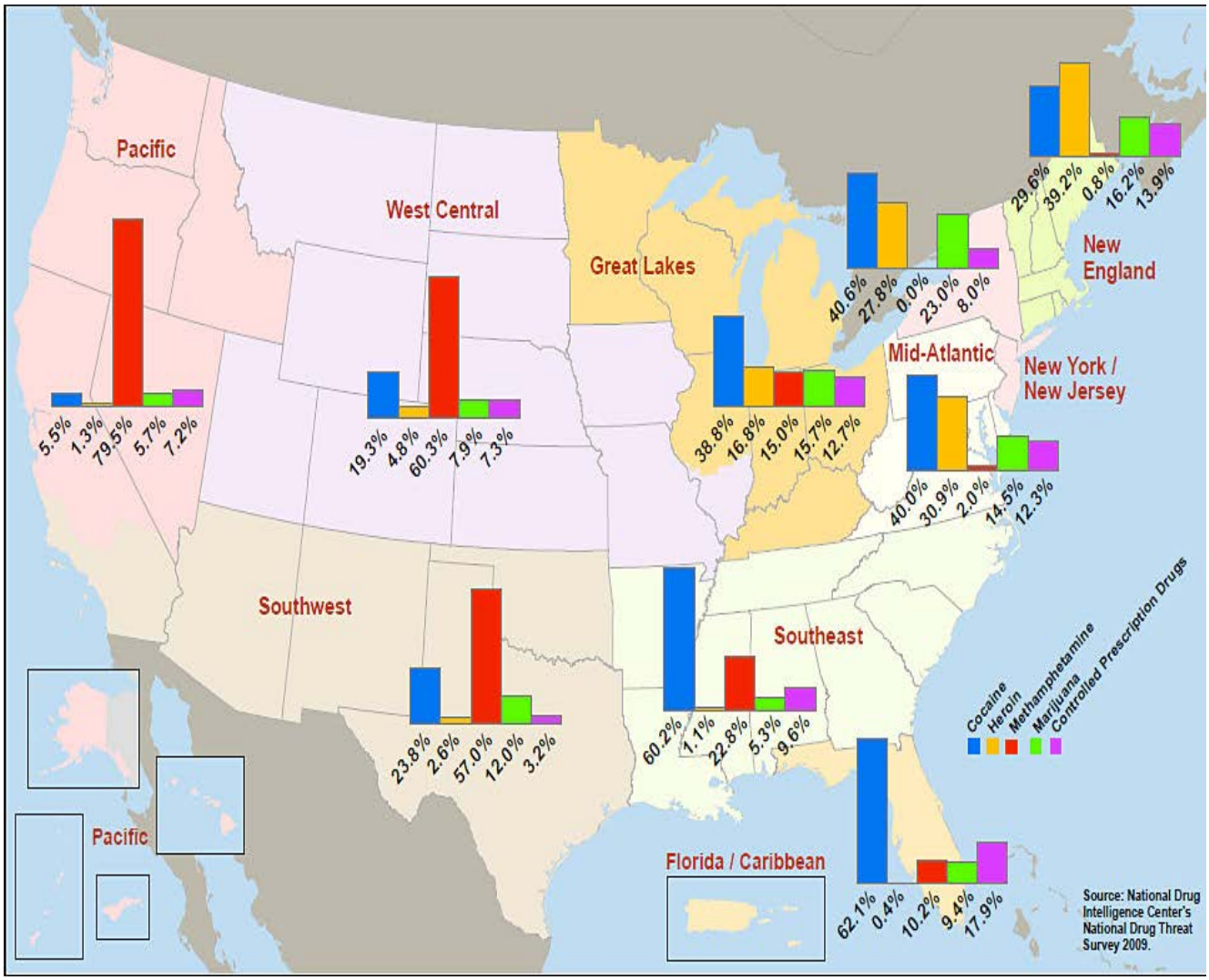
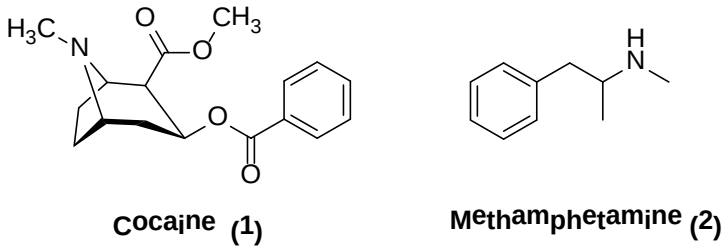



**Figure 1.1.** Illicit drug use profile in USA.[2]

**Cocaine and Methamphetamine**

Cocaine (**1**), (**Figure 1.2**) (street name: *Coke, snow, flake, blow*) is a tropane alkaloid that is obtained from the leaves of *Erythroxylum coca* plant. The genus Erythroxylum contains about 250 species and many of the members produce cocaine.[3] The amount of cocaine in the plant is less than 1%. It is a weakly alkaline compound (an "alkaloid"), and can therefore combine with acidic compounds to form various salts. Cocaine hydrochloride in its purest form is a white, crystalline product. [3]




Cocaine (1) Methamphetamine (2)

**Figure 1.2.** Cocaine **(1)** and Methamphetamine **(2)**

As a psychostimulant, methamphetamine **(2) (Figure 1.2)** (METH) (street name: *Speed, meth, chalk, ice, crystal, glass*) differs significantly from cocaine. METH is a phenyl-ethyl-amine and a member of the amphetamine class of psychostimulants. Methamphetamine can be readily synthesized by reduction of commercially available ephedrine or pseudoephedrine found in over the counter cold and allergy medicines.[4] It is a white, odorless, bitter-tasting powder which dissolves in water or alcohol. METH was developed early last century from its parent drug, amphetamine, and was used originally as a nasal decongestant and in bronchial inhalers. Methamphetamine causes increased activity, decreased appetite and a general sense of well-being. In high concentration, high levels of methamphetamine get into the brain, making it a more potent stimulant drug with long lasting and harmful effects on the central nervous system. METH is a Schedule 2 stimulant, which means it is a drug that has been classified for having a

high potential for being abused, and it is available only by prescription. It is prescribed for the treatment for narcolepsy and attention deficit hyperactivity disorder but these medical uses are limited, and the doses prescribed are much lower than those typically abused. METH can exist in two enantiomeric forms, dextrorotatory and levorotatory. The (*d*)-methamphetamine elicits the psychostimulant effects of the drug, while levo form is inactive on central nervous system (CNS).[3]

**Physiological effects of METH**

Methamphetamine causes anorexia, hyperactivity, dilated pupils, flushed skin, excessive sweating, restlessness, dry mouth and bruxism, diarrhea, and constipation. In high doses, METH can cause convulsions, stroke, heart attack and death.[5] Withdrawal symptoms of methamphetamine primarily consist of fatigue, depression, and increased appetite. Symptoms may last for days with occasional use, and weeks or months with chronic use. The severity is dependent on the length of time and the amount of methamphetamine used. Withdrawal symptoms may also include anxiety, irritability, headaches, agitation, restlessness, excessive sleep, vivid or lucid sleep, deep REM sleep and suicidal ideation.[3, 5]

**Pharmacological actions of METH**

Important differences exist between the neuropharmacological mechanisms of action of cocaine and METH. Cocaine mediates its effects at monoamine transporters. The stimulant and reinforcing effects of cocaine are primarily associated with the blockade of dopamine reuptake **(Figure 1.3).**[4, 6]

Cocaine binds to dopamine re-uptake transporters on the pre-synaptic membranes of dopaminergic neurones. This binding inhibits the removal of dopamine from the synaptic cleft and its subsequent degradation by monoamine oxidase in the nerve terminal. Dopamine remains in the synaptic cleft and is free to bind to its receptors on the post synaptic membrane, producing further nerve impulses. This increased activation of the dopaminergic reward pathway leads to the feelings of euphoria and the 'high' associated with cocaine use **(Figure 1.3).**

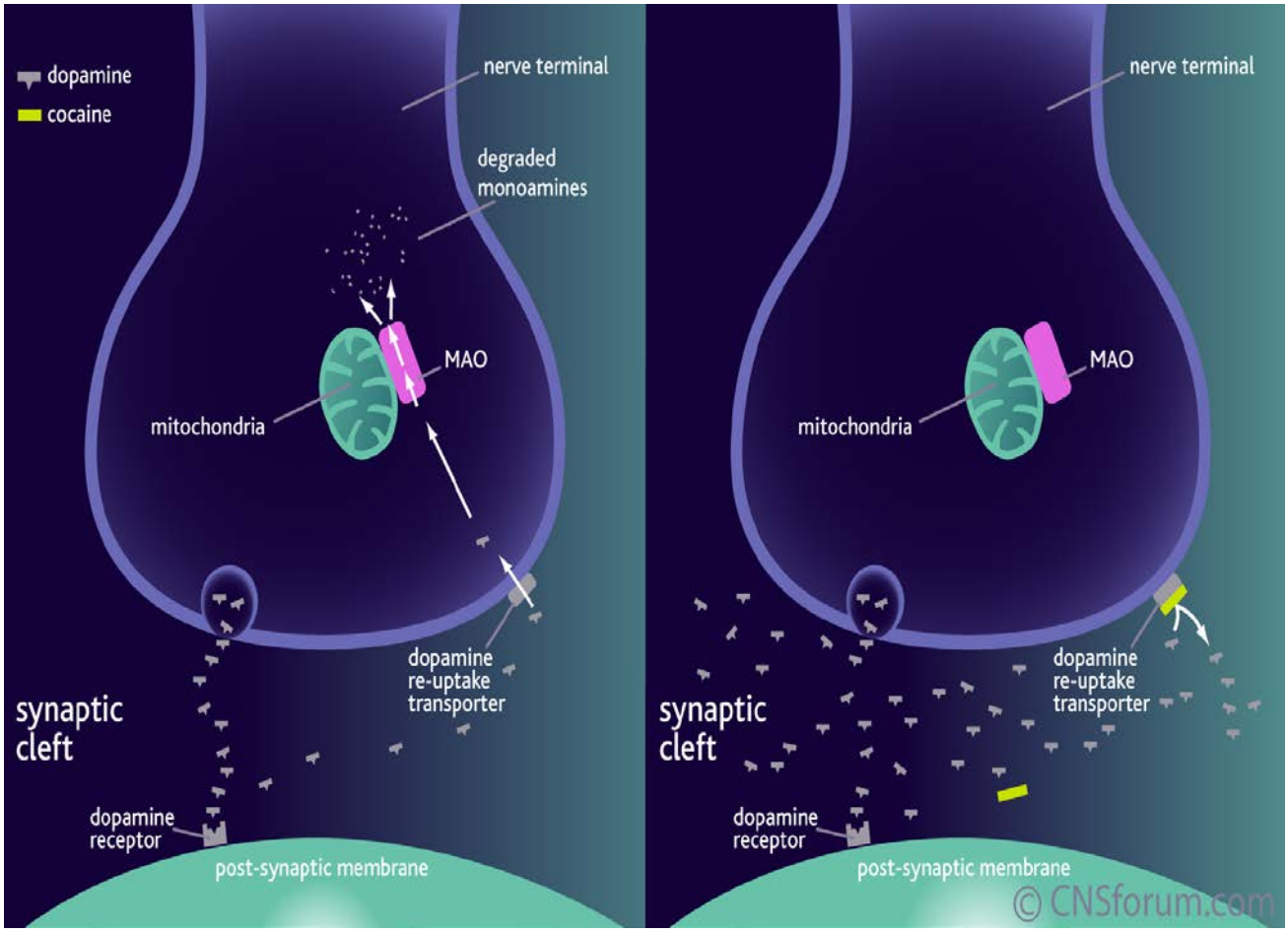



**Figure 1.3.** Mechanism of cocaine action on the dopamine transporter[7]

Alternatively, the mechanism of action of METH appears to be more complex. METH is a neurotransmitter releaser, triggering the release of monoamine neurotransmitters (dopamine,

serotonin, and norepinephrine) via the corresponding transporter system in the brain. At high doses, METH increases the concentration of dopamine in the synaptic cleft in 4 ways: (1) it can bind to the pre-synaptic membrane of dopaminergic neurons and induce the release of dopamine from the nerve terminal; (2) It can interact with dopamine containing synaptic vesicles, releasing free dopamine into the nerve terminal; (3) It can bind to monoamine oxidase in dopaminergic neurons and prevent the degradation of dopamine, leaving free dopamine in the nerve terminal; and (4) It can bind to the dopamine re-uptake transporter, causing it to act in reverse and transport free dopamine out of the nerve terminal. High-dose amphetamine has a similar effect on noradrenergic neurons; it can induce the release of noradrenaline into the synaptic cleft and inhibit the noradrenaline re-uptake transporter **(Figure 1.4)**.

Releasers and uptake inhibitors have dissimilar outcomes at the synapses.[6] Although both mechanisms increase synaptic neurotransmitter concentrations, releasers produce larger increases in extracellular neurotransmitter concentration. Moreover, the increased concentration effects are not regulated by neurotransmitter autoreceptor mechanisms. Thus releasers and uptake inhibitors produce significantly different cellular responses.[4]

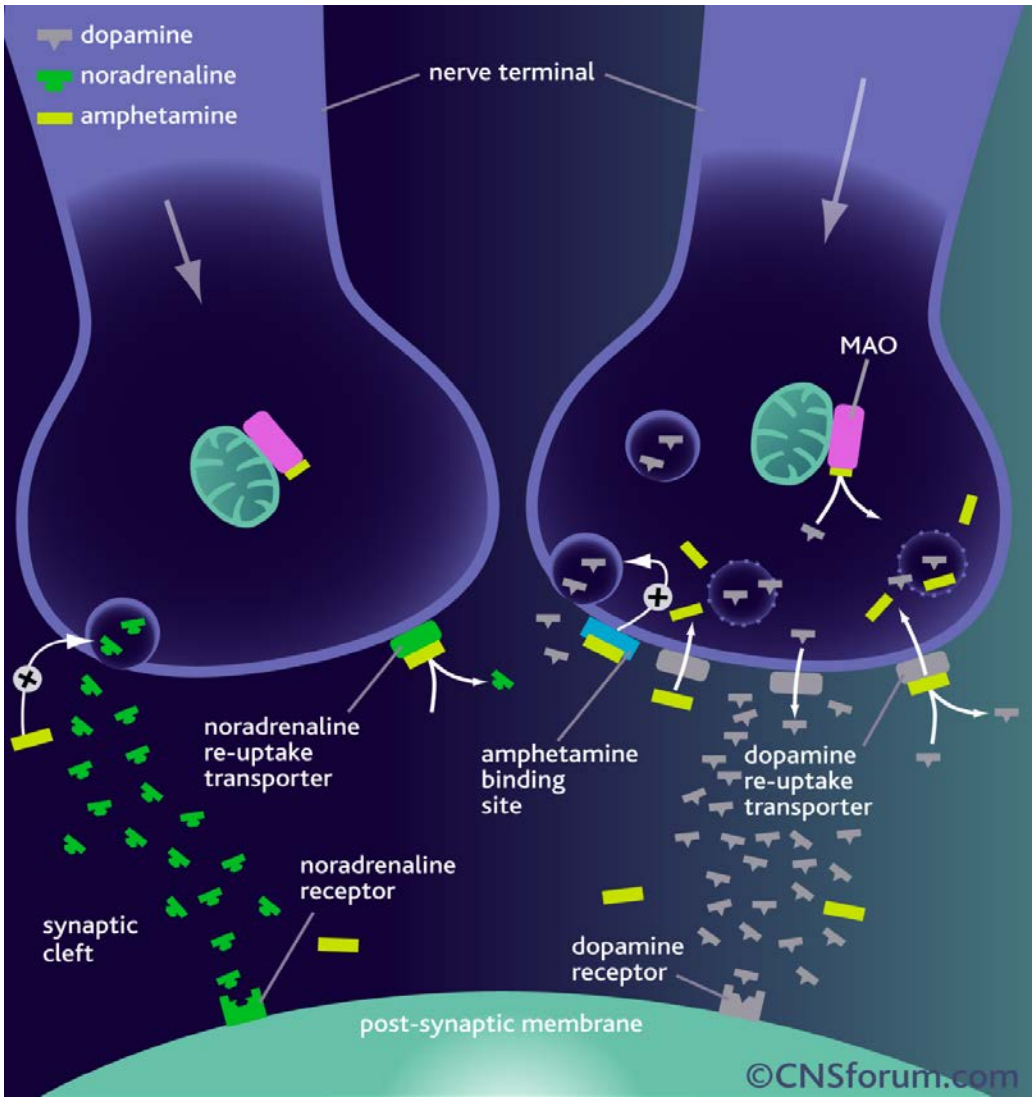



**Figure 1.4.** Mechanism of METH action[8]

It has long been the assumption that disruption of dopaminergic circuitry is the primary mechanism of action of METH. Post-mortem studies of METH-users have shown that striatal (caudate and putamen) dopamine levels are severely depleted, suggesting that METH can cause release of stored dopamine in sufficient amounts to deplete tissue stores of the neurotransmitter.[6,7] In addition, it has been reported that striatal concentrations of the dopamine transporter (DAT) in the post-mortem brains of METH-users are significantly decreased. In

contrast to dopamine, serotonin depletion is not observed to the same extent. However, recent positron emission tomography (PET) imaging studies indicate significant loss of the serotonin transporter (SERT) in both cerebral cortical and sub-cortical brain regions of chronic METH-users. Furthermore, the extent of the SERT binding decrease was more severely affected than the corresponding DAT binding or that reported for SERT in chronic users of ecstasy i.e. (3, 4-methylenedioxymethamphetamine (MDMA) a known serotonergic hallucinogen. These results are consistent with the behavioral effects associated with METH exposure (e.g., problems in cognition and aggression) and could well be explained by a disruption of serotonergic circuitry.

**Treatment of METH dependence**

To date there is no pharmacological therapy for METH-dependence or the adverse side effects associated with craving and withdrawal. A variety of medications have been investigated as potential treatment strategies, however, none have been identified as having significant promise.[10]

**Dopamine agonists**

Some modest success with dopamine agonist bupropion (**3**) has been reported.[4, 11] Bupropion was reported to reduce METH use among "light "abusers but was not effective against "heavy" METH-users. Alternatively, modafinil (**4**) showed no clear evidence of efficacy in reducing METH use.[12] In addition, other clinical trials have shown that the dopamine partial agonist aripirizole (**5**) and GABAergic agent gabapentin (**6**) exhibited no efficacy toward reduction of METH-use **(Figure 1.5)**.[13, 14]

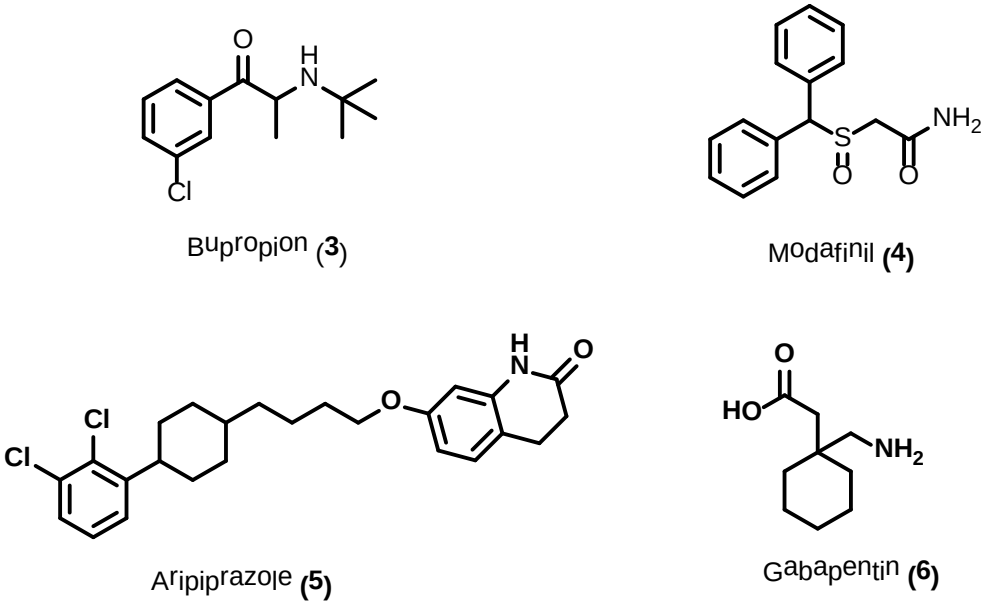



**Figure 1.5.** Dopamine agonists

**Selective serotonin reuptake inhibitors**

Studies have shown that some selective serotonin uptake inhibitors (SSRIs, e.g., fluoxetine (**7**), paroxetine (**8**) block the effects of METH in animals, [15, 16] but clinical studies with SSRIs have been much less promising.[15, 17-19] Recent clinical findings have indicated that treatment of chronic METH-users with the SSRI sertaline (**9**) resulted in sustained METH-craving and an elevated likelihood of relapse **(Figure 1.6)**.[20]

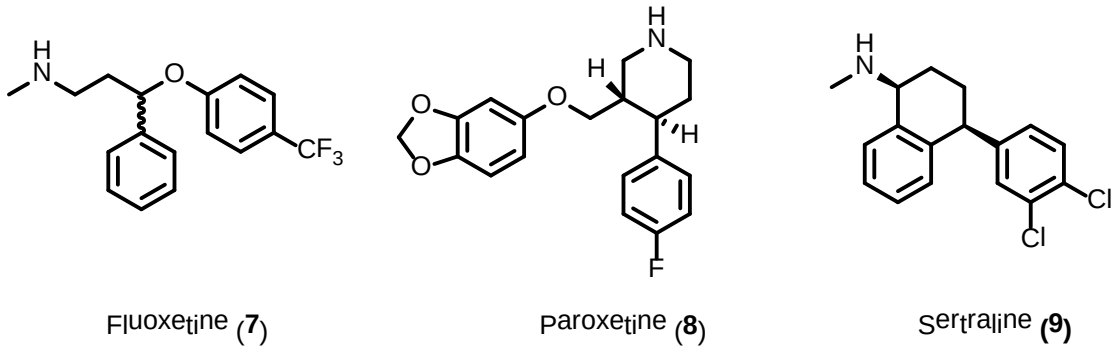



**Figure 1.6.** Selective serotonin uptake inhibitors (SSRIs) - fluoxetine (**7**), paroxetine (**8**), Sertraline (**9**)

It is clear from the studies above that new medications are needed for METH–cessation. Currently available medications that have application to other abused substances fall short of being effective in treating the complex pharmacology of METH addiction.

**Dual acting DAT/SERT approach**

To date there is mounting evidence that in addition to dopaminergic systems, brain serotonergic systems also modulate responses in cocaine-induced behaviors and to a greater extent in methamphetamine-induced behaviors.[21] However, it has become evident that a single dopaminergic or serotonergic agent cannot adequately attenuate the behavioral effects associated with psychostimulant abuse. The abuse liability of selective dopaminergic agents has diminished enthusiasm for an agonist based approach to medication development and clearly SSRIs have not been effective in the clinic. However, it has been suggested that the development of an appropriately calibrated dual acting DAT/SERT agent may be more effective as a medication than a singularly selective transporter agent. For METH addiction, a dual acting DAT/SERT agent could be used to attenuate the reinforcing effects while providing protection from the psychotic effects associated with METH cessation.[21-23]

Based on the pharmacological evidence presented, it is clear that attenuation of dopaminergic and serotonergic pathways can affect the behaviors associated with METH abuse and addiction. However the question remains: What level of attenuation is required of each monoaminergic system to positively modify the behavioral effects of METH abuse? We believe that the proper balance of dopaminergic/serotonergic (and noradrenergic) reuptake inhibition can restore the monoaminergic tone of METH disrupted neuronal systems and lead to diminished craving, psychosis, depression and other symptoms of withdrawal.

Based on that approach in the past, our laboratory has focused upon the structure activity

relationships of meperidine **(10)** and related molecule. From the SAR of the meperidine derivatives and WIN analogues (**11),** it was found that the 3, 4-dichlorophenyl group is important moiety for the molecular recognition at the DAT.[24] Moreover, meperidine is more selective for the serotonin transporter over the dopamine transporter. Studies on aryl substituted meperidine analogues reveled that dopamine transporter affinity of these could be enhanced with predominant SERT activity. This effect of aryl substitution on the DAT affinity of meperidine analogues is paralleled with the SAR for reported tropane analogues and piperidine analogues. However unlike these piperidine and tropane analogues that are DAT selective 3, 4-dichloromeperidine (**12**), exhibit high potency at the SERT ($K_i$ = 19nM) and was slightly SERT-selective (DAT/SERT=6.7) **(Figure 1.7)**.[25]

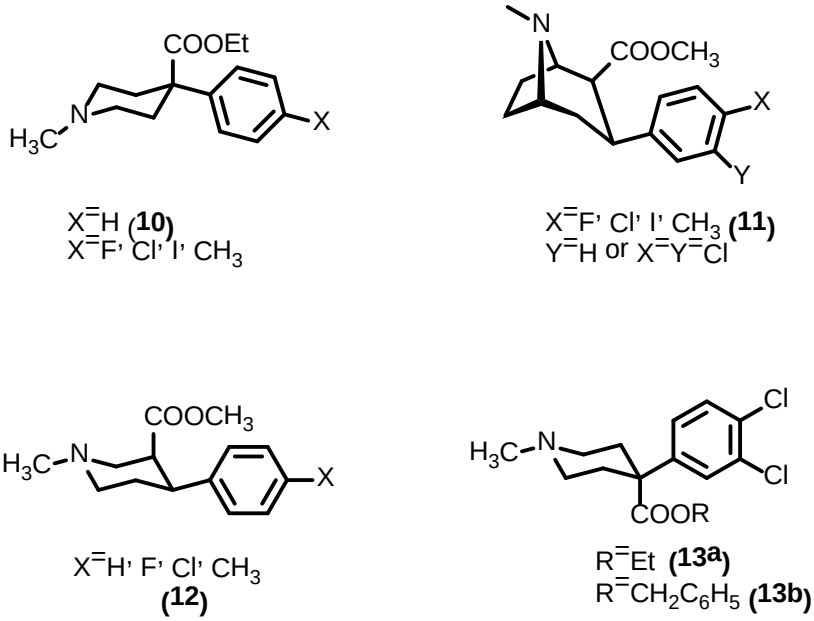
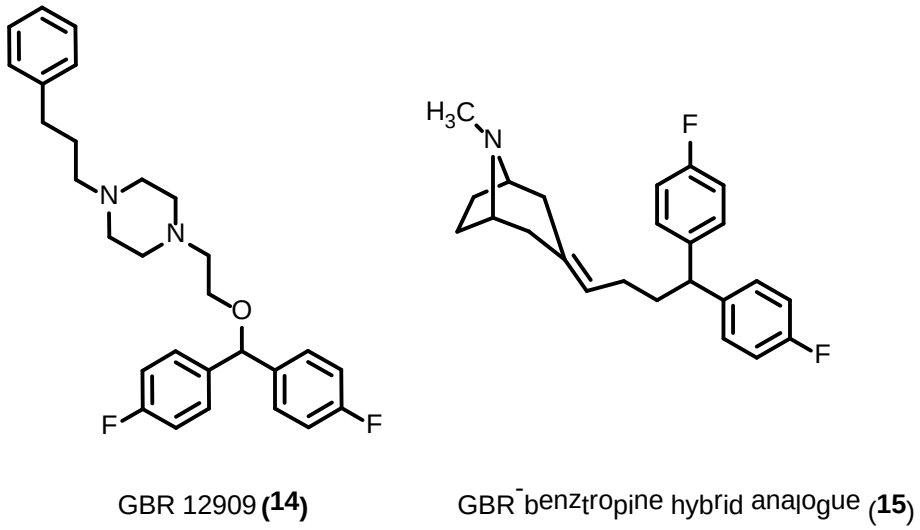



**Figure 1.7.** Meperidine analogues

Our group explored the structure activity relationships of 3, 4-dichloromeperidine analogues (**13**) at dopamine and serotonin transporters. It was found that chemical modification of the ester group generally led to compounds with increased SERT activity. The benzyl ester **(13b)** was

found to be the most potent and most selective ligand of this study.[26]

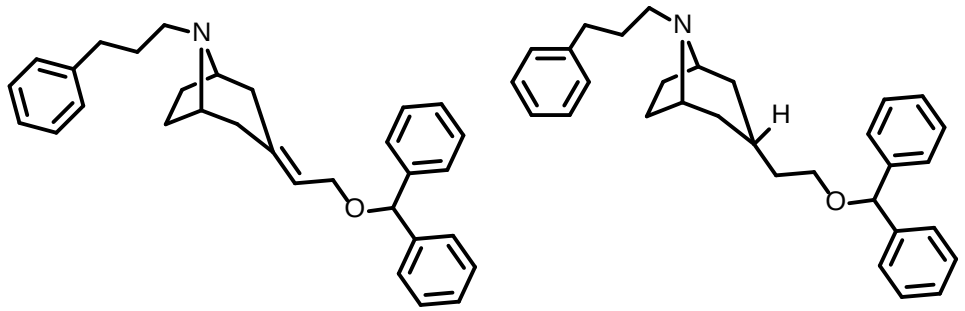
The disubstituted piperazine GBR 12909 **(14)** is a selective high affinity dopamine transporter ligand and a selective dopamine uptake inhibitor. The behavioral studies with GBR 12909 and related derivatives have shown potential for the development of an agonist based medicinally important molecule for the cocaine addiction. GBR 12909 exhibited slower onset and duration of action than cocaine while possessing much higher affinity for the DAT with slower dissolution rate. It also shown to antagonize the cocaine induced elevation of extracellular dopamine levels, The favorable pharmacological profile of GBR 12909 resulted to in-vivo studies that demonstrated its ability to suppress the cocaine self-administration behavior in rhesus monkeys, and exhibit non stimulant properties in humans. Although the development of GBR 12909 as cocaine medication was halted after phase I, human safety studies identified problematic cardiovascular effects. Due to the unique pharmacological profile of GBR 12909, it has served as a template for the synthesis of high affinity selective dopamine transporter ligands. The further results showed that the piperazine ring is not necessary for the affinity of GBR 12909 for the dopamine transporters. The tropane and piperidine based derivatives of the GBR 12909 have been also found to exhibit moderate to high affinity for the DAT with improved selectivity over the serotonin transporter **(Figure 1.8)**.[27]




GBR 12909 **(14)** GBR-benztropine hybrid analogue **(15)**

**Figure 1.8.** GBR 12909 **(14)** and GBR-benztropine hybrid analogue **(15)**

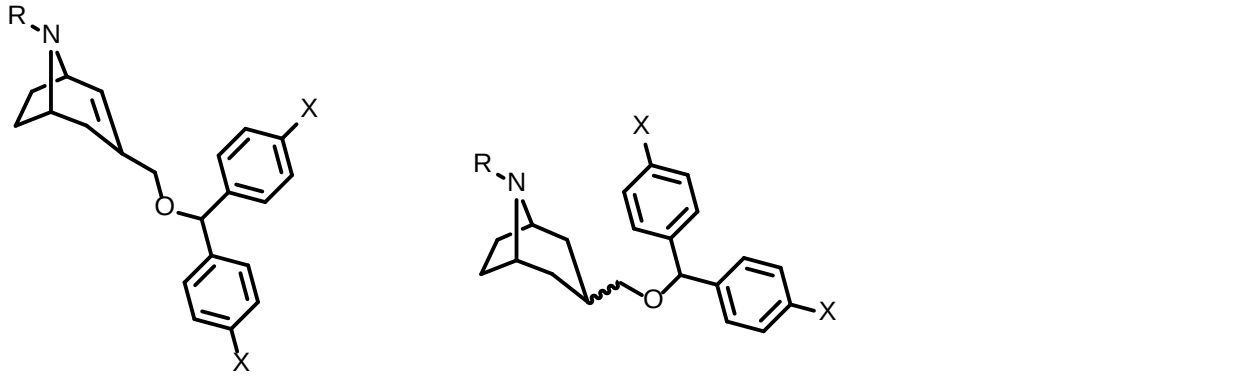
Rice and coworkers have reported the GBR-benztropane analogue **(15)** was found to be selective for DAT. The pharmacological profile of **15** was found to be more like the GBR compounds than benztropine.[19] Further, our laboratories have synthesized 3-(2-(diarylmethoxyethylidene)-8-alkyl-aryl-8-azabicyclo[3.2.1]octane analogues and the dopamine transporter affinity was determined. The ethylidene analogues exhibited higher selectivity for binding at the DAT over the SERT, with **16** nearly 10-fold more selective than GBR-12909. It was evident from studies that 3-ethylidenyl-8-azabicyclo[3.2.1]octane ring system is an important structural feature for selective molecular recognition at the DAT. This compound also exhibited similar potency as that of corresponding 3α-tropane congeners **15** but were significantly more selective for the DAT than **18**. The structure-activity relationship studies of **16** and related tropane analogues, suggest that the high selectivity of **16** resulted from either the rigid conformation of 3-ethylidenyltropane ring system or the stereochemical effects imparted by unsaturation at C3. **(Figure 1.9)**.[28]




3-ethylidenyl-8-azabicyclo-[3.2.1]octane derivative (**16**) Tropane congener (**17**)

**Figure 1.9.** 3-ethylidenyl-8-azabicyclo-[3.2.1]octane derivative **(16)** and Tropane congener **(17)**

Our group investigated the effects of unsaturation and stereochemistry at C3 of these tropane-GBR 12909 hybrid analogues on DAT and SERT binding affinities. For investigation of this effect, our group designed and synthesized a series of 3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo [3.2.1] oct-2-enes (**18**). Furthermore, to address the question of stereochemical proximity effects of the benzhydryl ether moiety relative to DAT affinity, the 3α- and 3 β-diarylmethoxymethyl-8-alkylaryl-8-azabicyclo-[3.2.1]-octane derivatives were synthesized (**19**) **(Figure 1.10)**.[28]




3-diarylmethoxymethyl-8-arylalkyl-8-azabicyclo [3.2.1] oct-2-ene (**18**) Diarylmethoxymethyl-8-alkylaryl-8-azabicyclo [3.2.1] octane (**19**)

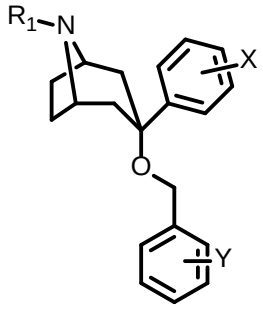
**Figure 1.10.** 3-Diarylmethoxymethyl-8-arylalkyl-8-azabicyclo [3.2.1] oct-2-ene **(18)** and its saturated analogues **(19)**

It was found that diarylmethoxytropane analogues exhibited similar DAT structure activity to that of 3α-diarylmethoxyethyl and 3-diarylethylidienyltropane analogues. The results suggested that conformational strain imparted by unsaturation at C3 is important for selectivity at the dopamine transporter over the serotonin transporter. This is supported by SAR of 3α-isomers in this series, which despite the reduced ether length between benzhydryl ether moiety and the tropane ring system exhibited similar DAT binding affinity to the 3-arylmethoxyethylidinyltropanes but were less selective for DAT over SERT. The compounds with 3α-stereochemistry were not as well accommodated by transporter constraints for potent molecular recognition.[27, 28]

Our efforts to develop a novel scaffold for targeting monoamine transporter systems have led to the development of several class of DAT and SERT ligands. There have been a number of reports that describe 3-aryltropane derivatives exhibiting high affinity and selectivity for the DAT.[28] Furthermore, we also have reported on a series of piperidine derivatives that exhibit affinity and selectivity for SERT. Our group has devised a new pharmacophore by merging these two classes of molecules. Furthermore, the arylmethoxy moiety was also included which is common in many of the prototypical SSRIs and SNRIs.[30, 31]

The designed 3-arylmethoxy-3-aryltropane pharmacophore by merging two pharmacophore found active on DAT and SERT. It has showed SERT selectivity and exhibited high affinity for the SERT. The monochloro derivative exhibited good affinity for all three transporters. However, high lipophilicity of these compounds precluded its progress to further development into clinical trials. The 3-arylmethoxy-3-aryltropanes was a unique class of monoamine transporter ligands that possess tunable affinity for dopamine and serotonin transporters.[32] This prompted us a broader examination of the structure-activity relationships of this molecular

scaffold in search of compounds with dual affinity for dopamine and serotonin transporters. It was of interest to explore condensed ring systems that would accommodate the pharmacophore requirements while reducing the overall molecular weight and lipophilicity inherent to the tropane derivatives (**Figure 1.11)**.[32]




Pharmacophore 1.

**Figure 1.11.** Design of Pharmacophore 1

Recently, In order to devise novel molecular scaffolds targeting monoamine transporters, our group has identified the condensed ring system with low molecular weight and lipophilicity, 3-arylmethoxy-3-arylazetidines as viable targets for the synthesis and biological evaluation at monoamine transporters. It was found that the arylazetidines exhibited high affinity for the SERT and were generally selective for the SERT over the DAT. However, it was also clear that the DAT affinity can be improved with proper substitution of the 3-aryl group.[33]

## 1.3. Design of new Pharmacophore

In search of a new pharmacophore we decided to merge structural characteristics of **Pharmacophore 1** and piperidine derivatives (which have been found to be active at SERT). Given the similar structural characteristics of these two classes of molecules 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 affinities. The new **pharmacophore 2** was designed **(Figure 1.12)**.

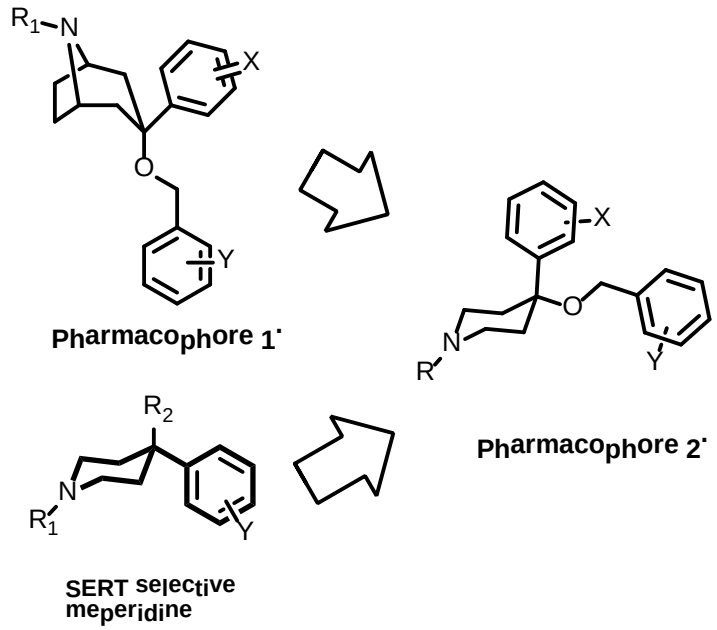



**Figure 1.12.** Design of Pharmacophore 2

## 1.4. Objectives

Based on the pharmacological evidence presented, it is clear that attenuation of dopaminergic and serotonergic pathways can affect the behaviors associated with METH abuse and addiction. We believe that the proper balance of dopaminergic/serotonergic (and noradrenergic) reuptake inhibition can restore the monoaminergic tone of METH disrupted neuronal systems and lead to diminished craving, psychosis, depression and other symptoms of withdrawal.

Based on the above hypothesis, the objective of this study is to explore dual DAT/SERT inhibitor for treatment of METH addiction. The focus of this study will be to design a SAR for the novel set of aryl piperidine derivatives. The developed SAR will be utilized to optimize potency and alter selectivity at the various transporters. The results of this project will provide the foundation for future studies aimed at the development of new medications for

methamphetamine addiction.

The designed pharmacophore analogues will be prepared from commercially available starting material 1-Boc-4-piperidone. Further, the method will be standardized for the synthesis of final target molecules by optimizing various conditions. After standardization of the synthetic method, a variety of electron withdrawing and electron releasing substituents will be introduced on the aromatic ring to produce a library of derivatives for biological evaluation.

Biological evaluation will consist of in initial in vitro screening at DAT and SERT to determine the binding affinity. In-Vitro binding affinity for monoamine transporters will be determined by ability of compounds to displace the radilabeled ligand from rat caudate-putmen tissue. The binding affinity for the DAT will be determined by inhibition of [$^3$H] WIN35,428 (**20**) and at SERT by inhibition of [$^3$H]Citalopram (**21**) **(Figure 1.13)**.[32]

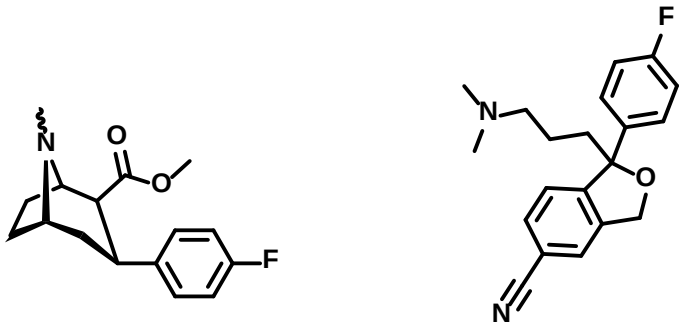
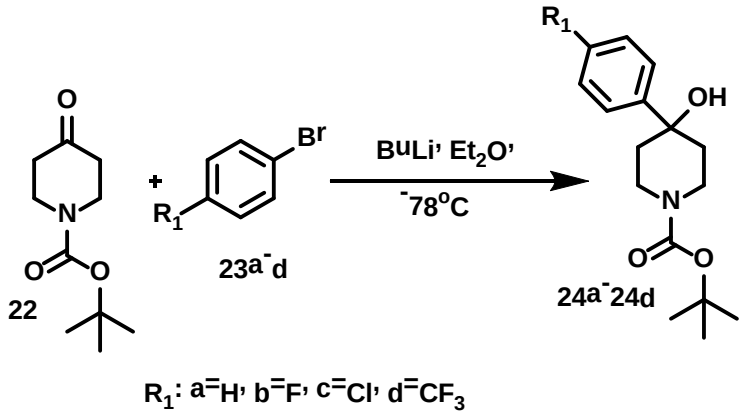



**Figure 1.13.** Radiolabelled ligands for the transporters for the binding studies.

## 1.5. Results and Discussion

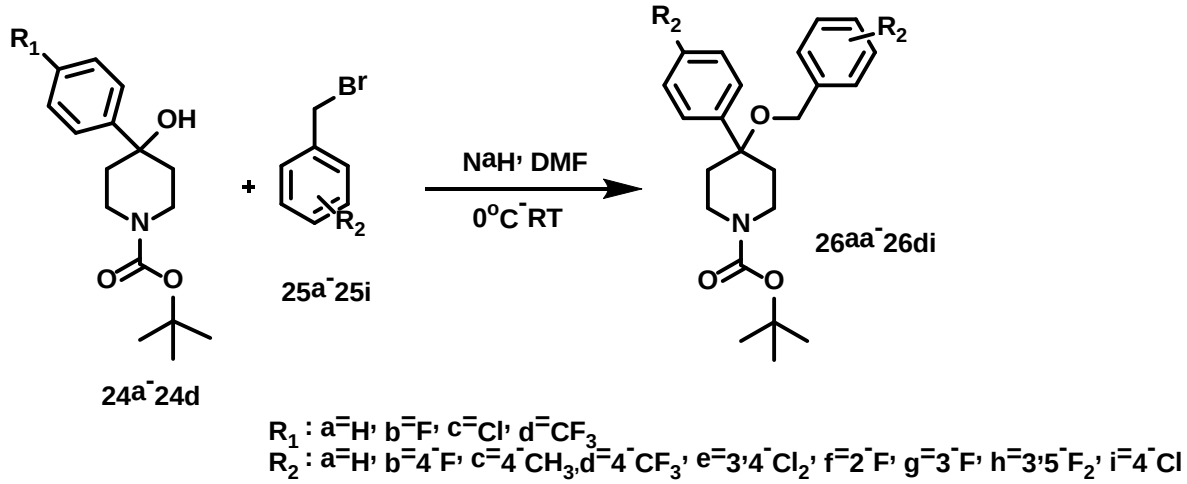
### Synthesis of target compounds

The commercially available 1-(Boc)-4-piperidone (**21**) was used for the synthesis of the target molecules. The 4-aryl moiety was introduced with a preformed aryl lithium reagent by addition to the ketone of 1-(Boc) 4-piperidone. A variety of substituents were installed on the aryl moiety to furnish intermediates **24a-24d (Scheme 1.1.)**. [32]



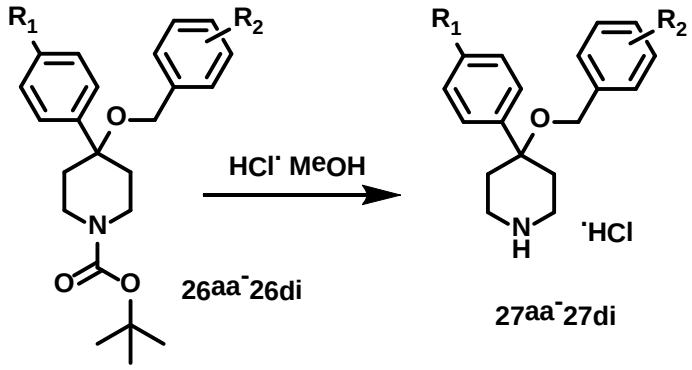

**Scheme 1.1.** Synthesis of intermediates **24a-24d**

The alcohols **24a-24d** were reacted with variety of substituted benzyl bromides (**25a-25i**) in the presence of sodium hydride to yield compounds **26aa-26di** with 70-90% yield **(Scheme 1.2.).**




**Scheme 1.2.** Synthesis of intermediates **26aa-26di**

Removal of the N-Boc group was attempted using trifluoroacetic acid but only a trace amount of deprotected product was observed after the overnight reaction. An alternate method using hydrochloric acid and methanol was attempted which gave rapid deprotection within 2 hours and a quantitative yield of product as the hydrochloride salts **27aa-27di (Scheme 1.3.)**. The final compounds were then screened for binding affinity at monoamine transporters.

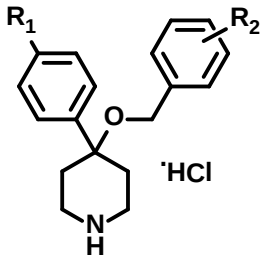



$R_1$ : a=H, b=F, c=Cl, d=$CF_3$
$R_2$ : a=H, b=4-F, c=4-$CH_3$, d=4-$CF_3$, e=3,4-$Cl_2$, f=2-F, g=3-F, h=3,5-$F_2$, i=4-Cl

**Scheme 1.3.** Synthesis of final compounds **27aa-27di**

**In-vitro screening of final compounds**

The binding affinities of all the compounds listed in **Table 1.1** were determined for DAT and SERT.



| Cmpd[a] | Code | $R_1$ | $R_2$ | DAT Ki (nM)[b] | SERT Ki (nM)[b] | DAT/SERT |
|---|---|---|---|---|---|---|
| 27aa | TAV-12 | H | H | 403 ± 100 | 145 ± 16 | 2.77 |
| 27ab | TAV-09 | H | 4-F | 1810 ± 1110 | 17.0 ± 0.90 | 106 |
| 27ac | TAV-52 | H | 4-$CH_3$ | 3108 ± 376 | 2.5 ± 0.20 | 1243.2 |
| 27ad | TAV-18 | H | 4-$CF_3$ | 10,000 ± 1960 | 2.6 ± 2.4 | 3846.1 |
| 27ae | TAV-19 | H | 3,4-$Cl_2$ | 976 ± 316 | 15.8 ± 17.2 | 61.7 |
| 27af | TAV-51 | H | 2-F | 502 ± 340 | 567 ± 453 | 0.0015 |
| 27ag | TAV-53 | H | 3-F | 536 ± 139 | 85.3 ± 24.7 | 65.2 |
| 27ah | TAV-54 | H | 3,5-$F_2$ | 1705 ± 785 | 40.5 ± 11.1 | 42 |
| 27ba | TAV-13 | F | H | 1494 ± 326 | 30.8 ± 2.90 | 48.5 |
| 27bb | TAV-07 | F | 4-F | 3970 ± 356 | 44.5 ± 44.7 | 89.2 |
| 27bc | TAV-67 | F | 4-$CH_3$ | 4693 ± 1552 | 2.1 ± 0.90 | 2234 |
| 27bd | TAV-15 | F | 4-$CF_3$ | 8134 ± 54 | 433 ± 21.2 | 18.7 |
| 27be | TAV-46 | F | 3,4-$Cl_2$ | 4110 ± 687 | 8.9 ± 10.6 | 461.7 |
| 27bf | TAV-68 | F | 2-F | 1471 ± 663 | 327 ± 105 | 4.5 |
| 27bg | TAV-72 | F | 3-F | 1470 ±130 | 79.9 ± 28.1 | 18.4 |
| 27bh | TAV-71 | F | 3,5-$F_2$ | 2836 ± 826 | 53.3 ± 14.1 | 53.2 |
| 27bi | TAV-45 | F | 4-Cl | 2368 ± 789 | 1.3 ± 1.4 | 1821 |
| 27ca | TAV-25 | Cl | H | 1039 ± 476 | 133 ± 108 | 7.8 |
| 27cb | TAV-29 | Cl | 4-F | 1960 ± 155 | 8.3 ± 4.5 | 236 |
| 27cc | TAV-34 | Cl | 4-$CH_3$ | 2171 ± 458 | 1.5 ± 0.70 | 1447.3 |
| 27cd | TAV-28 | Cl | 4-$CF_3$ | 5667 ± 2397 | 0.50 ± 0.50 | 11334 |
| 27ce | TAV-26 | Cl | 3,4-$Cl_2$ | 2277± 1191 | 0.60 ± 0.6 | 3795 |
| 27cf | TAV-61 | Cl | 2-F | 2035 ± 1006 | 193 ± 126 | 10.5 |
| 27cg | TAV-72 | Cl | 3-F | 2520 ± 471 | 35.7 ± 33.8 | 70.6 |
| 27ch | TAV-63 | Cl | 3,5-$F_2$ | 2835 ± 828 | 56.8 ± 39.9 | 49.9 |
| 27ci | TAV-64 | Cl | 4-Cl | 26% @ 100 μM | 199 ± 126 | - |
| 27da | TAV-37 | $CF_3$ | H | 1938 ± 139 | 135 ± 82 | 14.35 |
| 27db | TAV-40 | $CF_3$ | F | 2170 ± 263 | 35.8 ± 11.3 | 60.6 |
| 27dd | TAV-39 | $CF_3$ | 4-$CF_3$ | 5686 ± 35 | 3.7 ± 2.6 | 1536.7 |
| 27de | TAV-38 | $CF_3$ | 3,4-$Cl_2$ | 9183 ± 1472 | 7.5 ± 2.5 | 1224.4 |

[a]All compounds were tested as the HCl salts. [b]All values are the mean ± SEM of three experiments preformed in triplicate.

**Table 1.1.** Preliminary binding studies.

**Structure-activity relationship studies**

The preliminary binding studies show that the binding affinity varies with the type of substituent present on the aromatic ring. It was found that all the compounds showed strong affinity towards serotonin transporters. Transporter affinities of the 4-arylmethoxy-4-arylpiperidines were generally selective for the SERT over the DAT with exception of **27af** which displayed slight selectivity for the dopamine transporter over the serotonin transporter (DAT/SERT = 0.0015). Most notably, compounds **27cd** (*K*i = 0.05 nM) and **27ce** (*K*i = 0.06 nM) were the most potent ligands of the series at the serotonin transporter. The binding affinity of **27cd** and **27ce** exceeded the potency of the radiolabeled ligand citalopram, (*K*i = 2 nM) used for obtaining this data. In general, the compounds with 4-trifluromethyl, 4-methyl and 3, 4-dichloro groups on the aromatic ring of the benzyloxy group ring showed highest potency at the serotonin transporter. Therefore, it can be concluded that these groups are important substituents on the aryl ring of these piperidine analogues for molecular recognition at serotonin transporters.

The compound **27aa** (*K*i = 403 nM) was most potent ligands of the series at the dopamine transporter. However, it is noteworthy that **27aa** also exhibited nearly equal affinity for both DAT and SERT (DAT/SERT = 2.77). This confirms that the 4-aryl-4 arylmethoxypiperidines are viable targets for the development of selective serotonin transporter ligands with variable DAT affinity.

## 1.6. Conclusion

A series of 4-aryl-4-arylmethoxypiperidine analogues were synthesized and evaluated as dopamine and serotonin transporter ligands. The *in vitro* affinity (*K*i) for the dopamine transporter and the serotonin transporter of this series was determined by inhibition of [$^{3}$WIN]-35,428 and [$^{3}$H]citalopram, respectively, in rat caudate putamen tissue. The results of this study

clearly demonstrate that 4-aryl-4-arylmethoxypiperidines are selective ligands for the serotonin transporter over the dopamine transporter. The preliminary binding studies show that the 4-aryl-4-arylmethoxypiperidines exhibit high affinity for SERT and modest to low affinity for DAT. The analogue TAV-28 (**27cd**) showed highest affinity towards SERT transporters. Overall, this investigation suggested that the 4-trifluromethyl, 4-methyl and 3, 4-dichloro group on the aromatic ring of the benzyloxy group ring is a key structural feature for molecular recognition at the serotonin transporter as well as differentiation between the serotonin transporter and the dopamine transporter.

## 1.7. Experimental

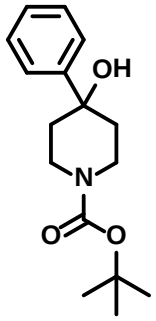
All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous Ethyl ether ($Et_2O$), Dimethylformamide (DMF), Methanol (MeOH), Dichloromethane (DCM) was purchased from Mallinckrodt Baker. Inc. Thin layer chromatography (TLC) 20×20 cm aluminium plates pre-coated with silica gel purchased from EMD Millipore USA and used to monitor reactions via visualization with short-wave UV light. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian 400 MHz NMR spectrometer at ambient temperature in $CDCl_3$. $^1$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 $CDCl_3$ (77.0 ppm). Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

**General procedure A. Synthesis of tertiary alcohols (24a-24d)**

In a clean, dry round-bottom flask was added substituted benzenes (2 equiv.) **(23a-23d)** in dry ethyl ether (20 ml). The solution of *n*-butyl lithium (2 equiv.) was added to the solution dropwise at -78 °C. The solution of 1-(Boc) 4-piperidone (1 equiv.) **(22)** in diethyl ether was added to the

solution at -78 °C. The solution was warmed to room temperature and stirred for 2h. The reaction mixture was diluted with ammonium chloride solution. The reaction mixture was extracted with ethyl ether (3×30 ml). The organic extract was washed with brine solution (30 ml) and dried over sodium sulphate. The solvent was evaporated under reduced pressure. The crude mixture was purified using column chromatography to obtain compounds **24a-24d.**

**Tert-butyl-4-hydroxy-4-phenylpiperidine-1-carboxylate (24a)**

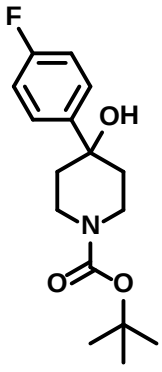



General procedure A: This compound was obtained as a white solid (2 g, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.25-7.48 (m, 5H), 3.98 (s, 1H), 3.24 (s, 2H), 2.00 (d, *J* =11.6 Hz, 2H), 1.74 (d, *J*=11.2 Hz, 2H), 1.44-1.59 (m, 11H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 76.3, 79.6, 127.9, 128.8, 129.5, 144.1, 155.1.

**Tert-butyl-4-(4-fluorophenyl-4-hydroxypiperidine-1-carboxylate (24b)**

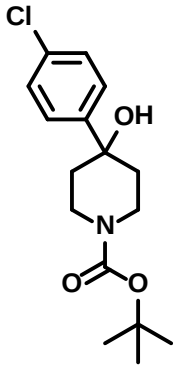


General procedure A: This compound was obtained as a white solid (2.4 g, 82%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.25-7.43 (m, 2H), 7.03-7.05 (t, *J*=8.8 Hz, 2H), 3.95 (s, 1H), 3.20 (s, 2H), 1.88 (d, *J*=11.6 Hz, 2H), 1.63 (d, *J*=11.2 Hz, 2H), 1.42-1.61 (m, 11H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 76.3, 79.6, 125.4, 129.5, 143.2, 144.1, 155.1.

**Tert-butyl-4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxylate (24c)**

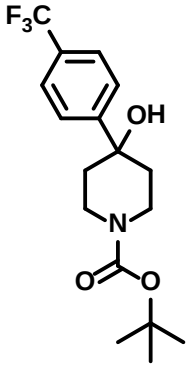



General procedure A: This compound was obtained as a white solid (2.3g, 78%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.45 (m, 4H), 3.98 (s, 1H), 3.18 (s, 2H), 1.88 (d, *J*=10.8Hz 2H), 1.64 (d, *J*=11.6Hz, 2H), 1.40-1.59 (m, 11H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.4, 34.5, 39.5, 75.8, 79.7, 128.6, 128.9, 133.6, 143.3 155.1.

**Tert-butyl-4-hydroxy-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (24d)**



General procedure A: This compound was obtained as a white solid (1.8 g, 72%).

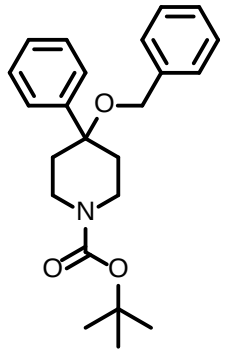
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, *J*=8.0Hz, 2H), 7.60 (d, *J*=8.0Hz, 2H), 4.01 (s, 1H), 3.14 (s, 2H), 2.00 (s, 2H), 1.74 (s, 2H), 1.44-1.63 (m, 11H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 35.7, 40.1, 76.1, 79.7, 125.7, 125.8, 126.8, 128.6, 129.3, 155.1,

**General procedure B. Benzylation of alcohols (26aa-26di)**

The solution of alcohols (**24a-24d,** 1 equiv.) was stirred in dimethylformamide at 0 °C. To the solution was added sodium hydride at 0 °C. The benzyl bromide (**25a-25i,** 1.1 equiv.) was added to the solution and the reaction was stirred for 2 h. The reaction was quenched with water and extracted with ethyl acetate (3×20 ml). The organic solvent was washed with brine solution and dried over sodium sulphate. The crude product was purified using column chromatography to obtain compounds **26aa-26di**.

**N-(*tert*-Butoxycarbonyl)-4-(phenylmethoxy)-4-phenyl-piperidine (26aa, TAV-08)**

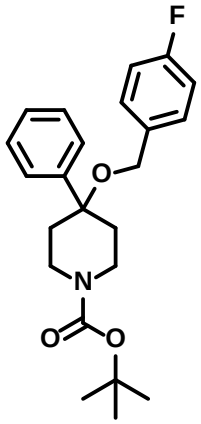



General procedure B: This compound was obtained as a colorless liquid (300 mg, 80%).

**$^{1}$H NMR (100 MHz, $CDCl_3$):** δ 7.40-7.43 (m, 3H), 7.25-7.34 (m, 5H), 7.08 (t, *J*=8.8Hz, 2H), 4.08 (s, 4H), 3.26 (s, 2H), 2.13 (d, *J*=6.0Hz, 2H), 1.88 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (400 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.4, 76.3, 79.6, 125.4, 126.0, 127.4, 127.9, 128.8, 129.5, 143.2, 144.1, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-fluorophenyl)methoxy]-4-phenyl-piperidine (26ab, TAV-08)**

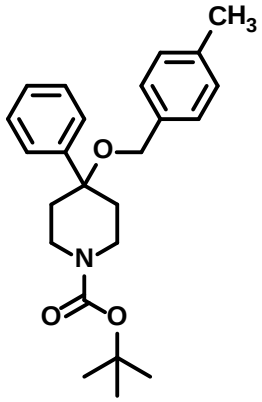



General procedure B: This compound was obtained as a colorless liquid (315 mg, 79%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.43 (m, 6H), 7.28-7.32 (m, 2H), 7.02-7.11 (m, 1H), 4.05 (s, 4H), 3.24 (s, 2H), 2.13 (d, *J*=12.4Hz, 2H), 1.93 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 62.8, 76.4, 79.6, 126.0, 126.6, 128.0, 128.9, 129.2, 132.5, 139.4, 144.0, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-methylphenyl)methoxy]-4-phenyl-piperidine (26ac, TAV-47)**

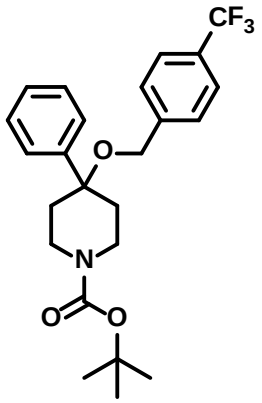


General procedure B: This compound was obtained as a colorless liquid (271mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.49 (d, *J*=12.0Hz, 2H), 7.41 (t, *J*=8.0Hz, 2H), 7.30 (t, J=8.0, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 4.10 (s, 4H), 3.20 (s, 2H), 2.37 (s, 3H), 2.17 (d, *J*=10.8Hz, 2H), 1.95 (s, 2H), 1.51 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 155.2, 144.8, 137.2, 136.0, 129.3, 128.8, 127.8, 126.2, 79.6, 76.0, 64.2, 39.5, 34.6, 28.7, 21.4.

**N-(*tert*-Butoxycarbonyl)-4-[(4-trifluoromethylphenyl)methoxy]-4-phenyl-piperidine (26ad, TAV-16)**

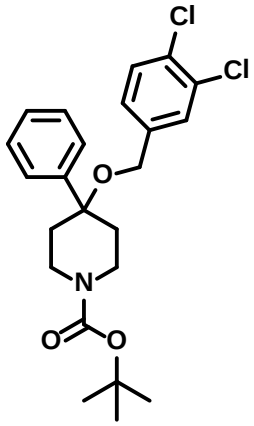


General procedure B: This compound was obtained as a colorless liquid (350 mg, 89%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.58 (d, *J*=8.0Hz, 2H), 7.36-7.45 (m, 6H), 7.29-7.32 (m, 1H), 4.17 (s, 2H), 4.03 (s, 2H), 3.26 (s, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.95 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.4, 76.3, 79.6, 125.4, 126.0, 127.4, 127.9, 128.8, 129.5, 129.8, 143.2, 144.1, 155.1

**N-(*tert*-Butoxycarbonyl)-4-[(4-chlorophenyl)methoxy]-4-phenyl-piperidine (26ae, TAV-17)**

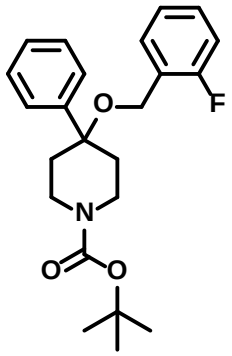



General procedure B: This compound was obtained as a colorless liquid (310 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.43 (m, 5H), 7.28-7.32 (m, 2H), 7.02-7.11 (m, 1H), 4.05 (s, 4H), 3.24 (s, 2H), 2.13 (d, *J*=12.4Hz, 2H), 1.93 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 62.8, 76.4, 79.6, 126.0, 126.6, 128.0, 128.8, 128.9, 129.2, 130.4, 131.2, 144.0, 155.1, 161.5.

**N-(*tert*-Butoxycarbonyl)-4-[(2-fluorophenyl)methoxy]-4-phenyl-piperidine (26af, TAV-48)**

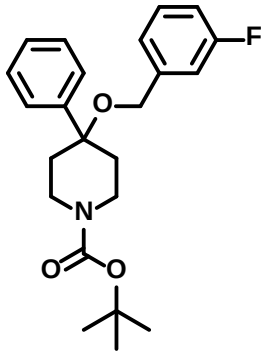



General procedure B: This compound was obtained as a colorless liquid (280 mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.45-7.50 (m, 3H), 7.37 (t, *J*=7.2 Hz, 2H), 7.21-7.31 (m, 2H), 7.13 (t, *J*=7.2 Hz, 1H), 6.71 (t, *J*=8.4Hz, 1H), 4.18 (s, 2H), 4.02 (s, 2H), 3.29 (s, 2H), 2.15 (d, *J*=13.2Hz, 2H), 1.93 (s, 2H), 1.51 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.9, 159.5, 155.1, 144.3, 129.9, 129.2, 128.8, 127.8, 126.1, 124.3, 115.4, 79.5, 76.3, 58.1, 39.5, 34.8, 28.7.

**N-(*tert*-Butoxycarbonyl)-4-[(3-fluorophenyl)methoxy]-4-phenyl-piperidine (26ag, TAV-49)**

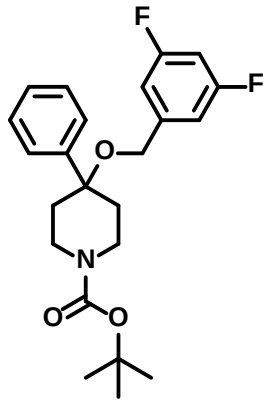



General procedure B: This compound was obtained as a colorless liquid (300 mg, 82%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.45 (d, *J*=7.6 Hz, 2H), 7.38 (t, *J*=8.0Hz, 2H), 7.23-7.31 (m, 2H), 7.06 (t, *J*=7.6 Hz, 2H), 6.94 (t, *J*=8.0Hz, 1H), 4.11 (s, 4H), 3.29 (s, 2H), 2.15 (d, *J*=12.4Hz, 2H) 1.94 (s, 2H), 1.50 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 164.3, 161.9, 155.1, 144.3, 141.8, 130.0, 128.8, 127.9, 126.1, 122.8, 114.2, 79.6, 76.2, 63.4, 40.3, 34.5, 28.7.

**N-(*tert*-Butoxycarbonyl)-4-[(3,5-difluorophenyl)methoxy]-4-phenyl-piperidine (26ah, TAV-50)**

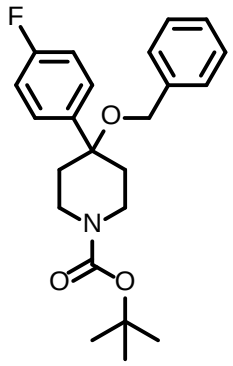



General procedure B: This compound was obtained as a colorless liquid (284 mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.28-7.43 (m, 5H), 6.82 (d, *J*=6.4Hz, 2H), 6.65-6.70 (m, 1H), 4.09 (s, 4H), 3.25 (s, 2H), 2.13-2.16 (m, 2H), 1.94 (s, 2H), 1.45-1.48 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.4, 39.5, 63.0, 76.4, 79.7, 109.8, 126.0, 128.0, 128.9, 143.0, 143.9, 155.1, 162.0, 164.5.

**N-(*tert*-Butoxycarbonyl)-4-benzyloxy-4-(4-fluorophenyl)-piperidine (26ba, TAV-11)**

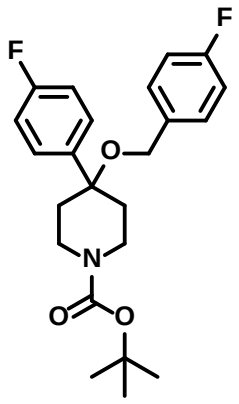


General procedure B: This compound was obtained as a colorless liquid (290 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.43 (m, 2H), 7.25-7.34 (m, 5H), 7.08 (t, *J*=8.8Hz, 2H), 4.08 (s, 4H), 3.26 (s, 2H), 2.13 (d, *J*=6.0Hz, 2H), 1.88 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.4, 76.3, 79.6, 125.4, 126.0, 127.4, 127.9, 129.5, 129.8, 143.2, 144.1, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-fluorophenyl)methoxy]-4-(4-fluorophenyl-piperidine ( 26bb, TAV-06)**

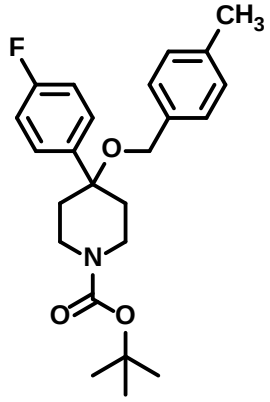


General procedure B: This compound was obtained as a colorless liquid (275mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.40 (m, 2H), 7.21-7.26 (m, 2H), 7.00-7.04 (m, 4H), 6.88-6.93 (m, 1H), 4.06 (s, 4H), 3.24 (s, 2H), 2.12 (d, *J*=13.2Hz, 2H), 1.87 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.4, 75.8, 79.6, 114.0, 114.4, 115.7, 122.7, 127.9, 129.9, 140.1, 141.5, 163.6.

**N-(*tert*-Butoxycarbonyl)-4-[(4-methylphenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bc, TAV-65)**

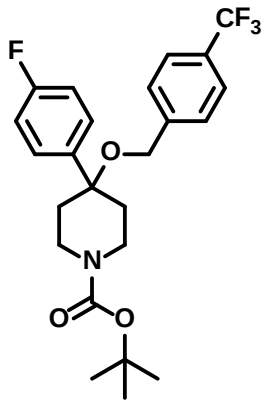



General procedure B: This compound was obtained as a colorless liquid (280 mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.42-7.46 (m, 2H), 7.22 (d, *J*=8.0Hz, 2H), 7.16 (d, *J*=8.0Hz, 2H), 7.05-7.09 (m, 2H), 4.07 (s, 4H), 3.29 (s, 2H), 2.35 (s, 3H), 2.13 (d, *J*=12.0Hz, 2H), 1.90 (s, 2H), 1.51 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 28.7, 34.7, 39.5, 64.1, 75.6, 79.6, 115.4, 127.9, 129.3, 135.8, 137.3, 140.6, 155.1, 161.1, 163.5.

**N-(*tert*-Butoxycarbonyl)-4-[(4-trifluoromethylphenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bd, TAV-14)**

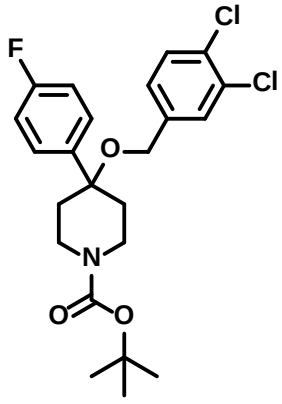



General procedure B: This compound was obtained as a colorless liquid (285 mg, 71%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=8.4Hz, 2H), 7.38-7.42 (m, 4H), 7.03 (t, *J*= 7.2Hz, 2H), 4.01 (s, 2H), 4.02 (s, 2H), 3.24 (s, 2H), 2.13 (d, *J*=12.4Hz, 2H), 1.91 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.5, 34.6, 40.2, 63.3, 76.0, 79.6, 115.7, 125.4, 127.2, 129.8, 140.0, 142.9, 155.1, 161.1, 163.6.

**N-(*tert*-Butoxycarbonyl)-4-[(3,4-dichlorophenyl)methoxy]-4-(4-fluorophenyl-piperidine (26be, TAV-42)**

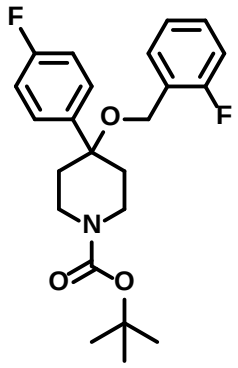



General procedure B: This compound was obtained as a colorless liquid (285 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.38 (m, 4H), 7.00-7.08 (m, 3H), 4.01 (s, 4H), 3.21 (s, 2H), 2.09 (d, *J*=12.0Hz, 2H), 1.87 (s, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 163.6, 161.1, 155.0, 139.1, 132.5, 131.3, 130.4, 129.1, 127.8, 126.6, 115.5, 79.7, 76.0, 62.8, 39.5, 35.8, 28.6.

**N-(*tert*-Butoxycarbonyl)-4-[(2-fluorophenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bf, TAV-66)**

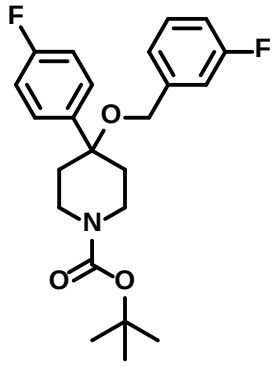



General procedure B: This compound was obtained as a colorless liquid (310 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.45 (m, 3H) 7.21-7.25 (m, 1H), 6.96-7.14 (m, 4H), 4.13 (s, 2H) 4.02 (s, 2H) 3.25 (s, 2H) 2.11-2.14 (d, *J*=12.0Hz, 2H) 1.88 (t, 2H) 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.3, 58.0, 75.9, 79.6, 115.2, 124.3, 125.8, 127.8, 128.3, 129.9, 140.3, 141.5, 155.1, 159.4, 163.6.

**N-(*tert*-Butoxycarbonyl)-4-[(3-fluorophenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bg, TAV-70)**

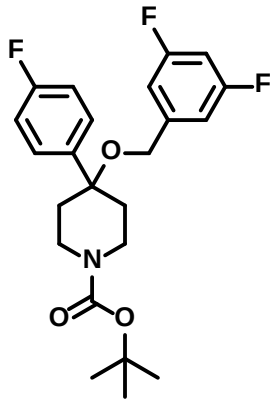



General procedure B: This compound was obtained as a colorless liquid (275mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.40 (m, 2H), 7.21-7.26 (m, 2H), 7.00-7.04 (m, 4H), 6.88-6.93 (m, 1H), 4.06 (s, 4H), 3.24 (s, 2H), 2.12 (d, *J*=13.2Hz, 2H), 1.87 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.4, 75.8, 79.6, 114.0, 114.4, 115.7, 122.7, 127.9, 129.9, 140.1, 141.5, 155.1, 161.1, 163.6.

**N-(*tert*-Butoxycarbonyl)-4-[(3,5-difluorophenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bh, TAV-69)**

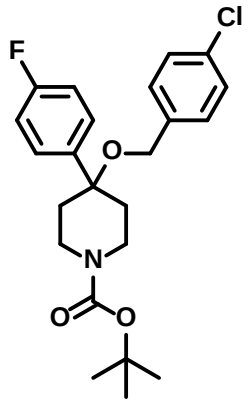



General procedure B: This compound was obtained as a colorless liquid (268 mg, 64%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.33-7.37 (m, 2H), 6.99 (t, *J*=8.4Hz, 2H), 6.75-6.80 (m, 2H), 6.59-6.64 (m, 1H), 4.03 (s, 4H), 3.20 (s, 2H), 2.07-2.10 (d, *J*=12.0Hz, 2H), 1.86 (s, 2H), 1.44 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.5, 34.4, 39.3, 62.9, 76.0, 79.6, 102.3, 109.5, 115.5, 127.7, 139.8, 142.9, 155.0, 162.0, 164.4.

**N-(*tert*-Butoxycarbonyl)-4-[(4-chlorophenyl)methoxy]-4-(4-fluorophenyl)-piperidine (26bi, TAV-43)**

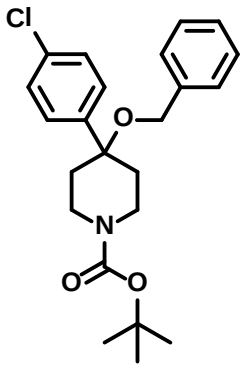



General procedure B: This compound was obtained as a colorless liquid (274mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.39 (m, 2H), 7.18-7.26 (m, 4H), 7.02 (d, *J*=9.6Hz, 2H), 4.03 (s, 4H), 3.23 (s, 2H), 2.10 (d, *J*=12.8Hz, 2H), 1.87 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 35.7, 40.2, 63.4, 75.8, 79.6, 115.4, 127.6, 128.6, 128.8, 133.2, 140.1, 155.0, 161.1, 163.5.

**N-(*tert*-Butoxycarbonyl)-4-(phenylmethoxy)-4-(4-chlorophenyl)-piperidine (26ca, TAV-16)**

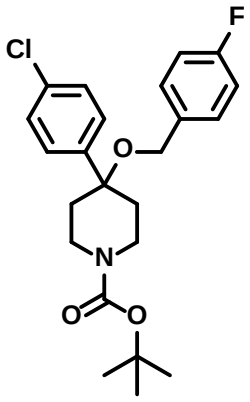



General procedure B: This compound was obtained as a colorless liquid (280mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.25-7.40 (m, 9H), 4.09 (s, 4H), 3.26 (s, 2H), 2.10 (s, 2H), 1.88 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.7, 34.5, 39.4, 64.3, 72.3, 75.8, 79.7, 127.5, 127.7, 128.0, 128.6, 128.9, 133.6, 138.7, 143.3, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-fluorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26cb, TAV-26)**

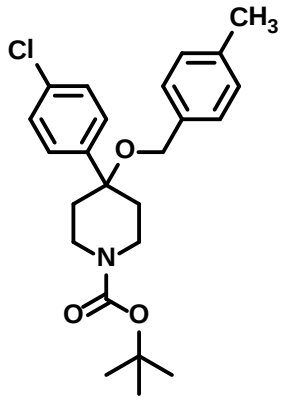



General procedure B: This compound was obtained as a colorless liquid (268 mg, 65%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.39 (m, 2H), 7.18-7.26 (m, 4H), 7.02 (d, *J*=9.6Hz, 2H), 4.03 (s, 4H), 3.23 (s, 2H), 2.10 (d, *J*=12.8Hz, 2H), 1.87 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 35.7, 40.2, 63.4, 75.8, 79.6, 115.4, 127.6, 128.6, 128.8, 133.2, 137.3, 140.1, 155.0, 161.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-methylphenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26cc, TAV-33)**

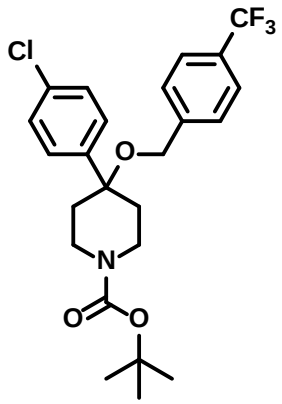



General procedure B: This compound was obtained as a colorless liquid (238 mg, 64%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.42-7.46 (m, 2H), 7.22 (d, *J*=8.0Hz, 2H), 7.16 (d, *J*=8.0Hz, 2H), 7.05-7.09 (m, 2H), 4.07 (s, 4H), 3.29 (s, 2H), 2.35 (s, 3H), 2.13 (d, *J*=12.0Hz, 2H), 1.90 (s, 2H), 1.51 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 28.7, 34.7, 39.5, 64.1, 75.6, 79.6, 115.4, 127.9, 129.3, 135.8, 137.3, 140.6, 155.1, 161.1, 163.5.

**N-(*tert*-Butoxycarbonyl)-4-[(4-trifluromethylphenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26cd, TAV-24)**

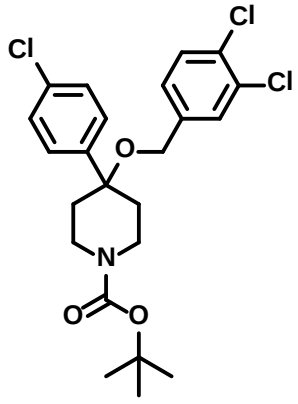



General procedure B: This compound was obtained as a colorless liquid (275mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=8.0Hz, 2H), 7.32-7.41 (m, 6H), 4.15 (s, 2H), 4.05 (s, 2H), 3.24 (s, 2H), 2.13 (d, *J*=13.2Hz, 2H), 1.90 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.5, 76.1, 79.7, 123.0, 125.4, 127.5, 129.0, 129.6, 129.9, 133.8, 142.3, 142.8, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(3,4-dichlorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26ce, TAV-23)**

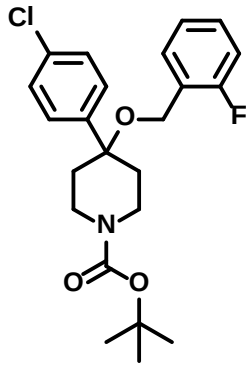



General procedure B: This compound was obtained as a colorless liquid (310mg, 82%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.34-7.39 (m, 5H), 7.25 (s, 1H), 7.08 (dd, *J*=2.0Hz, 8.0Hz, 1H), 4.03 (s, 4H), 3.21(s, 2H), 2.09 (d, *J*=12.0Hz, 2H), 1.88 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.4, 39.3, 62.9, 76.1, 79.8, 126.6, 127.5, 129.0, 129.2, 130.5, 131.5, 132.6, 133.8, 138.9, 142.6, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(2-fluorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26cf, TAV-57)**

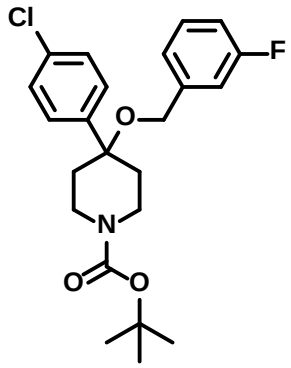



General procedure B: This compound was obtained as a colorless liquid (285mg, 74%).

**$^{1}$H NMR (400 MHz, $CDCl_3$) :** δ 7.32-7.45 (m, 5H), 7.21-7.25 (m, 1H) 7.12 (t, *J*= 7.2Hz, 1H), 7.00 (t, *J*=8.8Hz, 1H), 4.14 (s, 2H), 4.02 (s, 2H), 3.24 (s, 2H), 2.12 (m, 2H), 1.87 (m, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.7, 39.4, 58.2, 76.0, 79.7, 115.2, 124.3, 125.7, 128.9, 129.3, 129.9, 133.6, 141.4, 143.0, 155.1, 159.4.

**N-(*tert*-Butoxycarbonyl)-4-[(3-fluorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26cg, TAV-58)**

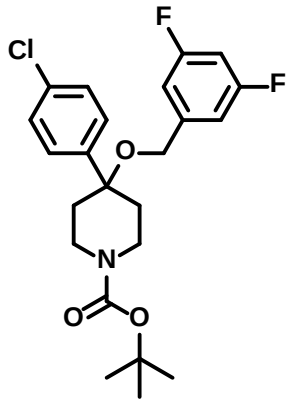



General procedure B: This compound was obtained as a colorless liquid (278mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.21 (m, 5H), 7.00-703 (m, 2H), 6.89-6.94 (m, 1H), 4.72-4.75 (m, 4H), 3.23 (s, 2H), 2.08-2.12 (m, 2H), 1.87 (s, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.5, 39.4, 63.5, 75.9, 79.7, 114.2, 122.7, 127.6, 129.0, 130.0, 133.7, 141.3, 142.9, 155.1, 161.9, 164.3.

**N-(*tert*-Butoxycarbonyl)-4-[(3,5-fluorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26ch, TAV-59)**

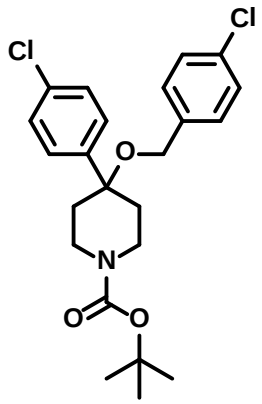



General procedure B: This compound was obtained as a colorless liquid (280 mg, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.28-7.33 (m, 4H), 6.80 (d, *J*=7.2Hz, 2H), 6.64 (t, *J*=8.8Hz, 1H), 4.05 (s, 2H), 3.20 (s, 2H), 2.11 (d, *J*=12.0Hz, 2H), 1.87 (s, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.5, 34.4, 39.3, 62.9, 76.0, 79.6, 102.3, 109.5, 115.5, 127.7, 139.8, 142.9, 155.0, 162.0, 164.4.

**N-(*tert*-Butoxycarbonyl)-4-[(4-chlorophenyl)methoxy]-4-(4-chlorophenyl)-piperidine (26ci, TAV-60)**

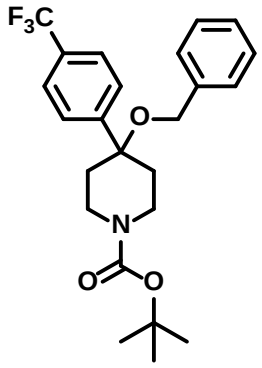



General procedure B: This compound was obtained as a colorless liquid (264 mg, 63%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.37 (m, 4H), 7.29 (d, *J*=8.8Hz, 2H), 7.20 (d, *J*=8.0Hz, 2H), 4.05 (s, 4H), 3.23 (s, 2H), 2.10 (d, *J*=12.0Hz, 2H), 1.88 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.8, 39.4, 63.6, 75.9, 79.8, 127.6, 128.7, 128.8, 129.0, 133.4, 133.7, 137.1, 143.0, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-(phenylmethoxy)-4-(4-trifluoromethyl)-phenyl-piperidine (26da, TAV-32)**

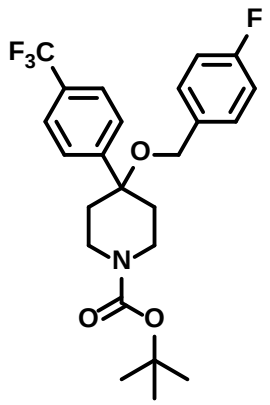


General procedure B: This compound was obtained as a colorless liquid (280mg, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.65 (d, *J*=8.0Hz, 2H), 7.59 (d, *J*=8.0Hz, 2H), 7.28-7.37 (m, 5H), 4.14 (s, 4H), 3.30 (s, 2H), 2.16 (d, *J*=8.8Hz, 2H), 1.94 (s, 2H), 1.51 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 22.8, 35.7, 40.1, 64.5, 76.1, 79.7, 125.7, 125.8, 125.8, 126.6, 127.5, 127.7, 128.6, 138.5, 148.9, 155.1.

**N-(*tert*-Butoxycarbonyl)-4-[(4-fluorophenyl)methoxy]-4-(4-trifluoromethylphenyl)-piperidine (26db, TAV-36)**

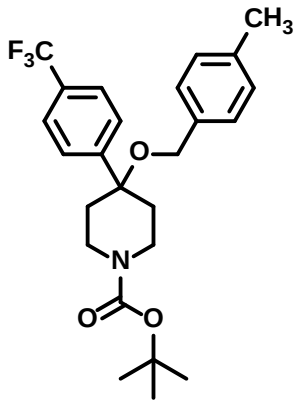



General procedure B: This compound was obtained as a colorless liquid (265 mg, 70%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.62 (d, *J*=8.4Hz, 2H), 7.55 (m, *J*=8.4Hz, 2H), 7.25 (m, 2H), 6.98 (t, *J*=8.4Hz, 2H), 4.06 (s, 4H), 3.25 (s, 2H), 2.12 (d, *J*=12.8Hz, 2H), 1.90 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.5, 35.6, 40.1, 63.8, 76.1, 79.7, 115.5, 125.7, 126.5, 129.1, 130.1, 134.2, 148.7, 155.0, 161.1, 163.6.

**N-(*tert*-Butoxycarbonyl)-4-[(4-methylphenyl)methoxy]-4-(4-trifluoromethylphenyl)-piperidine (26dc, TAV-41)**

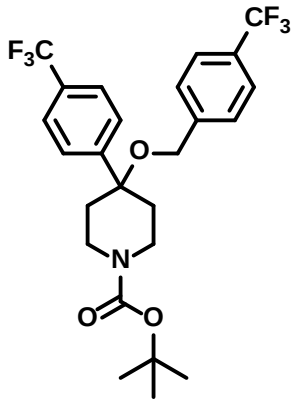


General procedure B: This compound was obtained as a colorless liquid (285 mg, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.66 (d, *J*=8.4Hz, 2H), 5.60 (d, *J*=8.4Hz, 2H), 7.22 (d, *J*=8.0Hz, 2H), 7.17 (d, *J*=8.0Hz, 2H), 4.10 (s, 4H), 3.30 (s, 2H), 2.36 (s, 3H), 2.15 (d, *J*=12.0Hz, 2H), 1.93 (s, 2H), 1.50 (s, 9H)**.**

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 155.1, 149.0, 137.5, 135.4, 130.1, 129.8, 129.3, 127.7, 126.6, 125.8, 79.7, 76.0, 64.4, 40.1, 35.9, 28.6, 21.3

**N-(*tert*-Butoxycarbonyl)-4-[(4-trifluoromethylphenyl)methoxy]-4-(4-trifluoromethylphenyl-piperidine (26dd, TAV-35)**

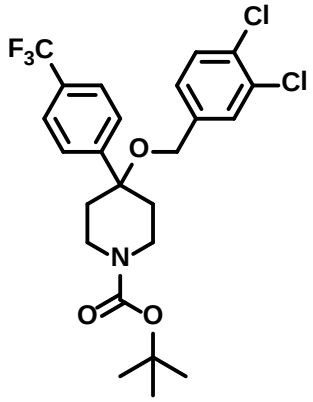


General procedure B: This compound was obtained as a colorless liquid (268mg, 64%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J*=8.4Hz, 2H), 7.55-7.58 (m, 4H), 7.42 (d, *J*=8.0Hz, 2H), 4.18 (s, 2H), 4.06 (s, 2H), 3.26 (s, 2H), 2.15 (d, *J*=8.8Hz, 2H), 1.94 (s, 2H), 1.47 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.5, 34.6, 36.3, 63.6, 76.3, 79.8, 125.4, 125.5, 125.8, 126.4, 127.3, 129.6, 129.9, 130.2, 142.6, 148.6, 155.0.

**N-(*tert*-Butoxycarbonyl)-4-[(3,4-dichlorophenyl)methoxy]-4-(4-trifluoromethylphenyl)-piperidine (26de, TAV-33)**

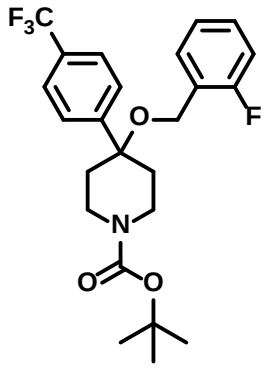



General procedure B: This compound was obtained as a colorless liquid (314 mg, 82%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.60 (d, *J*=8.0Hz, 2H), 7.52 (d, *J*=8.0Hz, 2H), 7.32-7.36 (m, 2H),7.07-7.10 (d, *J*=8.0Hz, 1H), 4.04 (s, 4H), 3.21 (s, 2H), 2.09-2.13 (d, *J* =13.2Hz, 2H), 1.90 (s, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 28.6, 34.5, 38.4, 63.0, 76.4, 79.8, 125.7, 125.8, 125.9, 126.4, 126.5, 129.1, 130.5, 131.4, 132.6, 138.3, 155.0, 160.3.

**N-(*tert*-Butoxycarbonyl)-4-[(2-fluorophenyl)methoxy]-4-(4-trifluoromethyphenyl)-piperidine (26df, TAV-73)**

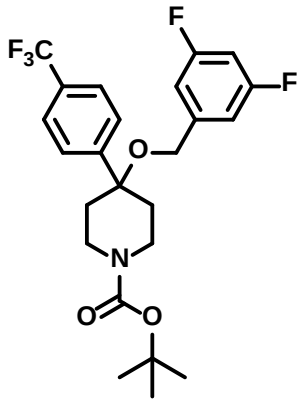


General procedure B: This compound was obtained as a colorless liquid (264mg, 69%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.64 (d, *J*=8.4Hz, 2H), 7.58 (d, *J*=8.0Hz, 2H), 7.46 (t, *J*=7.6Hz, 1H), 7.23-7.29 (m, 1H), 7.15 (t, *J*=7 .6Hz, 1H), 6.99 (t, *J*=9.2Hz, 1H), 4.17 (s, 4H), 3.27 (s, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.92 (s, 2H), 1.48 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.9, 159.5, 155.1, 148.6, 130.2, 129.9, 126.5, 125.8, 125.5, 124.3, 115.5, 102.8, 79.7, 75.9, 63.5, 39.4, 34.5, 28.6.

**N-(*tert*-Butoxycarbonyl)-4-[(3,5-difluorophenyl)methoxy]-4-(4-trifluoromethyphenyl)-piperidine (26dh, TAV-73)**

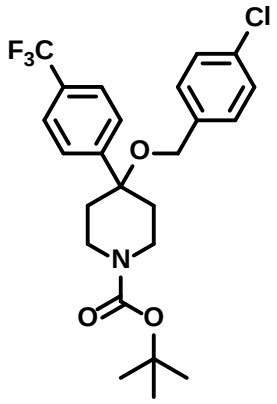


General procedure B: This compound was obtained as a colorless liquid (285 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.61 (d, *J*=8.0Hz, 2H), 7.53 (d, *J*=8.0Hz, 2H), 6.81 (d, *J*=6.4Hz, 2H), 6.63 (t, *J*=9.2Hz, 1H), 4.09 (s, 4H), 3.23 (s, 2H), 2.13 (d, *J*=12.0Hz, 2H), 1.92 (s, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 164.4, 161.9, 155.0, 148.2, 142.6, 130.3, 126.4, 125.8, 109.6, 102.7, 79.7, 76.4, 63.1, 39.3, 34.7, 28.5.

**N-(*tert*-Butoxycarbonyl)-4-[(4-chlorophenyl)methoxy]-4-(4-trifluoromethyphenyl)-piperidine (26di, TAV-75)**




General procedure B: This compound was obtained as a colorless liquid (270 mg, 65%).

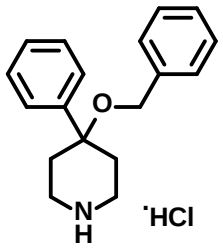
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.64 (d, *J*=8.4Hz, 2H), 7.55 (d, *J*=8.0Hz, 2H), 7.30 (d, *J*=8.4Hz, 2H), 7.23 (d, *J*=8.4Hz, 2H), 4.08 (s, 4H), 3.25 (s, 2H), 2.14 (d, *J*=12.0Hz, 2H), 1.92 (s, 2H), 1.48 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 155.1, 148.6, 142.4, 137.0, 133.5, 130.2, 129.9, 128.8, 126.5, 125.8, 79.8, 76.2, 63.7, 39.3, 34.4, 28.6.

**General procedure C. Synthesis of hydrochloride salts (27aa-27di)**

To the solution of **23aa-23di** in methanol (10 ml) was added to concentrated HCl (2ml) and stirred for 1h. The solvent was evaporated under reduced pressure. To the crude product was added water (20 ml) at 0 °C. The solid formed was filtered and dried under vacuum to get the hydrochloride salt of compounds **24aa-24di**.

**4-(Benzyloxy)-4-phenyl-piperidinium chloride (27aa, TAV-12)**



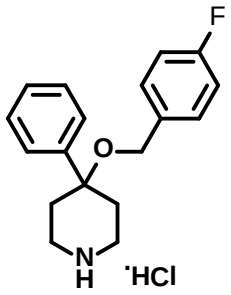

General procedure C: This compound was obtained as a white solid (200 mg, 95%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.48 (d, *J*=8.4Hz, 2H), 7.34 (t, *J*=7.6Hz, 3H), 7.30-7.34 (m, 4H), 7.27-7.28 (m, 1H), 4.11 (s, 2H), 3.16 (t, *J*=12.0Hz, 2H), 2.93 (d, *J*=12.0Hz, 2H), 2.15 (d, *J*=11.6Hz, 2H), 1.93 (t, *J*=12.0Hz, 2H), 1.72 (s, NH)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.9, 76.4, 126.2, 127.4, 127.5, 127.6, 128.5, 128.6, 139.3, 145.4.

Anal. Calcd for $C_{18}H_{22}ClNO.\ 2/3H_2O$: C, 68.48; H, 7.45; N, 4.44 Found: C, 68.22; H, 7.47; N, 4.47.

**4-(4-Fluorobenzyloxy)-4-phenyl-piperidinium chloride (27ab, TAV-09)**



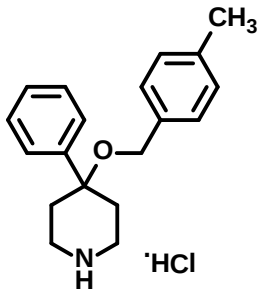

General procedure C: This compound was obtained as a white solid (194 mg, 94%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.42 (m, 2H), 7.23-7.40 (m, 2H), 6.97-7.01 (m, 4H), 4.03 (s, 2H), 3.14 (t, *J*=11.6Hz, 2H), 2.93 (d, *J*= 9.6Hz, 2H), 2.10 (d, *J*=13.2Hz, 2H), 1.86-1.93 (m, 2H), 1.62 (s, NH)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.1, 76.1, 115.2, 115.5, 127.9, 129.2, 134.8, 141.2, 161.1, 163.5.

Anal. Calcd for $C_{18}H_{21}ClF_2NO.\ H_2O$: C, 60.54; H, 6.16; N, 4.05 Found: C, 60.42; H, 6.20; N, 3.91.

**4-(4-Methylbenzyloxy)-4-phenyl-piperidinium chloride (27ac, TAV-52)**



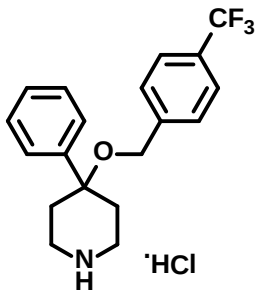

General procedure C: This compound was obtained as a white solid (172 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.45 (m, 3H), 7.19 (d, *J*=8.0Hz, 2H), 7.13 (d, *J*=7.6Hz, 2H), 7.03-7.07 (m, 2H), 4.03 (s, 2H), 3.15 (t, *J*=11.2Hz, 2H), 2.92-2.95 (m, 2H), 2.33 (s, 3H), 2.12 (d, *J*=13.2Hz, 2H), 1.85-1.92 (m, 2H), 1.70 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 36.6, 42.4, 63.7, 75.9, 115.2, 115.5, 127.7, 127.9, 128.0, 129.2, 136.1, 137.2.

Anal. Calcd for $C_{18}H_{21}ClF_2NO$. 2.1/4$H_2O$: C, 63.68; H, 8.02; N, 3.91 Found: C, 63.68; H, 8.02; N, 3.91.

**4-(4-Trifluoromethylbenzyloxy)-4-phenyl-piperidinium chloride (27ad, TAV-18)**



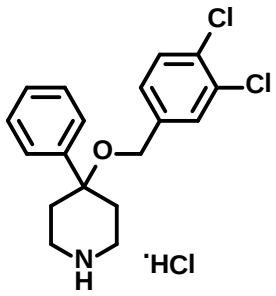

General procedure C: This compound was obtained as a white solid (165 mg, 87%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=8.4Hz, 2H), 7.45 (t, *J*=8.4Hz, 4H), 7.37 (t, *J*= 7.6Hz, 2H), 7.279 (t, *J*=7.6Hz, 1H), 4.16 (s, 2H), 3.15 (t, *J*=11.6Hz, 2H), 2.95 (s, *J*=12.0Hz, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.92-2.00 (m, 2H) 1.64 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.4, 42.5, 63.1, 76.7, 125.4, 125.8, 126.1, 127.4, 127.6, 128.7, 129.4, 143.5, 145.1.

Anal. Calcd for $C_{19}H_{21}ClF_3NO$. $H_2O$: C, 58.54; H, 5.95; N, 3.59 Found: C, 58.55; H, 5.43; N, 3.55.

**4-(3,4-Dichlorobenzyloxy)-4-phenyl-piperidinium chloride (27ae, TAV-19)**



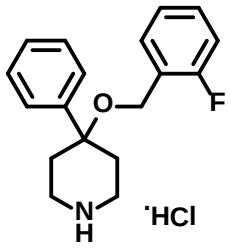

General procedure C: This compound was obtained as a white solid (210 mg, 96%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.44-7.35 (m, 6H), 7.29 (t, *J*=7.2Hz, 1H), 7.11 (dd, J=1.6Hz, 8.4Hz, 1H), 4.04 (s, 2H), 3.14 (t, *J*=12.0Hz, 2H), 2.95 (m, 2H), 2.15 (d, *J*=11.6Hz, 2H), 1.94 (t, *J*=12.0Hz, 2H), 1.71 (s, NH)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.5, 62.6, 76.7, 126.1, 126.6, 127.7, 128.7, 129.3, 130.4, 131.2, 132.5, 139.6, 144.9.

Anal. Calcd for $C_{18}H_{20}Cl_3NO$: C, 57.31; H, 5.48; N, 3.71 Found: C, 57.71; H, 5.57; N, 3.82

**4-(2-Fluorobenzyloxy)-4-phenyl-piperidinium chloride (27af, TAV-51)**



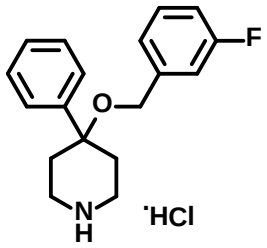

General procedure C: This compound was obtained as a white solid (175 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46-7.52 (m, 3H), 7.37 (t, *J*=7.6Hz, 2H), 7.22-7.30 (m, 2H), 7.14 (t, *J*=8.4Hz, 1H), 6.99 (t, *J*=9.2Hz, 1H), 4.16 (s, 2H), 3.15 (t, *J*=12.0Hz, 2H), 2.95 (d, *J*=12.4Hz, 2H), 2.15 (d, *J*=12.4Hz, 2H), 1.94 (t, *J*=12.0Hz, 2H), 1.80 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.8, 159.4, 145.2, 129.8, 129.0, 128.7, 127.5, 126.1, 124.2, 115.1, 76.6, 57.7, 42.4, 36.4.

Anal. Calcd for $C_{18}H_{21}ClFNO$: C, 64.47; H, 6.576; N, 4.18 Found: C, 64.51; H, 6.77; N, 4.25.

**4-(3-Fluorobenzyloxy)-4-phenyl-piperidinium chloride (27ag, TAV-53)**



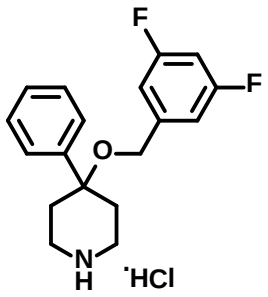

General procedure C: This compound was obtained as a white solid (182 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$) :** δ 7.46 (d, *J*= 7.2Hz, 2H), 7.37 (t, *J*=8.0Hz, 2H), 7.24-7.30 (m, 2H), 7.07 (t, *J*= 8.4Hz, 2H), 6.91-6.96 (m, 1H), 4.01 (s, 2H), 3.13-3.20 (m, 2H), 2.94-2.98 (m, 2H), 2.14 (d, *J*=12.0Hz, 2H), 1.92-1.99 (m, 2H), 1.81 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.4, 63.1, 76.5, 114.1, 114.2, 122.7, 126.1, 128.7, 142.0, 142.0, 145.1, 161.9, 164.0.

Anal. Calcd for $C_{18}H_{21}ClFNO.\ 3/4H_2O$: C, 67.18; H, 6.58; N, 4.35 Found: C, 64.47; H, 6.76; N, 4.18.

**4-(3,5-Difluorobenzyloxy)-4-phenyl-piperidinium chloride (27ah, TAV-54)**



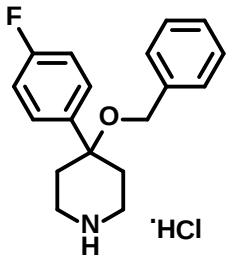

General procedure C: This compound was obtained as a white solid (180 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J*=8.4Hz, 2H), 7.56 (d, *J*=8.0Hz, 2H), 7.24-7.30 (m, 2H), 7.03-7.07 (m, 2H), 6.91-6.96 (m, 1H), 4.09 (s, 4H), 3.26 (s, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.93 (s, 2H), 1.48 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 164.3, 161.9, 155.1, 148.6, 125.8, 122.7, 114.2, 114.5, 79.8, 76.2, 63.6, 39.3, 35.7, 28.5.

Anal. Calcd for $C_{18}H_{20}ClF_2NO.\ H_2O$: C, 60.42; H, 6.20; N, 3.91. Found: C, 60.48; H, 6.18; N, 3.87.

**4-Benzyloxy-4-(4-fluorophenyl)-piperidinium chloride (27ba, TAV-13)**



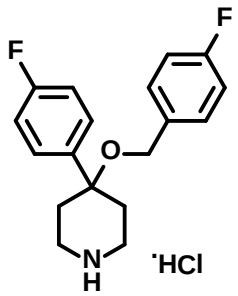

General procedure C: This compound was obtained as a white solid (196 mg, 96%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46 (d, *J*=8.8Hz, 1H), 7.34-7.39 (m, 2H), 7.23-7.31 (m, 5H), 6.99 (t, *J*=8.4Hz, 1H), 4.06 (s, 2H), 3.16 (t, *J*=12.0Hz, 2H), 2.93 (d, *J*=12.0Hz, 2H), 2.15 (d, *J*=11.6Hz, 2H), 1.94 (t, *J*=12.0Hz, 2H), 1.66 (s, NH)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.9, 76.4, 126.2, 127.4, 127.5, 127.6, 128.5, 128.6, 139.3, 145.4.

Anal. Calcd for $C_{18}H_{21}ClFNO.\ 3/4H_2O$: C, 67.18; H, 6.58; N, 4.35 Found: C, 66.25; H, 6.64; N, 4.29.

**4-(4-Fluorobenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bb, TAV-07)**



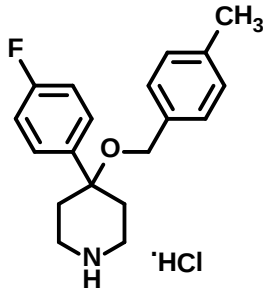

General procedure C: This compound was obtained as a white solid (205 mg, 95%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.43 (m, 2H), 7.23-7.26 (m, 2H), 6.97-7.01 (m, 4H), 4.03 (s, 3H), 3.14 (t, *J*=11.6Hz, 2H), 2.92 (d, *J*=12.0Hz, 2H), 2.10 (d, *J*=12.0Hz, 2H), 1.86-1.93 (m, 2H), 1.64 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.1, 76.1, 115.3, 115.5, 127.8, 129.2, 134.8, 141.2, 161.1, 163.4.

Anal. Calcd for $C_{18}H_{21}ClF_2NO.\ H_2O$: C, 60.54; H, 6.16; N, 4.05 Found: C, 60.42; H, 6.20; N, 3.91.

**4-(4-Methylbenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bc, TAV-67)**



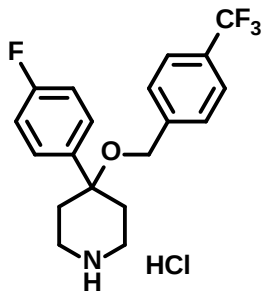

General procedure C: This compound was obtained as a white solid (172 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.45 (m, 2H), 7.19 (d, *J*=8.0Hz, 2H), 7.13 (d, *J*=7.6Hz, 2H), 7.03-7.07 (m, 2H), 4.03 (s, 2H), 3.15 (t, *J*=11.2Hz, 2H), 2.92-2.95 (m, 2H), 2.33 (s, 3H), 2.12 (d, *J*=13.2Hz, 2H), 1.85-1.92 (m, 2H), 1.70 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 36.6, 42.4, 63.7, 75.9, 115.2, 115.5, 127.7, 127.9, 128.0, 129.2, 136.1, 137.2.

Anal. Calcd for $C_{19}H_{23}ClFNO.\ H_2O$: C, 64.49; H, 7.12; N, 3.96 Found: C, 62.61; H, 7.09; N, 3.99.

**4-(4-Trifluoromethylbenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bd, TAV-15)**



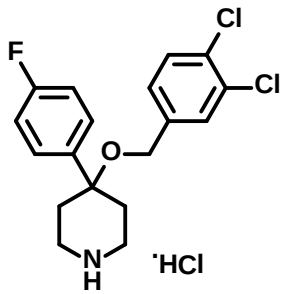

General procedure C: This compound was obtained as a white solid (185 mg, 90%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=12.0Hz, 2H), 7.39-7.43 (m, 4H), 7.05 (t, *J*=8.8Hz, 2H), 4.14 (s, 2H), 3.14 (t, *J*=12.0Hz, 2H), 2.95 (d, *J*=11.2Hz, 2H), 2.14 (d, *J*=12.0Hz, 2H), 1.89-1.96 (m, 2H), 1.77 (s, NH)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.4, 42.4, 63.1, 76.3, 115.4, 115.6, 125.3, 127.4, 127.8, 140.8, 143.2, 161.0, 163.5.

Anal. Calcd for $C_{19}H_{20}ClF_4NO$. $3/4H_2O$: C, 56.58; H, 5.37; N, 3.47 Found: C, 56.61; H, 5.31; N, 3.56.

**4-(4-Fluorobenzyloxy)-4-(3,4-dichlorophenyl)-piperidinium chloride (27be, TAV-46)**



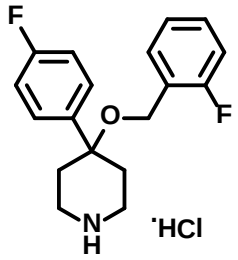

General procedure C: This compound was obtained as a white solid (210 mg, 96%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.44-7.35 (m, 5H), 7.29 (t, *J*=7.2Hz, 1H), 7.11 (dd, J=1.6Hz, 8.4Hz, 1H), 4.04 (s, 2H), 3.14 (t, *J*=12.0Hz, 2H), 2.95 (d, J=12.0Hz, 2H), 1.86-1.94 (m, 2H), 1.42 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.5, 62.6, 76.7, 126.1, 126.6, 127.7, 128.7, 129.3, 130.4, 131.2, 132.5, 139.6, 144.9.

Anal. Calcd for $C_{18}H_{20}Cl_2FNO$. $H_2O$: C, 55.33; H, 4.90; N, 3.58 Found: C, 55.09; H, 4.75; N, 3.63.

**4-(2-Fluoromethylbenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bf, TAV-68)**



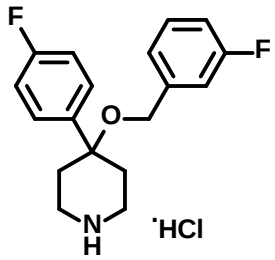

General procedure C: This compound was obtained as a white solid (175 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46-7.52 (m, 2H), 7.37 (t, *J*=7.6Hz, 2H), 7.22-7.30 (m, 2H), 7.14 (t, *J*=8.4Hz, 1H), 6.99 (t, *J*=9.2Hz, 1H), 4.16 (s, 2H), 3.15 (t, *J*=12.0Hz, 2H), 2.95 (d, *J*=12.4Hz, 2H), 2.15 (d, *J*=12.4Hz, 2H), 1.94 (t, *J*=12.0Hz, 2H), 1.80 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.8, 159.4, 145.2, 129.8, 129.0, 128.7, 127.5, 126.1, 124.2, 115.1, 76.6, 57.7, 42.4, 36.4.

Anal. Calcd for $C_{18}H_{21}ClF_2NO$: C, 67.18; H, 6.58; N, 4.35 Found: C, 66.92; H, 6.60; N, 4.36.

**4-(3-Fluoromethylbenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bg, TAV-72)**



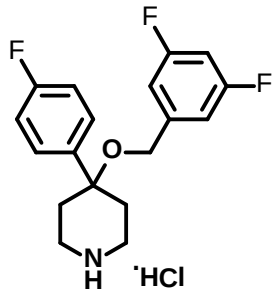

General procedure C: This compound was obtained as a white solid (182 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$) :** δ 7.46 (d, *J*=7.2Hz, 2H), 7.37 (t, *J*=8.0Hz, 2H), 7.24-7.30 (m, 2H), 7.07 (t, *J*=8.4Hz, 2H), 4.01 (s, 2H), 3.13-3.20 (m, 2H), 2.94-2.98 (m, 2H), 2.14 (d, *J*=12.0Hz, 2H), 1.92-1.99 (m, 2H), 1.81 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.4, 63.1, 76.5, 114.1, 114.2, 122.7, 126.1, 128.7, 142.0, 142.0, 145.1, 161.9, 164.

Anal. Calcd for $C_{18}H_{21}ClF_2NO$: C, 63.62; H, 5.93; N, 4.12 Found: C, 63.42; H, 5.90; N, 4.10.

**4-(3, 4-Difluorobenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bh, TAV-71)**



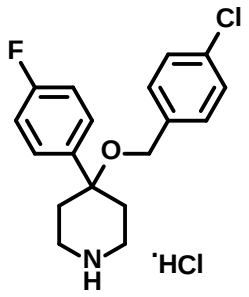

General procedure C: This compound was obtained as a white solid (180 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J*=8.4Hz, 2H), 7.56 (d, *J*=8.0Hz, 2H), 7.24-7.30 (m, 1H), 7.03-7.07 (m, 2H), 6.91-6.96 (m, 1H), 4.09 (s, 4H), 3.26 (s, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.93 (s, 2H), 1.48 (s, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 164.3, 161.9, 155.1, 126.5, 125.8, 122.7, 114.2, 114.5, 79.8, 76.2, 63.6, 39.3, 35.7.

Anal. Calcd for $C_{18}H_{19}ClF_3NO.\ H_2O$: C, 57.53; H, 5.63; N, 3.73 Found: C, 57.71; H, 5.64; N, 3.67.

**4-(3, 4-Chlorobenzyloxy)-4-(4-fluorophenyl)-piperidinium chloride (27bi, TAV-45)**



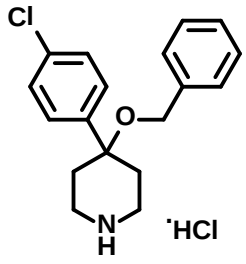

General procedure C: This compound was obtained as a white solid (200 mg, 95%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.43 (m, 2H), 7.23-7.26 (m, 2H), 6.97-7.01 (m, 4H), 4.03 (s, 3H), 3.14 (t, *J*=11.6Hz, 2H), 2.92 (d, *J*=12.0Hz, 2H), 2.10 (d, *J*=12.0Hz, 2H), 1.86-1.93 (m, 2H), 1.64 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.1, 76.1, 115.3, 115.5, 127.8, 129.2, 134.8, 141.2, 161.1, 163.4.

Anal. Calcd for $C_{18}H_{20}Cl_2FNO.\ H_2O$: C, 62.19; H, 5.81; N, 3.74 Found: C, 62.17; H, 5.87; N, 3.70.

**4-Benzyloxy-4-(4-chlorophenyl)-piperidinium chloride (27ca, TAV-25)**



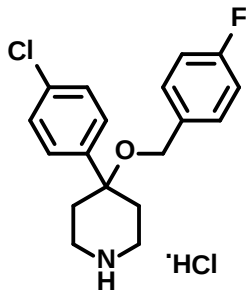

General procedure C: This compound was obtained as a white solid (295 mg, 87%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.25-7.42 (m, 9H), 4.09 (s, 2H), 4.05 (s, 2H), 3.15 (t, *J*=11.6Hz, 2H), 2.93 (d, *J*=12.0Hz, 2H), 2.12 (d, *J*=12.8Hz, 2H), 1.85-1.93 (m, 2H), 1.71 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.48, 42.46, 63.9, 76.1, 127.5, 127.6, 127.7, 128.5, 128.8, 133.3, 139.0, 144.2.

Anal. Calcd for $C_{18}H_{21}Cl_2NO$. $3/4H_2O$: C, 63.91; H, 6.26; N, 4.14 Found: C, 63.26; H, 6.05; N, 4.10.

**4-(4-Fluorobenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27cb, TAV-29)**



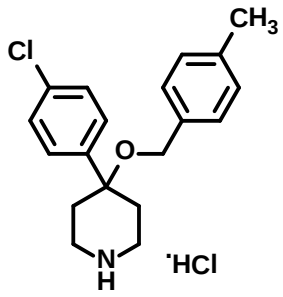

General procedure C: This compound was obtained as a white solid (185 mg, 82%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.39 (m, 4H), 7.23-7.27 (m, 2H), 6.97-7.03 (m, 2H), 4.04 (s, 2H), 3.10-3.16 (m, 2H), 2.92-2.96 (m, 2H), 2.10 (d, *J*=8.0Hz, 2H), 1.85-1.92 (m, 2H), 1.62 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.4, 42.4, 63.3, 76.2, 115.4, 127.6, 129.2, 133.3, 134.7, 144.0, 161.1, 163.5.

Anal. Calcd for $C_{19}H_{20}ClFNO$. $2/3H_2O$: C, 58.72; H, 5.84; N, 3.80 Found: C, 58.70; H, 5.61; N, 3.93.

**4-(4-Methylbenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27cc, TAV-34)**



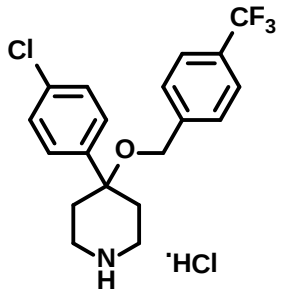

General procedure C: This compound was obtained as a white solid (172 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.45 (m, 2H), 7.19 (d, *J*=8.0Hz, 2H), 7.13 (d, *J*=7.6Hz, 2H), 7.03-7.07 (m, 2H), 4.03 (s, 2H), 3.15 (t, *J*=11.2Hz, 2H), 2.92-2.95 (m, 2H), 2.33 (s, 3H), 2.12 (d, *J*=13.2Hz, 2H), 1.85-1.92 (m, 2H), 1.70 (s, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 36.6, 42.4, 63.7, 75.9, 115.2, 115.5, 127.7, 127.9, 128.0, 129.2, 136.1, 137.2.

Anal. Calcd for $C_{19}H_{23}Cl_2NO$. $1/3H_2O$: C, 63.70; H, 6.66; N, 3.91 Found: C, 63.59; H, 6.31; N, 3.98.

**4-(4-Trifluoromehylbenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27cd, TAV-28)**



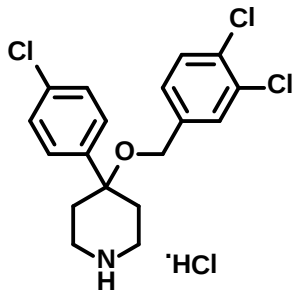

General procedure C: This compound was obtained as a white solid (198 mg, 90%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=8.0Hz, 2H), 7.31-7.43 (m, 6H), 4.14 (s, 2H), 3.14 (t, *J*=11.4Hz, 2H), 2.94 (d, *J*=12.0Hz, 2H), 2.10 (d, *J*=11.6Hz, 2H), 1.87-1.94 (m, 2H), 1.67 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.3, 42.4, 63.1, 125.4, 127.4, 127.6, 128.9, 129.8, 133.5, 137.3, 143.1, 143.7,

Anal. Calcd for $C_{19}H_{20}Cl_2F_3NO$. 3/4$H_2O$: C, 54.36; H, 5.16; N, 3.34 Found: C, 54.30; H, 5.14; N, 3.38.

**4-(3,4-Dichlorobenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27ce, TAV-26)**



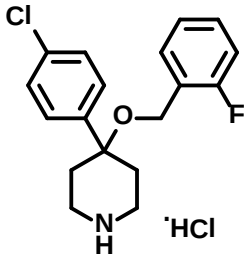

General procedure C: This compound was obtained as a white solid (165 mg, 76%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.40 (m, 5H), 7.10 (d, *J*=8.0Hz, 2H), 4.08-3.14 (t, *J*=12.4Hz, 2H), 2.93-2.96 (m, 2H), 2.07-2.11 (d, *J*=13.2Hz, 2H), 1.90-1.94 (m, 2H), 1.68 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.2, 42.4, 62.6, 76.4, 126.6, 127.5, 128.9, 129.2, 130.4, 131.3, 132.6, 133.5, 139.3, 143.5.

Anal. Calcd for $C_{18}H_{19}Cl_4NO$: C, 53.10; H, 4.70; N, 3.44 Found: C, 53.02; H, 4.95; N, 3.42.

**4-(2-Fluorobenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27cf, TAV-61)**



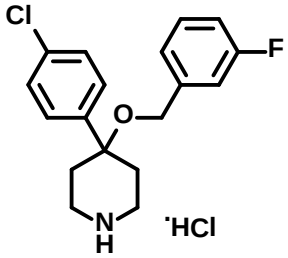

General procedure C: This compound was obtained as a white solid (175 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46-7.52 (m, 2H), 7.37 (t, *J*=7.6Hz, 2H), 7.22-7.30 (m, 2H), 7.14 (t, *J*=8.4Hz, 1H), 6.99 (t, *J*=9.2Hz, 1H), 4.16 (s, 2H), 3.15 (t, *J*=12.0Hz, 2H), 2.95 (d, *J*=12.4Hz, 2H), 2.15 (d, *J*=12.4Hz, 2H), 1.94 (t, *J*=12.0Hz, 2H), 1.80 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 161.8, 159.4, 145.2, 129.8, 129.0, 128.7, 127.5, 126.1, 124.2, 115.1, 76.6, 57.7, 42.4, 36.4.

Anal. Calcd for $C_{18}H_{20}Cl_2FNO$: C, 60.68; H, 5.66; N, 3.93 Found: C, 60.57; H, 5.81; N, 3.89.

**4-(3-Fluoromethylbenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27cg, TAV-72)**



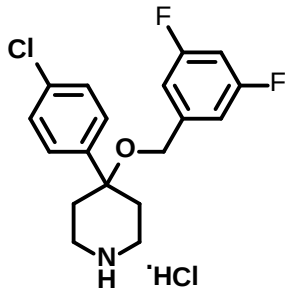

General procedure C: This compound was obtained as a white solid (182 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$) :** δ 7.46 (d, *J*= 7.2Hz, 2H), 7.37 (t, *J*=8.0Hz, 2H), 7.24-7.30 (m, 2H), 7.07 (t, *J*= 8.4Hz, 2H), 4.01 (s, 2H), 3.13-3.20 (m, 2H), 2.94-2.98 (m, 2H), 2.14 (d, *J*=12.0Hz, 2H), 1.92-1.99 (m, 2H), 1.81 (s, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.4, 63.1, 76.5, 114.1, 114.2, 122.7, 126.1, 128.7, 142.0, 142.0, 145.1, 161.9, 164.

Anal. Calcd for $C_{18}H_{21}Cl_2FNO.\ H_2O$: C, 60.54; H, 6.16; N, 4.05 Found: C, 60.42; H, 6.20; N, 3.91.

**4-(3, 4-Difluorobenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27ch, TAV-63)**



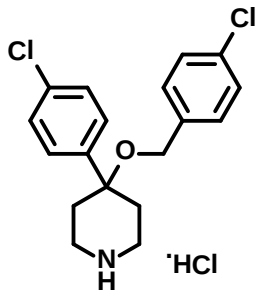

General procedure C: This compound was obtained as a white solid (180 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.63 (d, *J*=8.4Hz, 2H), 7.56 (d, *J*=8.0Hz, 2H), 7.24-7.30 (m, 1H), 7.03-7.07 (m, 2H), 6.91-6.96 (m, 1H), 4.09 (s, 4H), 3.26 (s, 2H), 2.15 (d, *J*=12.0Hz, 2H), 1.93 (s, 2H), 1.48 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 164.3, 161.9, 155.1, 148.6, 126.5, 122.7, 114.2, 114.5, 79.8, 76.2, 63.6, 39.3, 35.7.

Anal. Calcd for $C_{18}H_{19}Cl_2\ F_2NO$: C, 57.77; H, 5.12; N, 3.74 Found: C, 57.96; H, 5.15; N, 3.64.

**4-(4-Chlorobenzyloxy)-4-(4-chlorophenyl)-piperidinium chloride (27ci, TAV-64)**



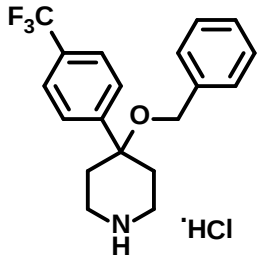

General procedure C: This compound was obtained as a white solid (200 mg, 95%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.43 (m, 2H), 7.23-7.26 (m, 2H), 6.97-7.01 (m, 4H), 4.03 (s, 3H), 3.14 (t, *J*=11.6Hz, 2H), 2.92 (d, *J*=12.0Hz, 2H), 2.10 (d, *J*=12.0Hz, 2H), 1.86-1.93 (m, 2H), 1.64 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.5, 42.5, 63.1, 76.1, 115.3, 115.5, 127.8, 129.2, 134.8, 141.2, 161.1, 163.4.

Anal. Calcd for $C_{18}H_{20}Cl_3NO$. $3/4H_2O$: C, 63.20; H, 5.93; N, 3.17 Found: C, 63.17; H, 6.13; N, 3.06.

**4-Benzyloxy-4-(4-trifluromethylphenyl)-piperidinium chloride (27da, TAV-37)**



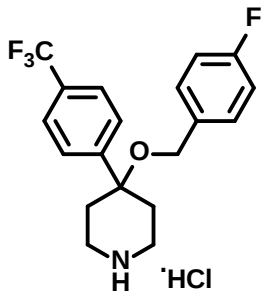

General procedure C: This compound was obtained as a white solid (170 mg, 78%).

**$^{1}$H NMR (100 MHz, $CDCl_3$):** δ 7.58-7.65 (m, 4H), 7.25-7.36 (m, 5H), 4.12 (s, 2H), 3.20 (t, *J*=12.0Hz, 2H), 2.96 (d, *J*=11.6Hz, 2H), 2.14 (d, *J*=12.4Hz, 2H), 1.90-1.97 (m, 2H), 1.70 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.4, 42.3, 64.1, 76.4, 125.6, 126.5, 127.6 128.6, 129.5, 129.8, 138.8, 149.8, 161.1

Anal. Calcd for $C_{19}H_{21}ClF_3NO$: C, 61.37; H, 5.69; N, 3.77 Found: C, 61.10; H, 5.72; N, 3.73.

**4-(4-Fluorobenzyloxy)-4-(4-trifluoromethylphenyl)-piperidinium chloride (27db, TAV-40)**



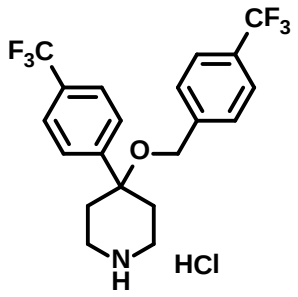

General procedure C: This compound was obtained as a white solid (175mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.64 (d, *J*=8.4Hz, 2H), 7.57 (d, *J*=8.4Hz, 2H), 7.25-7.29 (m, 2H), 7.01 (t, *J*=8.8Hz, 2H), 4.06 (s, 2H), 3.13-3.19 (t, *J*=12.0Hz, 2H), 2.96 (s, *J*=12.0Hz, 2H), 2.13 (d, *J*=12.0Hz, 2H), 1.93 (t, *J*=12.4Hz, 2H) 1.72 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 163.6, 161.1, 149.6, 134.5, 129.2, 126.5, 125.7, 115.5, 115.3, 76.5, 63.4, 42.3, 36.3.

Anal. Calcd for $C_{19}H_{20}ClF_4NO$: C, 58.54; H, 5.17; N, 3.59 Found: C, 58.25; H, 5.23; N, 3.66.

**4-(4-Trifluoromethylbenzyloxy)-4-(4-trifluoromethylphenyl)-piperidinium chloride (27dd, TAV-39)**



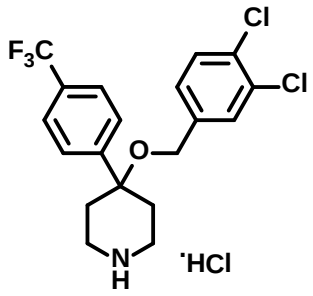

General procedure C: This compound was obtained as a white solid (200mg, 92%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.55-7.63 (m, 6H), 7.43 (d, *J*=8.0Hz, 2H), 4.16 (s, 2H), 3.15 (t, *J*=12.0Hz, 2H), 2.98 (d, *J*=11.6Hz, 2H), 2.14 (d, *J*=12.4Hz, 2H), 1.95 (t, *J*=12.0Hz, 2H), 1.80 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 36.3, 42.3, 63.3, 76.7, 123.4, 125.4, 125.6, 125.8, 126.4, 127.4, 129.9, 130.0, 142.9, 149.3.

Anal. Calcd for $C_{20}H_{20}ClF_6NO$: C, 54.62; H, 4.58; N, 3.18 Found: C, 54.52; H, 4.57; N, 3.12.

**4-(3, 4-Dichlorobenzyloxy)-4-(4-trifluoromethylphenyl)-piperidinium chloride (27de, TAV-38)**




General procedure C: This compound was obtained as a white solid (182 mg, 81%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.58-7.64 (m, 3H), 7.21 (d, *J*=8.4Hz, 2H), 7.15 (d, *J*=8.0Hz, 2H), 4.07 (s, 2H), 3.15 (m, 2H), 2.96 (d, *J*=12.0Hz, 2H), 2.34 (s, 3H), 2.113 (d, *J*=12.0Hz, 2H), 1.88-1.96 (m, 2H), 1.64 (s, NH).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 36.4, 42.3, 64.0, 76.3, 125.6, 126.6, 127.7, 128.6, 129.3, 129.5, 129.8, 133.3, 135.8, 137.3, 149.9

Anal. Calcd for $C_{19}H_{19}Cl_3F_3NO$: C, 51.78; H, 4.45; N, 3.81 Found: C, 51.59; H, 4.53; N, 2.91.

## 1.8. References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# Chapter 2: Design, synthesis and pharmacological evaluation of 3-aryl-3-aryl pyrrolidines as monoamine transporter ligands

## 2.1. Abstract

We have designed a novel pyrrolidine pharmacophore by combining structural features of previously active pharmacophore (i.e. piperidine and azetidine pharmacophore). The target compounds were prepared via a four step procedure from 1-Boc-pyrolidin-3-ol.

## 2.2. Introduction

The dual acting affinity of piperidine[1,2] and azetidine[3] series on monoamine transporters prompted an investigation to explore the pharmacophore by replacing azetidine or piperidine ring with pyrrolidine ring.[1-4]

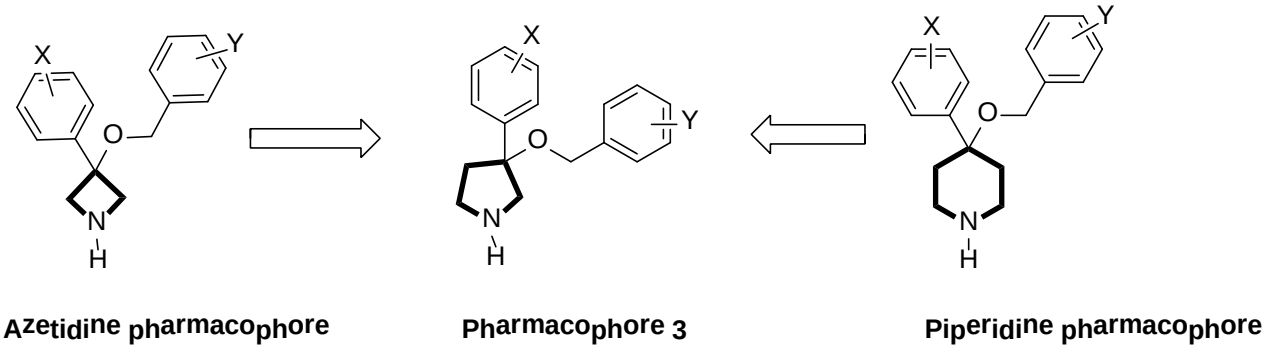


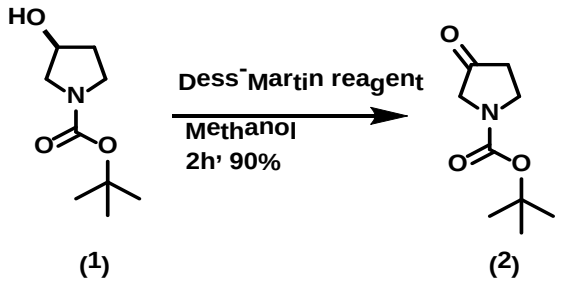

**Figure 2.1.** Design of pyrrolidine pharmacophore.

A novel pyrrolidine pharmacophore (**Pharmacophore 3**) was designed with aryl and arylmethoxy substitution on 3 position of ring. A variety of substituents on the aromatic ring would provide a potent and selective dual acting agent at monoamine transporter.[5-7]

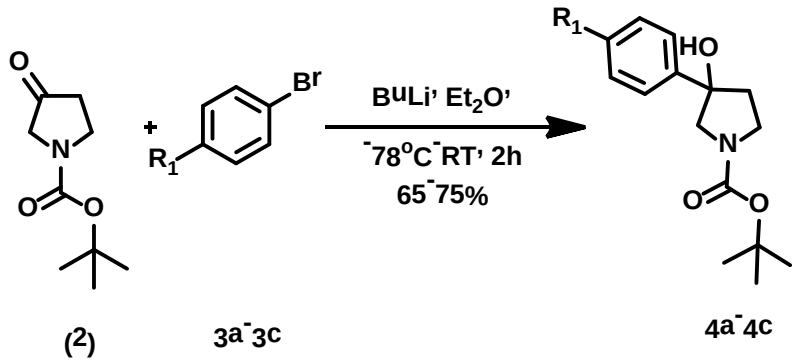
## 2.3. Results and discussion

### Synthesis of target compounds

The commercially available 1-Boc-pyrrolidin-3-ol was used for the synthesis of the target molecules. The substrate was oxidized using Dess–Martin periodinane to furnish corresponding ketone in excellent yields (**Scheme 2.1**).[8]



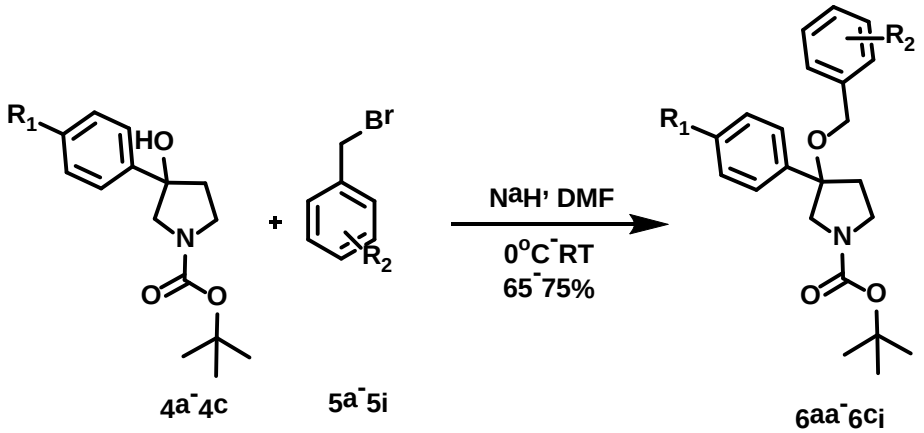

**Scheme 2.1.** Synthesis of Boc-pyrollidin-3-one




**Scheme 2.2.** Synthesis of tert-alcohol using aryl lithium reagent.

The ketone was further reacted with a pre-formed aryl lithium reagent that was synthesized in-situ using *n*-Butyl lithium and substituted bromobenzenes to produce tertiary alcohol in moderate

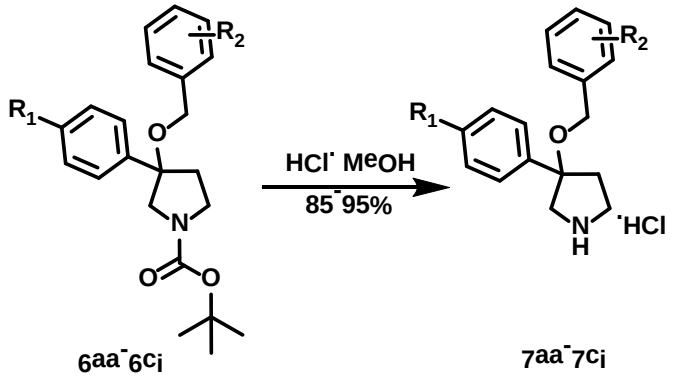
to good yields. A variety of substituents were installed on the aryl moiety to furnish intermediates **4a-4c (Scheme 2.2).**




$R_1$ : a=H, b=F, c=Cl
$R_2$ : a= H, b=4-F, c=4-Cl, d=3,4-$Cl_2$, e=4-$CF_3$,f=4-$CH_3$, g=3,5-$F_2$, h=2-F, i=3-Cl

**Scheme 2.3**. Alkylation of alcohol using substituted benzyl bromides.

The alcohols **4a-4c** were alkylated using variety of substituted benzyl bromides. The alkylation was performed using sodium hydride and dimethylformamide to furnish intermediates **6aa-6ci** in excellent yields **(Scheme 2.3).**




$R_1$ : a=H, b=F, c=Cl
$R_2$ : a= H, b=4-F, c=4-Cl, d=3,4-$Cl_2$, e=4-$CF_3$,f=4-$CH_3$, g=3,5-$F_2$, h=2-F, i=3-Cl

**Scheme 2.4.** Deprotection of Boc-group

Removal of the N-Boc group was performed using hydrochloric acid in methanol to give quantitative yield of the pyrrolidines as the hydrochloride salts **7aa-7ci (Table 2.1, Scheme 2.4.)**.

| **Cmpd**[a] | **code** | **$R_1$** | **$R_2$** |
|---|---|---|---|
| 7aa | TAV-91 | H | H |
| 7ab | TAV-85 | H | 4-F |
| 7ac | TAV-103 | H | 4-$CH_3$ |
| 7ad | TAV-84 | H | 3,4-$Cl_2$ |
| 7ae | TAV-130 | H | 2-F |
| 7af | TAV-104 | H | 3,5-$F_2$ |
| 7ag | TAV-87 | H | 4-Cl |
| 7ah | TAV-132 | H | 3-Cl |
| 7ba | TAV-94 | 4-F | H |
| 7bb | TAV-100 | 4-F | 4-F |
| 7bc | TAV-108 | 4-F | 4-$CH_3$ |
| 7bd | TAV-106 | 4-F | 3, 4-$Cl_2$ |
| 7ca | TAV-114 | 4-Cl | H |
| 7cb | TAV-124 | 4-Cl | 4-F |
| 7cf | TAV-122 | 4-Cl | 4-$CH_3$ |
| 7cd | TAV-120 | 4-Cl | 3,4-$Cl_2$ |
| 7cg | TAV-126 | 4-Cl | 3,5-$F_2$ |
| 7cc | TAV-116 | 4-Cl | 4-Cl |
| 7ci | TAV-136 | 4-Cl | 3-Cl |

[a]All compounds were synthesized as the HCl salts.

**Table 2.1.** Final pyrrolidine derivatives.

All the compounds will be tested as hydrochloride salts. Binding affinities for the dopamine, serotonin and norepinephrine transporters will be determined by the ability of the drug to displace the radiolabeled ligands [$^3$H] WIN35,428, [$^3$H] Citalopram, and [$^3$H] nisoxetine respectively, from the monoamine transporters in rat brain tissue using previously reported assays.

All the compounds synthesized in this study are in the process of biological evaluation. The potency and efficacy that is determined for these compounds will provide the direction for further studies with these novel tropane derivatives. All the biological studies will be reported in due course.

## 2.5. Conclusion

We have synthesized 3-aryl-3-arylmethoxy pyrrolidines using 1-Boc-3-pyrrolidinol using a 4 step synthesis methods. All the final compounds were synthesized with 15-45% of overall yields. We will perform the screening of these compounds on monoamine transporters and study the structure activity relationship in future.

## 2.6. Experimental

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous Ethyl ether ($Et_2O$), Dimethylformamide (DMF), Methanol (MeOH), Dichloromethane (DCM) was purchased from Mallinckrodt Baker. Inc. Thin layer chromatography (TLC) 20×20 cm aluminium plates precoated with silica gel purchased from EMD Millipore USA and used to monitor reactions via visualization with short-wave UV light. $^1H$ NMR (400 MHz) and $^{13}C$ NMR (400 MHz) spectra were recorded on a Varian 400 MHz NMR spectrometer at ambient temperature in $CDCl_3$. $^1H$ 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 $CDCl_3$ (77.0 ppm). Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

**Synthesis of *tert*-butyl 3-oxopyrrolidine-1-carboxylate**

To a clean dry flask was added tert-butyl-3-hydroxypyrrolidine-1-carboxylate (10.7 mmol, 1 equiv.) in dry methanol (20 ml). To the reaction mixture was then added Dess–Martin periodinane (16.1 mmol, 1.5 equiv.) in portions. The reaction mixture was stirred for 3 h at room temperature. After the completion of reaction, the solvent was evaporated under reduced pressure and the crude mixture was diluted with water and extract with ethyl ether (3×20ml). The organic extract was dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to get final product as white solid. (Yield : 1.85g, 90%)

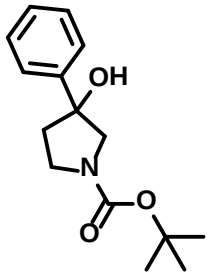
**$^{1}$H NMR (400 MHz, $CDCl_3$):** 4.32 (d, *J* = 12.8, 2H), 4.12 (s, 2H), 2.71 (d, *J* = 12.4, 2H), 1.40 (s, 9H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 27.5, 37.0, 56.7, 79.5, 159.0, 192.5

**General procedure A. Synthesis of tertiary alcohols (4a-4c)**

In a clean, dry round-bottom flask was added substituted benzenes (2 equiv.) **(3a-3c)** in dry ethyl ether (20 ml). The solution of n-Butyl lithium (2.1 equiv.) was added to the solution dropwise at 0ºC. The solution of 1-(Boc) 4-pyrrolidinone (1 equiv.) **(2)** in diethyl ether was added to the solution at -78°C. The solution was warmed to room temperature and stirred for 2h. The reaction mixture was diluted with ammonium chloride solution. The reaction mixture was extracted with ethyl ether (3×30 ml). The organic extract was washed with brine solution (30 ml) and dried over sodium sulphate. The solvent was evaporated under reduced pressure. The crude mixture was purified using column chromatography to obtain compounds **4a-4c.**

**Tert-butyl-3-hydroxy-3-phenylpyrrolidine-1-carboxylate**

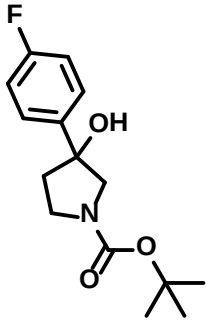



General procedure A: This compound was obtained as a colorless liquid (2.2 g, 70%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.47 (d, *J* = 7.6Hz, 2H), 7.36 (t, *J* = 8.0Hz, 2H), 7.28 (t, *J*= 7.2Hz, 1H), 3.52-3.67 (m, 4H), 3.12 (brs, 1H), 2.12-2.23 (m, 2H), 1.42 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 44.4, 44.8, 64.5, 77.9, 79.7, 126.7, 126.8, 128.6, 128.9, 155.0

**Tert-butyl-3-(4-fluorophenyl)-3-hydroxypyrrolidine-1-carboxylate**

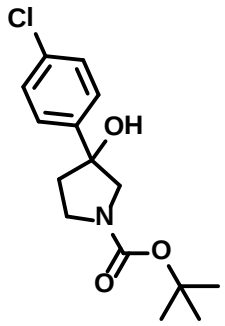



General procedure A: This compound was obtained as a colorless liquid (1.8g, 55%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.42-7.45 (m, 2H), 7.06-7.12 (m, 2H), 3.42-3.65 (m, 4H), 3.18 (brs, 1H), 2.15-2.21 (m, 2H), 1.41 (s, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 44.4, 44.8, 65.9, 75.3, 79.6, 115.6, 127.7, 128.7, 136.1, 154.8.

**Tert-butyl-3-(4-chlorophenyl)-3-hydroxypyrrolidine-1-carboxylate**




General procedure A: This compound was obtained as a colorless liquid (2.1g, 62%).

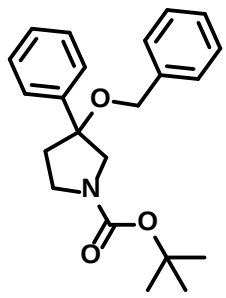
**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.30 (m, 2H), 7.42 (m, 2H), 3.30-3.92 (m, 4H), 3.12 (brs, 1H), 2.15-2.30 (m, 2H), 1.39 (s, 9H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 44.4, 44.8, 66.0, 76.3, 79.6, 128.3, 129.0, 134.2, 138.4, 154.7.

**General procedure B. Benzylation of alcohols (6aa-6ch)**

The solution of compounds **4a-4c** was stirred in dimethylformamide at $0^0$C. To the solution was added sodium hydride (2.2 equiv.) at $0^0$C. Variety of benzyl bromides (1.2 equiv.) **(5a-5h)** was added to the solution and the reaction was stirred for 2 h. The reaction was quenched with water and extracted with ethyl acetate (3×20 ml). The organic solvent was washed with brine solution and dried over sodium sulphate. The crude product was purified using column chromatography to obtain compounds **6aa-6ch**.

**N-(*tert*-Butoxycarbonyl)-3-(phenylmethoxy)-3-phenyl-pyrrolidine (6aa, TAV-82)**

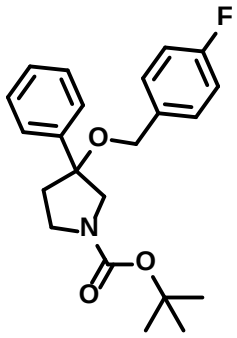


General procedure B: This compound was obtained as a colorless liquid (280 mg, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.24-7.7.48 (m, 10H), 3.93-4.26 (m, 3H), 3.52-3.73 (m, 3H), 2.51-2.52 (m, 1H), 2.12-2.27 (m, 1H), 1.49 (d, *J*=11.2Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.5, 44.2, 44.6, 54.8, 56.9, 66.0, 79.8, 85.0, 86.2, 126.8, 127.6, 127.7, 128.5, 128.6, 128.9, 138.9, 140.6, 154.8.

**N-(*tert*-Butoxycarbonyl)-3-[(4-fluorophenyl)methoxy]-3-phenyl-pyrrolidine (6ab, TAV-83)**

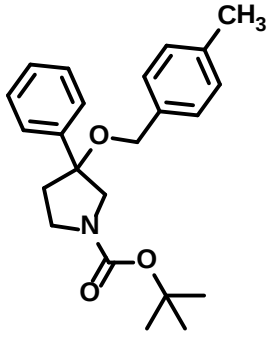



General procedure B: This compound was obtained as a colorless liquid (270 mg, 65%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.34-7.45 (m, 5H), 7.16-7.20 (m, 2H), 6.94-6.97 (m, 2H), 3.91-4.20 (m, 3H), 3.51-3.63 (m, 3H), 2.48-2.52 (m, 1H), 2.17-2.27 (m, 1H), 1.49 (d, *J*=11.2Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 36.5, 44.4, 44.8, 53.8, 55.9, 65.3, 79.6, 85.0, 86.0, 115.5, 126.8, 128.9, 129.3, 134.4, 140.0, 154.8, 161.2, 163.6.

**N-(*tert*-Butoxycarbonyl)-3-[(4-methylphenyl)methoxy]-3-phenyl-pyrrolidine (6ac, TAV-101)**

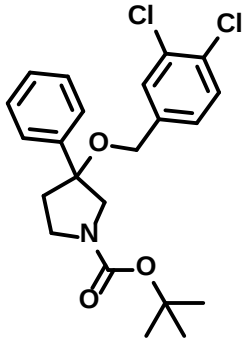


General procedure B: This compound was obtained as a colorless liquid (285 mg, 75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.35-7.49 (m, 5H), 7.14 (m, 4H), 3.94-4.22 (m, 3H), 3.56-3.74 (m, 3H), 2.51-2.54 (m, 1H), 2.34 (s, 3H) 2.23-2.26 (m, 1H), 1.52 (d, *J*=11.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 38.8, 33.9, 36.5, 44.5, 44.9, 54.0, 56.1, 65.9, 79.5, 84.9, 85.8, 126.8, 127.8, 128.3, 128.8, 129.2, 135.7, 137.3, 140.3, 155.0.

**N-(*tert*-Butoxycarbonyl)-3-[(3,4-dichlorophenyl)methoxy]-3-phenyl-pyrrolidine (6ad, TAV-82)**

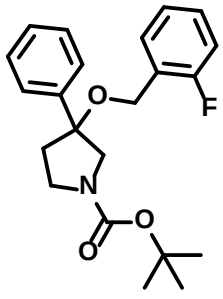



General procedure B: This compound was obtained as a colorless liquid (255 mg, 55%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.30-7.41 (m, 6H), 7.00-7.05 (m, 1H), 3.88-4.18 (m, 3H), 3.52-3.69 (m, 3H), 2.46-2.51 (m, 1H), 2.18-2.28 (m, 1H), 1.47 (d, *J*=9.2Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 36.4, 44.4, 44.8, 53.7, 55.9, 64.5, 79.7, 85.3, 86.2, 126.7, 126.8, 128.6, 128.9, 129.3, 130.4, 131.3, 132.5, 139.0, 139.6, 155.0.

**N-(*tert*-Butoxycarbonyl)-3-[(3-fluorophenyl)methoxy]-3-phenyl-pyrrolidine (6ae, TAV-129)**

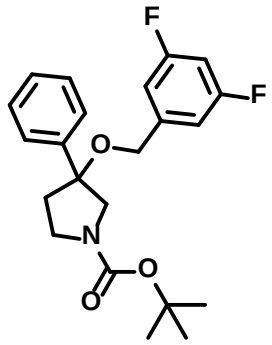



General procedure B: This compound was obtained as a colorless liquid (270 mg, 70%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.31-7.46 (m, 6H), 7.21-7.22 (m, 1H), 7.07-7.12 (m, 1H), 6.94-6.99 (m, 1H), 4.28 (t, *J*=12.4Hz, 1H), 4.146 (t, *J*=12.0Hz, 1H), 3.96 (d, *J*=12.4Hz, 1H), 3.51-3.65 (m, 3H), 2.50-2.51 (m, ,1H), 2.20-2.25 (m, 1H), 1.48 (d, *J*=13.2Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 35.9, 44.4, 44.8, 54.4, 56.1, 59.6, 79.5, 85.1, 86.0, 115.1, 115.3, 124.2, 124.3, 126.7, 128.4, 128.8, 129.3, 129.9, 139.8, 155.6

**N-(*tert*-Butoxycarbonyl)-3-[(3,5-difluorophenyl)methoxy]-3-phenyl-pyrrolidine (7af, TAV-102)**

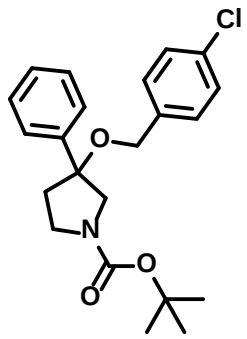



General procedure B: This compound was obtained as a colorless liquid (250 mg, 55%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.25-7.41 (m, 5H), 6.61-6.74 (m, 3H), 4.04-4.21 (m, 2H), 3.68 (d, *J*=11.2Hz, 1H), 3.52-3.69 (m, 3H), 2.47-2.51 (m, 1H), 2.18-2.28 (m, 1H), 1.48 (d, *J*=8.0Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.6, 33.9, 36.5, 44.4, 44.8, 53.6, 55.8, 64.7, 79.7, 85.3, 86.2, 115.7, 126.6, 128.5, 129.3, 132.5, 135.5, 138.9, 154.7, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(4-chlorophenyl)methoxy]-3-phenyl-pyrrolidine (6ag, TAV-86)**

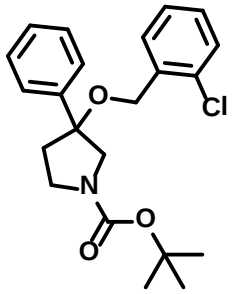


General procedure B: This compound was obtained as a colorless liquid (275 mg, 65%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.44 (m, 5H), 7.24-7.27 (m, 2H), 7.13-7.16 (m, 2H), 4.06-4.21 (m, 2H), 3.90 (d, *J*=11.6Hz, 1H), 3.51-3.71 (m, 3H), 2.47-2.51 (m, 1H), 2.17-2.25 (m, 1H), 1.48 (d, *J*=11.2Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.5, 44.4, 44.9, 53.8, 55.9, 65.2, 79.6, 85.1, 86.0, 126.7, 126.8, 128.4, 128.5, 128.6, 133.3, 133.4, 137.2, 137.3, 139.9, 140.0, 154.8

**N-(*tert*-Butoxycarbonyl)-3-[(3-chlorophenyl)methoxy]-3-phenyl-pyrrolidine (6ah, TAV-131)**

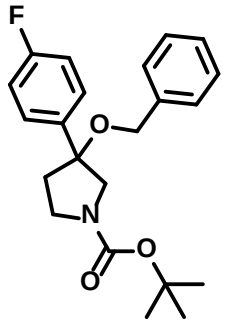



General procedure B: This compound was obtained as a colorless liquid (250 mg, 50%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.42 (m, 5H), 7.19-7.26 (m, 3H), 7.07-7.10 (m, 1H), 3.91-4.21 (m, 3H), 3.52-3.70 (m, 3H), 2.49-2.51 (m, 1H), 2.18-2.21 (m, 1H), 1.49 (d, *J*=9.4Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 36.4, 44.4, 44.9, 53.8, 56.0, 65.1, 79.6, 85.1, 86.1, 125.5, 126.8, 127.5, 127.7, 128.5, 128.9, 129.7, 134.3, 139.8, 140.7, 154.8

**N-(*tert*-Butoxycarbonyl)-3-phenylmethoxy-3-(4-fluorophenyl)-pyrrolidine (6ba, TAV-93)**

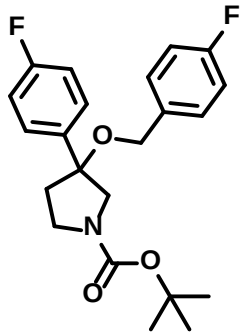


General procedure B: This compound was obtained as a colorless liquid (280 mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.42-7.45 (m, 2H), 7.22-7.33 (m, 4H), 7.06-7.12 (m, 2H), 3.92-4.24 (m, 3H), 3.51-3.68 (m, 3H), 2.49-2.53 (m, 1H), 2.16-2.22 (m, 1H), 1.50 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.4, 44.4, 44.8, 54.1, 56.1, 65.9, 79.6, 84.5, 85.4, 115.6, 127.6, 127.7, 128.7, 136.1, 138.6, 154.8, 161.4, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(4-fluorophenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6bb, TAV-99)**

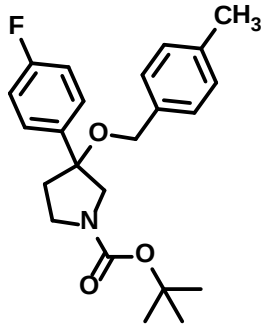


General procedure B: This compound was obtained as a colorless liquid (265 mg, 62%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.38-7.43 (m, 2H), 7.14-7.18 (m, 2H), 7.06-7.11 (m, 2H), 6.94-7.00 (m, 2H), 3.87-4.18 (m, 3H), 3.49-3.67 (m, 3H), 2.45-2.50 (m, 1H), 2.14-2.24 (m, 1H), 1.47 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.6, 44.4, 44.8, 53.9, 56.0, 65.3, 79.7, 84.5, 85.4, 115.3, 115.8, 128.6, 129.4, 134.2, 136.0, 154.9, 161.4, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(4-methylphenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6bc, TAV-107)**

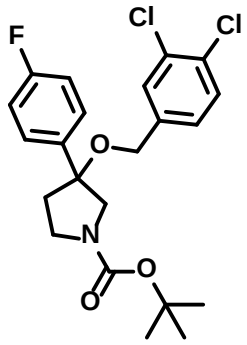



General procedure B: This compound was obtained as a colorless liquid (282 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.41-7.45 (m, 2H), 7.06-7.12 (m, 6H), 4.04-4.20 (m, 2H), 3.93 (d, *J*=11.6Hz, 1H), 3.51-3.65 (m, 3H), 2.48-2.52 (m, 1H), 2.32 (s, 3H), 2.15-2.21 (m, 1H), 1.50 (d, *J*=10.0Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 28.7, 34.04, 36.4, 44.4, 44.8, 54.2, 56.1, 65.8, 79.6, 84.4, 85.3, 115.6, 127.7, 128.6, 129.2, 136.2, 137.3, 154.8, 161.4, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(3,4-dichlorophenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6bd, TAV-105)**

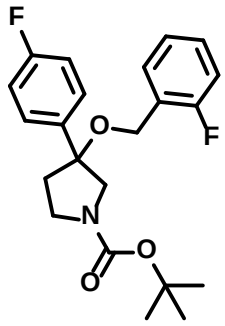



General procedure B: This compound was obtained as a colorless liquid (278 mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.25-7.39 (m, 4H), 6.99-7.09 (m, 3H), 4.00-4.16 (m, 2H), 3.87 (d, *J*=11.6Hz, 1H), 3.50-3.64 (m, 3H), 2.44-2.49 (m, 1H), 2.15-2.24 (m, 1H), 1.46 (d, *J*=8.4Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.4, 44.4, 44.8, 53.8, 55.9, 64.5, 79.7, 84.7, 85.7, 115.7, 126.6, 128.5, 130.5, 131.4, 132.5, 135.5, 138.9, 154.7, 161.5, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(2-fluorophenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6be, TAV-111)**

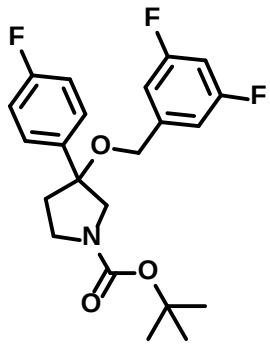



General procedure B: This compound was obtained as a colorless liquid (280mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.31-7.43 (m, 3H), 7.21-7.25 (m, 1H), 6.93-7.11 (m, 4H), 3.88-4.27 (m, 3H), 3.46-3.65 (m, 3H), 2.49-2.52 (m, 1H), 2.16-2.27 (m, 1H), 1.45-1.47 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 35.9, 44.4, 44.8, 54.5, 56.1, 59.6, 79.6, 84.6, 85.5, 115.8, 124.2, 124.3, 125.5, 128.5, 129.3, 129.9, 135.8, 154.7, 161.4, 163.9.

**N-(*tert*-Butoxycarbonyl)-3-[(3,5-difluorophenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6bf, TAV-109)**

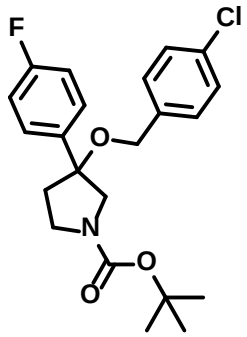



General procedure B: This compound was obtained as a colorless liquid (264 mg, 62%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.34-7.39 (m, 2H), 7.02-7.07 (m, 2H), 6.59-6.71 (m, 3H), 4.00-4.18 (m, 2H), 3.88 (d, *J*=11.6Hz, 1H), 3.51-3.59 (m, 3H), 2.43-2.48 (m, 1H), 2.14-2.20 (m, 1H), 1.44 (d, *J*=6.4Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.6, 34.0, 36.4, 44.3, 44.8, 53.8, 55.8, 64.6, 79.7, 84.8, 85.7, 102.7, 109.8, 115.7, 128.5, 135.5, 142.7, 154.7, 161.8, 164.3.

**N-(*tert*-Butoxycarbonyl)-3-[(4-chlorophenyl)methoxy]-3-(4-fluorophenyl)-pyrrolidine (6bg, TAV-95)**

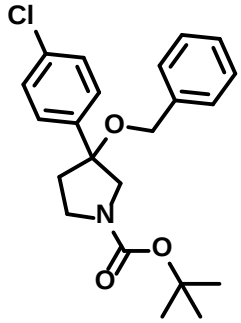



General procedure B: This compound was obtained as a colorless liquid (270 mg, 68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.37-7.40 (m, 2H), 7.21-7.24 (m, 2H), 7.12 (d, *J*=8.0Hz, 2H), 7.03- 7.08 (m, 2H), 3.87-4.17 (m, 3H), 3.50-3.64 (m, 3H), 2.45-2.48 (m, 1H), 2.13-2.23 (m, 1H), 1.46 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.4, 44.4, 44.8, 54.0, 55.9, 65.1, 79.6, 84.6, 85.5, 115.8, 128.6, 128.9, 133.4, 135.8, 137.1, 154.9, 161.4, 163.9

**N-(*tert*-Butoxycarbonyl)-3-phenylmethoxy-3-(4-chlorophenyl)-pyrrolidine (6ca, TAV-113)**

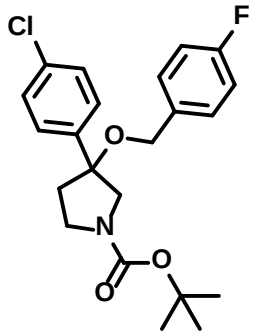


General procedure B: This compound was obtained as a colorless liquid (284 mg, 86%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.21-7.38 (m, 9H), 4.04-4.23 (m, 2H), 3.91(d, *J*=11.6Hz, 1H), 3.52-3.68 (m, 3H), 2.47-2.48 (m, 1H), 2.15-2.18 (m, 1H), 1.49 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.1, 36.5, 44.4, 44.8, 54.0, 55.9, 66.0, 79.6, 84.5, 85.4, 127.6, 127.6, 128.2, 128.3, 128.5, 129.0, 134.2, 138.4, 138.9, 154.7.

**N-(*tert*-Butoxycarbonyl)-3-[(4-fluorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6cb, TAV-123)**

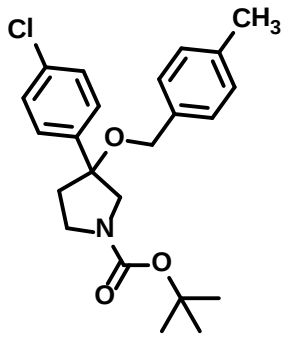



General procedure B: This compound was obtained as a colorless liquid (272 mg, 64%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.36-7.37 (m, 4H), 7.15-7.18 (m, 2H), 6.94-6.99 (m, 2H), 4.01-4.18 (m, 2H), 3.87 (d, *J*=11.6Hz, 1H), 3.50-3.61 (m, 3H), 2.46-2.49 (m, 1H), 2.13-2.20 (m, 1H),1.45 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.6, 44.4, 44.8, 53.8, 55.8, 65.4, 79.7, 84.5, 85.5, 115.5, 128.2, 129.1, 129.4, 134.2, 138.6, 154.7, 161.2, 163.6.

**N-(*tert*-Butoxycarbonyl)-3-[(4-methylphenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6cc, TAV-121)**

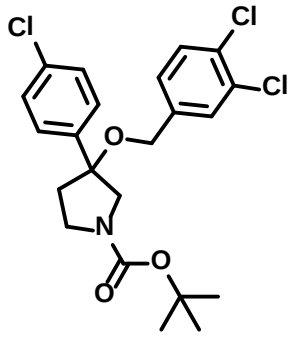



General procedure B: This compound was obtained as a colorless liquid (265 mg, 60%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.39-7.29 (m, 4H), 7.12 (d, *J*=0.8Hz, 4H), 4.03-4.20 (m, 2H), 3.90 (d, *J*=11.6Hz, 1H), 3.49-3.68 (m, 3H), 2.48-2.50 (m, 1H), 2.33 (s, 3H), 2.16-2.21 (m, 1H), 1.48 (d, *J*=10.4Hz, 9H).

**$^{13}$C NMR (400 MHz, $CDCl_3$):** 21.3, 28.7, 34.0, 36.6, 44.4, 44.8, 53.9, 56.0, 66.0, 79.6, 84.4, 85.4, 128.3, 129.0, 129.2, 129.3, 134.2, 135.4, 137.6, 139.0, 154.8

**N-(*tert*-Butoxycarbonyl)-3-[(3,4-dichlorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6cd, TAV-119)**

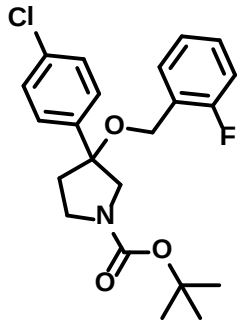



General procedure B: This compound was obtained as a colorless liquid (285 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.25-7.36 (m, 6H), 6.99-7.03 (m, 1H), 3.99-4.16 (m, 2H), 3.84 (d, *J*=11.6Hz, 1H), 3.50-3.64 (m, 3H), 2.44-2.47 (m, 1H), 2.13 (s, 1H), 1.46(d, *J*=8.4Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.0, 36.4, 44.3, 44.7, 53.7, 55.7, 64.6, 79.8, 84.8, 85.7, 126.6, 128.1, 129.1, 129.3, 130.4, 131.5, 132.6, 134.5, 138.3, 138.7, 154.7.

**N-(*tert*-Butoxycarbonyl)-3-[(3,5-difluorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6ce, TAV-133)**

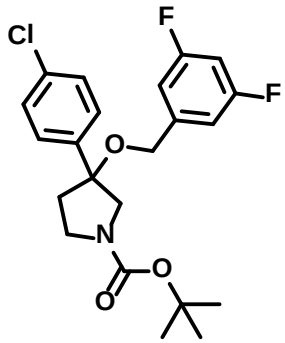



General procedure B: This compound was obtained as a colorless liquid (260 mg, 61%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33 (m, 4H), 6.60-6.72 (m, 4H), 3.85-4.19 (m, 3H), 3.51-3.63 (m, 3H), 2.46-2.47 (m, 1H), 2.14-2.20 (m, 1H), 1.45 (d, *J*=6.0Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.6, 34.0, 36.5, 44.3, 44.8, 53.6, 55.7, 64.8, 79.8, 84.8, 85.7, 102.8, 109.8, 127.7, 127.8, 128.1, 129.1, 134.4, 138.2, 142.7, 154.6, 161.9

**N-(*tert*-Butoxycarbonyl)-3-[(3,5-difluorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6cf, TAV-125**)

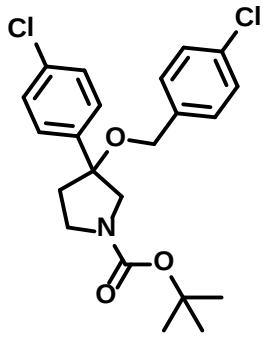



General procedure B: This compound was obtained as a colorless liquid (270 mg, 65%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.31-7.37 (m, 4H), 7.19-7.21 (m, 1H), 7.05-7.10 (m, 1H), 6.93-6.97 (m, 1H), 4.21 (t, *J*=11.2Hz, 1H), 4.10-4.16 (t, *J*=11.2Hz, 1H), 3.90 (d, *J*=11.6Hz, 1H), 3.48-3.64 (m, 3H), 2.47-2.50 (m, 1H), 2.10-2.19 (m, 1H), 1.45 (d, *J*=8.0Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 35.9, 44.3, 44.7, 54.4, 55.9, 59.7, 79.7, 84.6, 85.5, 115.4, 124.2, 128.2, 129.0, 129.3, 129.9, 134.2, 138.5, 154.7.

**N-(*tert*-Butoxycarbonyl)-3-[(4-chlorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6cg, TAV-115)**

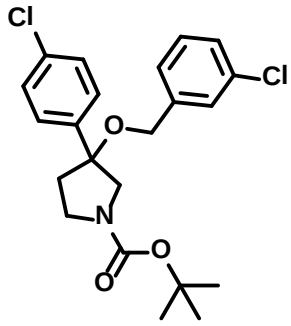



General procedure B: This compound was obtained as a colorless liquid (275 mg, 72%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.34 (d, *J*=3.6Hz, 4H), 7.23-7.26 (m, 2H), 7.12-7.14 (m, 2H), 4.00-4.18 (m, 2H), 3.86 (d, *J*=12.0Hz, 1H), 3.48-3.65 (m, 3H), 2.44-2.47 (m, 1H), 2.13-2.19 (m, 1H), 1.46 (d, *J*=9.6Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 34.1, 36.5, 44.4, 44.8, 53.8, 55.8, 65.3, 79.7, 84.6, 85.6, 125.5, 127.4, 128.1, 128.2, 129.1, 134.4, 138.4, 142.6, 154.7

**N-(*tert*-Butoxycarbonyl)-3-[(3-chlorophenyl)methoxy]-3-(4-chlorophenyl)-pyrrolidine (6ch, TAV-135)**




General procedure B: This compound was obtained as a colorless liquid (290 mg, 81%).

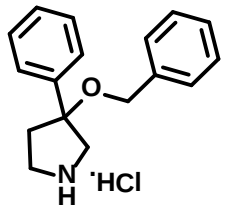
**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.31-7.32 (m, 4H), 7.15-7.17 (m, 3H), 7.03-705 (m, 1H), 3.98-4.16 (m, 2H), 3.86 (d, *J*=11.2Hz, 1H), 3.49-3.62 (m, 3H), 2.42-2.45 (m, 1H), 2.14-2.17 (m, 1H), 1.44 (d, *J*=8.0Hz, 9H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 28.7, 33.9, 36.3, 44.3, 44.7, 53.9, 55.8, 65.2, 79.7, 84.6, 85.6, 125.4, 127.5, 127.7, 127.8, 128.2, 129.1, 129.8, 134.3, 138.4, 140.5, 154.

**General procedure C. Synthesis of hydrochloride salts (7aa-7eh)**

To the solution of **6aa-6ch** in methanol (15ml)was added to conc. HCl (2 ml) and stirred for 1h. The solvent was evaporated under reduced pressure. To the crude product was added water (20ml) at $0^0$C. The solid formed was filtered and dried under vaccum to get hydrochloride salt of compounds **7aa-7ch**.

**3-(Benzyloxy)-3-phenylpyrrolidine hydrochloride (7aa, TAV-91)**



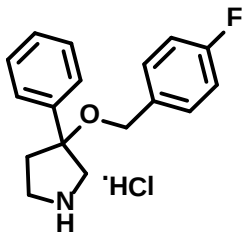

General procedure C: This compound was obtained as a white solid (182 mg, 81%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.23-7.41 (m, 10H), 4.10-4.20 (m, 2H), 3.43 (d, *J*=12.0Hz, 1H), 3.26-3.30 (m, 1H), 3.10 (s, 1H), 2.91-2.94 (m, 1H), 2.37-2.48 (m, 2H), 2.10-2.18 (m, 1H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.2, 58.2, 65.8, 88.0, 127.5, 127.7, 128.5, 128.6, 128.8, 133.6, 138.8, 140.1.

Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.46; H, 6.96; N, 4.83 Found: C, 69.80; H, 6.79; N, 4.87.

**3-(4-Fluorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7ab, TAV-85)**



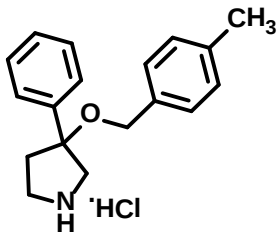

General procedure C: This compound was obtained as a white solid (190 mg, 88%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.39 (m, 5H), 7.17-7.20 (m, 2H), 6.96-7.00 (m, 2H), 4.05-4.14 (m, 2H), 3.41 (dd, *J*=1.2Hz, 12.0Hz, 1H),3.26-3.29 (m, 1H), 3.09-3.11 (m, 1H), 2.91 (d, *J*=12.4Hz, 1H), 2.38-2.41 (m, 2H), 2.12-2.18 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.1, 88.1, 115.3, 128.5, 128.9, 129.2, 129.3, 133.7, 134.5, 140.0.

Anal. Calcd for $C_{17}H_{19}ClFNO$. $1/4H_2O$: C, 65.38; H, 6.12; N, 4.54 Found: C, 65.46; H, 6.23; N, 4.62.

**3-(4-Methylbenzyloxy)-3-phenylpyrrolidine hydrochloride (7ac, TAV-103)**



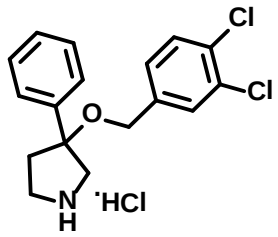

General procedure C: This compound was obtained as a white solid (186 mg, 85%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.40 (m, 5H), 7.12-7.25 (m, 4H), 4.05-4.15 (m, 2H), 3.41 (d, *J*=12.0Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90 (d, *J* =12.4Hz, 1H), 2.35-2.42 (m, 2H), 2.32 (s, 3H), 2.13-2.16 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 36.1, 46.1, 58.1, 65.7, 87.9, 127.6, 128.5, 128.8, 129.3, 133.6, 135.7, 137.4, 140.1.

Anal. Calcd for $C_{18}H_{22}ClNO.\ 1/3H_2O$: C, 69.79; H, 7.37; N, 4.52 Found: C, 69.43; H, 7.11; N, 4.65.

**3-(3,4-Dichlorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7ad, TAV-84)**



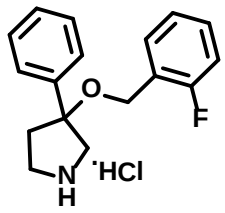

General procedure C: This compound was obtained as a white solid (175mg, 80%).

**$^1$H NMR (400 MHz, $CDCl_3$):** 7.33-7.35 (m, 6H), 7.03 (d, *J*=8.4Hz, 2H), 4.04-4.12 (m, 2H), 3.43 (d, *J*=11.6Hz, 1H), 3.27 (brs, 1H), 2.97-3.12 (m, 2H), 2.35-2.38 (m, 1H), 2.13-2.19 (s, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 35.9, 45.9, 57.7, 64.4, 88.2, 126.6, 128.4, 129.0, 129.2, 130.5, 132.5, 133.6 134.0, 139.0, 139.4.

Anal. Calcd for $C_{17}H_{18}Cl_3NO.\ 2H_2O$: C, 56.92; H, 5.05; N, 3.90 Found: C, 51.72; H, 5.57; N, 3.58.

**3-(2-Fluorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7ae, TAV-130)**



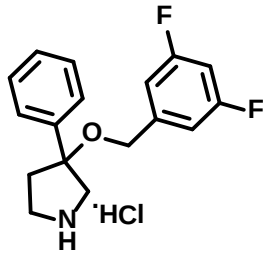

General procedure C: This compound was obtained as a white solid (190 mg, 89%).

**$^1$H NMR (400 MHz, $CDCl_3$):** 7.35-7.39 (m, 4H), 7.10 (t, *J*=7.6Hz, 2H), 6.96-7.00 (t, *J*=9.2Hz, 1H), 4.14-4.23 (m, 2H), 3.43-3.46 (d, *J*=12.4Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90-2.93 (d, *J*=12.0Hz, 1H), 2.37-2.43 (m, 2H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.0, 59.7, 88.1, 115.3, 124.3, 128.5, 128.8, 129.4, 129.9, 130.5, 133.7, 138.9 139.7.

Anal. Calcd for $C_{17}H_{19}ClFNO$: C, 66.34; H, 6.22; N, 4.55 Found: C, 66.05; H, 6.28; N, 4.72.

**3-(3,5-Difluorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7af, TAV-104)**



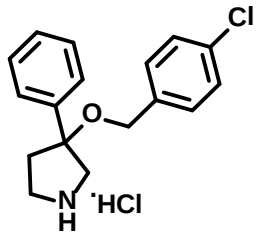

General procedure C: This compound was obtained as a white solid (182 mg, 79%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.39 (m, 4H), 7.21-7.25 (m, 1H), 7.10 (t, *J*=7.6Hz, 2H), 6.96-7.00 (t, *J*=8.8Hz, 1H), 4.14-4.23 (m, 2H), 3.43-3.46 (d, *J*=12.4Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90-2.93 (d, *J*=12.0Hz, 1H), 2.37-2.43 (m, 2H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.0, 59.7, 88.1, 115.3, 124.3, 128.5, 128.8, 129.4, 129.9, 133.7, 139.7.

Anal. Calcd for $C_{17}H_{18}ClF_2NO$: C, 62.67; H, 5.57; N, 4.30 Found: C, 62.40; H, 5.53; N, 4.39.

**3-(4-Chlorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7ag, TAV-87)**



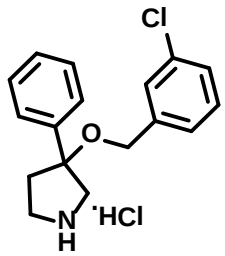

General procedure C: This compound was obtained as a white solid (174 mg, 78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.37 (m, 5H), 7.26 (d, *J*=8.4Hz, 2H), 7.15 (d, *J*=8.4Hz, 2H), 4.05-4.15 (m, 2H), 3.41 (d, *J*=12.1Hz, 1H), 3.26-3.28 (m, 1H), 3.09 (brs, 1H), 2.91-2.93 (m, 2H), 2.34-2.40 (m, 1H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.0, 128.4, 128.7, 128.8, 128.9, 133.4, 133.8, 137.3, 139.8.

Anal. Calcd for $C_{17}H_{19}Cl_2NO$. $3/4H_2O$: C, 62.97; H, 5.91; N, 4.32 Found: C, 62.68; H, 6.00; N, 4.37.

**3-(3-Chlorobenzyloxy)-3-phenylpyrrolidine hydrochloride (7ah, TAV-132)**



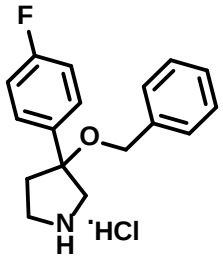

General procedure C: This compound was obtained as a white solid (188mg, 83%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.35-7.39 (m, 5H), 7.25-7.27 (m, 2H), 7.20 (t, *J*=8.4Hz, 2H), 4.05-4.15 (m, 2H), 3.42 (d, *J*=12.4Hz, 2H), 3.27 (m, 1H), 2.91-2.93 (m, 2H), 2.38-2.40 (m, 1H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.0, 88.1, 115.3, 128.4, 128.7, 128.8, 128.9, 131.2, 133.4, 133.8, 137.3, 139.7.

Anal. Calcd for $C_{17}H_{19}Cl_2NO$: C, 60.45; H, 6.12; N, 4.15 Found: C, 60.15; H, 5.38; N, 4.63.

**3-(Benzyloxy)-3-(4-fluorophenyl)-pyrrolidine hydrochloride (7ba, TAV-94)**



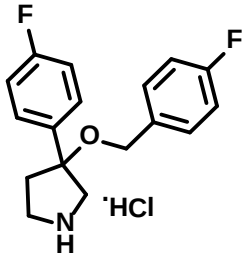

General procedure C: This compound was obtained as a white solid (180 mg, 83%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.23-7.41 (m, 5H), 7.17-7.20 (m, 2H), 6.96-7.00 (m, 2H), 4.10-4.20 (m, 2H), 3.43 (d, *J*=12.0Hz, 1H), 3.26-3.30 (m, 1H), 3.10 (s, 1H), 2.91-2.94 (m, 1H), 2.37-2.48 (m, 2H), 2.10-2.18 (m, 1H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.2, 58.2, 65.8, 88.0, 127.5, 127.7, 128.5, 128.6, 128.8, 133.6, 138.8, 140.1.

Anal. Calcd for $C_{17}H_{19}ClFNO$. $3/4H_2O$: C, 63.55; H, 6.43; N, 4.36 Found: C, 63.70; H, 6.37; N, 4.66.

**3-(4-Fluorobenzyloxy)-3-(4-fluorophenyl)-pyrrolidine hydrochloride (7bb, TAV-100)**



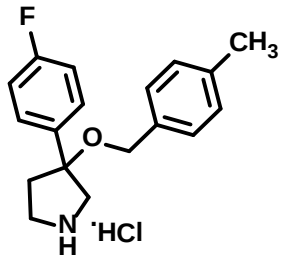

General procedure C: This compound was obtained as a white solid (176 mg, 80%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.39 (m, 4H), 7.20-7.24 (m, 2H), 6.96-7.00 (m, 2H), 4.05-4.14 (m, 2H), 3.41 (dd, *J*=1.2Hz, 11.6Hz, 1H),3.26-3.29 (m, 1H), 3.09-3.11 (m, 1H), 2.91 (d, *J*=12.4Hz, 1H), 2.38-2.41 (m, 2H), 2.12-2.18 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.1, 88.1, 115.3, 128.5, 128.9, 129.2, 129.3, 133.7, 134.5, 140.0.

Anal. Calcd for $C_{17}H_{18}ClF_2$ NO. $1/2H_2O$: C, 60.99; H, 5.72; N, 4.18 Found: C, 61.11; H, 5.55; N, 4.34.

**3-(4-Methylbenzyloxy)-3-(4-fluorophenyl)-pyrrolidine hydrochloride (7bc, TAV-108)**



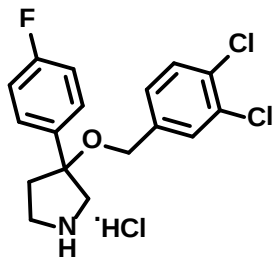

General procedure C: This compound was obtained as a white solid (195 mg, 90%).

**$^1$H NMR (400 MHz, $CDCl_3$):** 7.33-7.40 (m, 4H), 7.09-7.29 (m, 4H), 4.05-4.15 (m, 2H), 3.41 (d, *J*=12.0Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90 (d, *J* =12.4Hz, 1H), 2.35-2.42 (m, 2H), 2.32 (s, 3H), 2.13-2.16 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 36.1, 46.1, 58.1, 65.7, 87.9, 127.6, 128.5, 128.8, 129.3, 133.6, 135.7, 137.4, 140.1.

Anal. Calcd for $C_{17}H_{21}ClFNO.2/3H_2O$: C, 64.79; H, 6.74; N, 4.20 Found: C, 64.48; H, 6.44; N, 4.45.

**3-(3,4-Dichlorobenzyloxy)-3-(4-fluorophenyl)-pyrrolidine hydrochloride (7bd, TAV-106)**



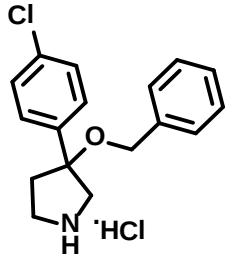

General procedure C: This compound was obtained as a white solid (185 mg, 81%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.35 (m, 2H), 7.25-7.27 (m, 2H), 7.20 (t, *J*=8.4Hz, 2H), 7.03 (d, *J*=8.4Hz, 1H), 4.04-4.12 (m, 2H), 3.43 (d, *J*=11.6Hz, 1H), 3.27 (brs, 1H), 2.97-3.12 (m, 2H), 2.35-2.38 (m, 1H), 2.13-2.19 (s, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 35.9, 45.9, 57.7, 64.4, 88.2, 126.6, 128.4, 129.0, 129.2, 130.5, 132.5, 133.6 134.0, 139.0, 139.4.

Anal. Calcd for $C_{17}H_{17}Cl_3FNO$: C, 54.21; H, 4.55; N, 3.72 Found: C, 53.95; H, 4.44; N, 3.71.

**3-(Benzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7ca, TAV-114)**



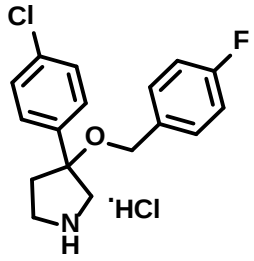

General procedure C: This compound was obtained as a white solid (172 mg, 79%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.23-7.41 (m, 9H), 4.10-4.20 (m, 2H), 3.43 (d, *J*=12.0Hz, 1H), 3.26-3.30 (m, 1H), 3.10 (s, 1H), 2.91-2.94 (m, 1H), 2.37-2.48 (m, 2H), 2.10-2.18 (m, 1H)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.2, 58.2, 65.8, 88.0, 127.5, 127.7, 128.5, 128.6, 128.8, 133.6, 138.8, 140.1

Anal. Calcd for $C_{17}H_{19}Cl_2NO$: C, 62.97; H, 5.91; N, 4.32 Found: C, 62.72; H, 5.74; N, 4.27.

**3-(4-Fluorobenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7cb, TAV-124)**



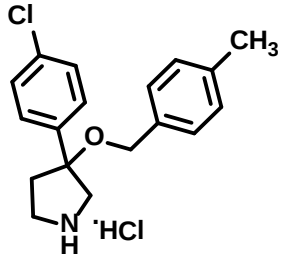

General procedure C: This compound was obtained as a white solid (190 mg, 87%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.39 (m, 4H), 7.17-7.20 (m, 2H), 6.96-7.00 (m, 2H), 4.05-4.14 (m, 2H), 3.41 (dd, *J*=1.2Hz, 12.0Hz, 1H),3.26-3.29 (m, 1H), 3.09-3.11 (m, 1H), 2.91 (d, *J*=12.4Hz, 1H), 2.38-2.41 (m, 2H), 2.12-2.18 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.1, 88.1, 115.3, 128.5, 128.9, 129.2, 129.3, 133.7, 134.5, 140.0.

Anal. Calcd for $C_{17}H_{18}Cl_2FNO$: C, 59.66; H, 5.30; N, 4.09 Found: C, 59.38; H, 5.40; N, 4.06.

**3-(4-Methylbenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7cc, TAV-122)**



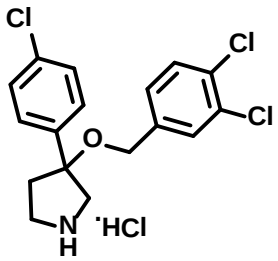

General procedure C: This compound was obtained as a white solid (198 mg, 91%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.40 (m, 4H), 7.12-7.25 (m, 4H), 4.05-4.15 (m, 2H), 3.41 (d, *J*=12.0Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90 (d, *J* =12.4Hz, 1H), 2.35-2.42 (m, 2H), 2.32 (s, 3H), 2.13-2.16 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 21.3, 36.1, 46.1, 58.1, 65.7, 87.9, 127.6, 128.5, 128.8, 129.3, 133.6, 135.7, 137.4, 140.1.

Anal. Calcd for $C_{18}H_{21}Cl_2NO.\ H_2O$: C, 60.88; H, 6.51; N, 3.93 Found: C, 59.58; H, 6.26; N, 3.97.

**3-(3,4-Dichlorobenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7cd, TAV-120)**



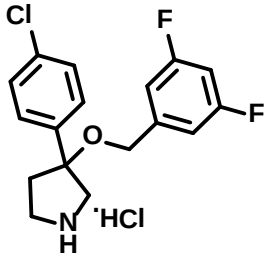

General procedure C: This compound was obtained as a white solid (184mg, 81%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.33-7.35 (m, 6H), 7.03 (d, *J*=8.4Hz, 1H), 4.04-4.12 (m, 2H), 3.43 (d, *J*=11.6Hz, 1H), 3.27 (brs, 1H), 2.97-3.12 (m, 2H), 2.35-2.38 (m, 1H), 2.13-2.19 (s, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 35.9, 45.9, 57.7, 64.4, 88.2, 126.6, 128.4, 129.0, 129.2, 130.5, 132.5, 133.6 134.0, 139.0, 139.4.

Anal. Calcd for $C_{17}H_{17}Cl_4NO$. $1/4H_2O$: C, 51.35; H, 4.44; N, 3.52 Found: C, 51.68; H, 4.40; N, 3.53.

**3-(3,5-Difluorobenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7cf, TAV-126)**



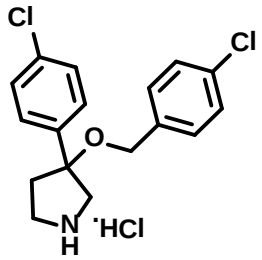

General procedure C: This compound was obtained as a white solid (188 mg, 84%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.39 (m, 4H), 7.21-7.25 (m, 1H), 7.10 (t, *J*=7.6Hz, 1H), 6.96-7.00 (t, *J*=8.8Hz, 1H), 4.14-4.23 (m, 2H), 3.43-3.46 (d, *J*=12.4Hz, 1H), 3.24-3.31 (m, 1H), 3.05-3.11 (m, 1H), 2.90-2.93 (d, *J*=12.0Hz, 1H), 2.37-2.43 (m, 2H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.0, 59.7, 88.1, 115.3, 124.3, 128.5, 128.8, 129.4, 129.9, 133.7, 139.7.

Anal. Calcd for $C_{17}H_{17}Cl_2F_2NO$: C, 56.68; H,4.76; N, 3.89 Found: C, 56.38; H, 4.81; N, 3.89.

**3-(4-Chlorobenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7cg, TAV-116)**



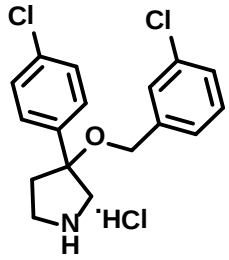

General procedure C: This compound was obtained as a white solid (175 mg, 79%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.37 (m, 4H), 7.26 (d, *J*=8.4Hz, 2H), 7.15 (d, *J*=8.4Hz, 2H), 4.05-4.15 (m, 2H), 3.41 (d, *J*=12.1Hz, 1H), 3.26-3.28 (m, 1H), 3.09 (brs, 1H), 2.91-2.93 (m, 2H), 2.34-2.40 (m, 1H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.0, 128.4, 128.7, 128.8, 128.9, 133.4, 133.8, 137.3, 139.8.

Anal. Calcd for $C_{17}H_{18}Cl_3NO$: C, 56.92; H, 5.05; N, 3.90 Found: C, 56.88; H, 5.21; N, 3.92.

**3-(3-Chlorobenzyloxy)-3-(4-chlorophenyl)-pyrrolidine hydrochloride (7ch, TAV-136)**




General procedure C: This compound was obtained as a white solid (190 mg, 87%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** 7.32-7.37 (m, 4H), 7.25-7.27 (m, 2H), 7.15 (t, *J*=8.4Hz, 2H), 4.05-4.15 (m, 2H), 3.42 (d, *J*=12.4Hz, 2H), 3.27 (m, 1H), 2.91-2.93 (m, 2H), 2.38-2.40 (m, 1H), 2.10-2.17 (m, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** 36.1, 46.1, 58.1, 65.0, 88.1, 115.3, 128.4, 128.7, 128.8, 128.9, 131.2, 133.4, 133.8, 137.3, 139.7.

Anal. Calcd for $C_{17}H_{18}Cl_3NO$: C, 56.92; H, 5.06; N, 3.90 Found: C, 56.62; H, 5.09; N, 3.93.

## 2.7. References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# Chapter 3. Application of Iridium catalyzed N-heterocyclization for synthesis of Natural products.

## 3.1. Abstract

The focus of these studies has been toward the development of new synthetic methods and procedures for the synthesis of novel compounds with unique biological properties. This research has led to the development of new synthetic strategy for the construction of pyridine alkaloids such as Nicotine and Anabasine. The developed method utilizes microwave condition and water as solvent for the reaction. The protocol is efficient, facile and short as compare to the previous methods reported for synthesis for these compounds. The key step involves the aqueous microwave-assisted, iridium-catalyzed N-heterocyclization reaction of pyridinylbutane-1, 4-diols and pyridinylpentane- 1, 5-diols with various amines. The microwave-assisted N-heterocyclization furnishes derivatives of nicotine and anabasine in good yields (50–75%) with overall yields ranging from 30–50%.

## 3.2. Introduction

Our group has been working on iridium catalyzed N-alkylation reaction of amines with alcohols over last 5 years. We have been utilizing iridium catalyzed methods for the total synthesis of medicinally important natural products.

In recent years many transition metals have been used for synthesis of substituted amines such as hydroamination of alkenes or alkynes, and amination of aryl halides have been developed. The traditional method of synthesis of substituted amines includes N-alkylation of amines with alkyl halides and reductive amination using carbonyl compounds. However, these conventional reaction conditions have some disadvantages from environmental point of view because they

generate equimolar amounts of wasteful salts as co-products. Moreover, the reaction with alkyl halides and reducing agent is undesirable. Similarly, the N-heterocyclization of amines has been performed for synthesis of nitrogen heterocycles such as pyrrolidine, piperidine, and morpholine using hydroamination and ring closing metathesis which requires drastic reaction conditions and generates harmful byproduct at the end of reaction.

## 3.3. Pyridine alkaloids

Nicotine and anabasine are pyridine alkloids commonly found in the solanaceae plant family such as *Nicotina tabacum* and *Nicotina rustica*.[1] Nicotine alkloids modulate neuronal acetyl chlorine receptors, which affect the central nervous system **(Figure 3.1)**.[2]

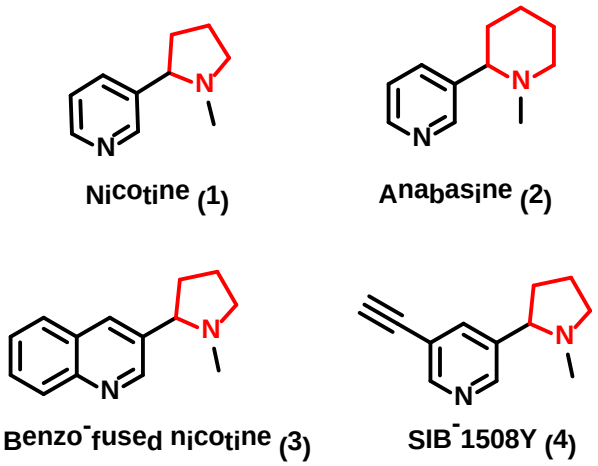



**Figure 3.1.** Pyridine alkloids- Nicotine derivatives

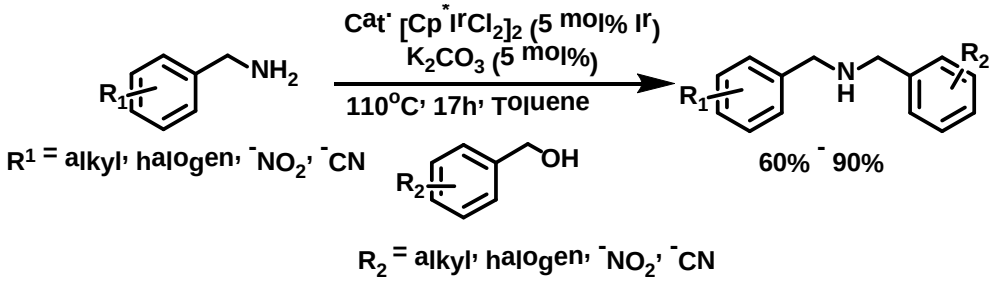
The pharmacological action of nicotine alkloids and related derivatives on the central nervous system has attracted considerable attention as potential therapeutic targets for the variety of disease states and pathological conditions mediated by nicotinic acetylcholine receptors.[2-5] However, toxicity and abuse potential has limited the use of nicotine related drugs for central nervous system disorders.[2] Therefore, new analogues of nicotine with unique nicotinic acetylcholine receptor subtype selectivity remain important pharmacological targets for the

development of novel therapeutics with improved safety profiles. Nicotine has also been used for synthesis of Altinicline (SIB-1508Y), a preclinical drug candidate for Parkinson's disease. Benzo-fused nicotine derivative has found to shown similar binding affinity as nicotine. To this end, considerable effort has been focused on the development of new synthetic methods for the construction nicotine derivatives.[6-8] Although a variety of methods have been reported; there is still a need for versatile and practical methods for the synthesis of nicotine-related derivatives.

In the past, we have described the application of the iridium catalyzed N-heterocyclization reaction for the synthesis of nicotine related compounds, and the first total synthesis of the alkloid, Noranabasamine.[9, 10] Further studies by Zhao and co-workers showed that N-heterocyclization of simple amine/alcohol systems proceeded under solvent free, base-free microwave-assisted conditions.[11] Based on the past findings, it was of interest to explore the further application of these conditions for the green synthesis of nicotine and anabasine-related analogues.

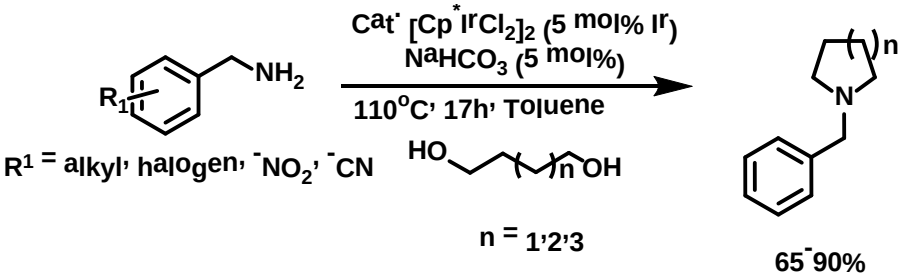
## 3.4. Application of iridium catalysis

N-Alkylation or N-heterocyclization of amines with alcohols or diols has been attracted considerable attention because the product of the reaction can be obtained from easily available starting materials in one step without generation of any harmful by products **(Scheme 3.1)**.[12]




**Scheme 3.1**. N-alkylation of primary amines with primary alcohol in the presence of Iridium catalyst

Alcohols or diols are more readily available than corresponding halides or carbonyl compounds in many cases. The reaction also works efficiently by the employment of equimolar amounts of starting materials, generating high atom economical system. Although, variety of catalytic system for N-alkylation or N-heterocyclizaton have been utilized using ruthenium and other transition metal catalysts but the requirement of high temperature and excess of use of alcohols or diols preclude use of these catalyst system for practical synthesis of nitrogen heterocycles and N-substituted amines.




**Scheme 3.2.** N-heterocyclization of amines with alcohols using iridium catalyst[12]

Fujita and co-workers reported the use of (pentamethylcyclopentadienyl) iridium dichloride dimer $([Cp^*IrCl_2])_2$ for N-alkylation of amines with alcohols and N-heterocyclization of amines with diols by primary amines **(Scheme 3.2)**.[12] The method works by hydrogen borrowing concept, which involves catalytic transfer of hydrogen from alcohol to form in-situ aldehydes or ketones. A possible mechanism for the $Cp^*$ Ir-catalyzed N-heterocyclization of primary amines with primary and secondary alcohols is shown in **Figure 3.2**.

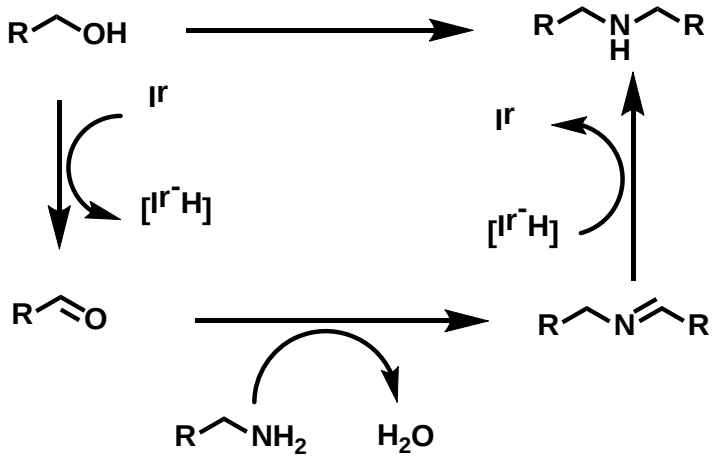
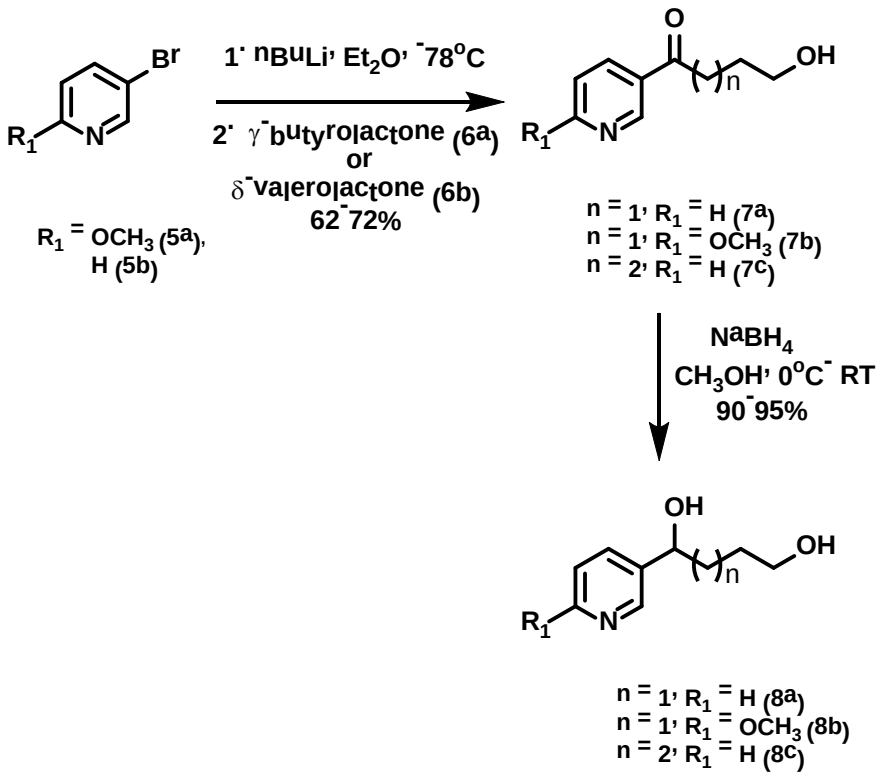



**Figure 3.2.** Mechanism of iridium catalysis

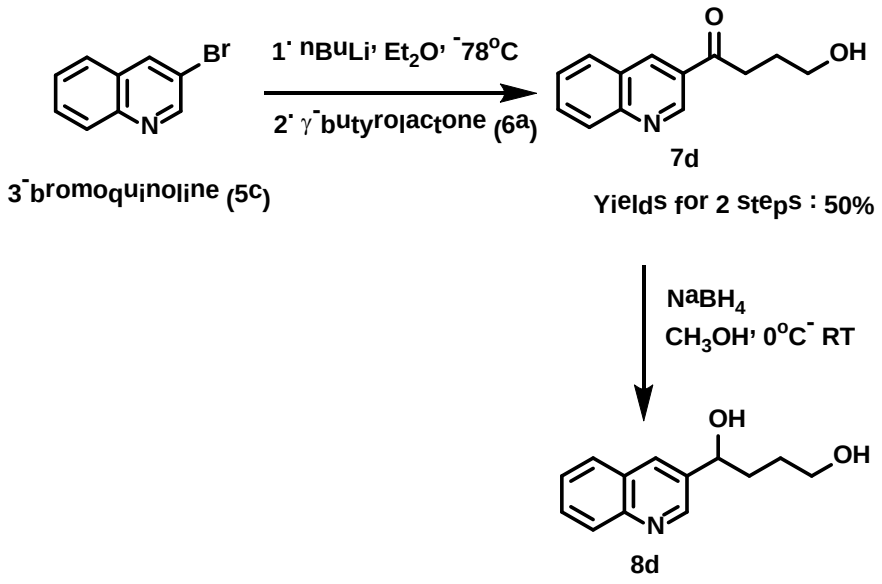
## 3.5. Results and discussion

We utilized approach using methodology already developed in our laboratory for the synthesis of 1-(3-pyridinyl) diols. 3-bromopyridine or 5-bromo-2-methoxypyridine was treated with n-butyllithium at -78$^{o}$C in diethyl ether. Butyrolactone or valerolactone was then added to the resulting lithiated pyridine derivatives to afford the corresponding hydroxyl ketones in high yields. Further, subsequent reduction with sodium borohydride in methanol afforded the required intermediate diols in good to excellent yields **(Scheme 3.3)**.[13]



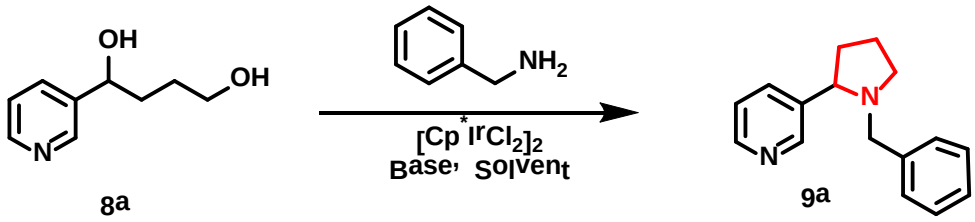

**Scheme 3.3.** Synthesis of 1,4 and 1,5- pyridine diols.

Similarly, 3-bromoquninoline and butyrolactone was used for synthesis of 3-quinoline-1, 4-diol using a two step synthesis procedure **(Scheme 3.4).**[13]




**Scheme 3.4.** Synthesis of quinoline butan-1, 4-diol

Initially, we decided to explore and optimize the reaction conditions for the synthesis of N-benzylnornicotine. The reaction of the diol and benzyl amine was performed under reflux and microwave assisted conditions. When the reaction was performed in the absence of a base and solvent compound was formed in low yields. Even using a base and toluene as the solvent did not improve substantially the yields of product. The highly polar nature and poor solubility of the diols in toluene encouraged us to explore the use of water as solvent for this transformation. It was found that reaction yield was considerably improved when water was used as the solvent under reflux conditions (**Scheme 3.5, Table 3.1**).



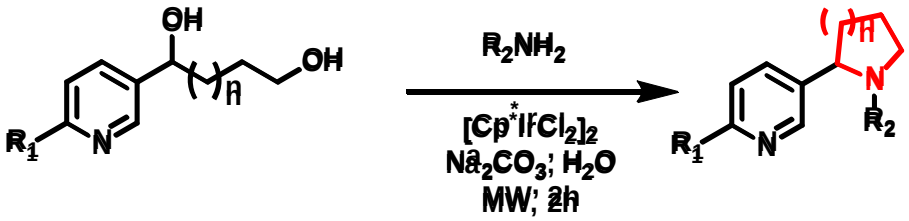

**Scheme 3.5.** Development of method for synthesis of N-benzyl nor-nicotine derivatives.

| Entry | Solvent | Base | Conditions | Yields (%) |
|---|---|---|---|---|
| 1 | - | - | Reflux, 17h | 10 |
| 2 | - | - | Microwave, 2h | 15 |
| 3 | Toluene | $NaHCO_3$ | Reflux, 17h | 10 |
| 4 | Toluene | $NaHCO_3$ | Microwave, 2h | 20 |
| 5 | $H_2O$ | $NaHCO_3$ | Reflux, 17h | 50 |
| 6 | $H_2O$ | $NaHCO_3$ | Microwave, 2h | 60 |
| 7 | $H_2O$ | NaOAc | Microwave, 2h | 65 |
| 8 | $H_2O$ | $Na_2CO_3$ | Microwave, 2h | 75 |
| 9 | $H_2O$ | $K_2CO_3$ | Microwave, 2h | 35 |

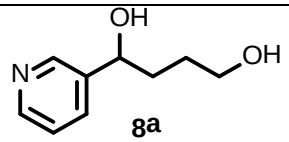
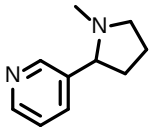
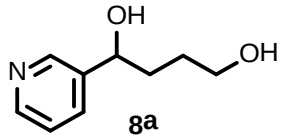
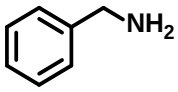
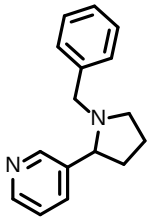
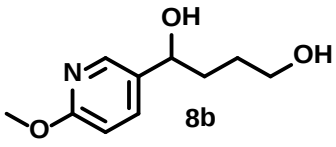
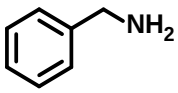
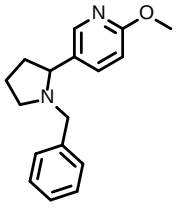
**Table. 3.1.** Optimization of the N-Heterocyclization Reaction.

Further, optimization was base showed that sodium carbonate was superior base than sodium bicarbonate, sodium acetate and potassium carbonate. And let to an optimized yield of 75%.[13]

To check scope and limitations of the developed method, we performed N-heterocyclization of 1,4-butandiols and 1, 5-pentandiols under optimized aqueous conditions to prepare series of nicotine and anabasine derivatives (**Table 3.2, Scheme 3.6**).[13]




**Scheme 3.6.** Synthesis of N-substituted nor-nicotine derivatives

| Diol | Amine | Product | Yield (%)* |
|---|---|---|---|
|  **8a** | **$CH_3NH_2$ (9a)** |  **10a** | 50 |
|  **8a** |  **9b** |  **10b** | 75 |
|  **8b** |  **9b** |  **10c** | 73 |

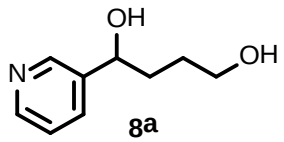
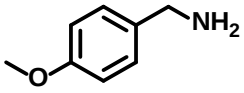
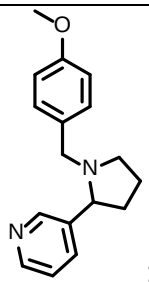
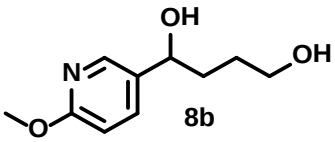
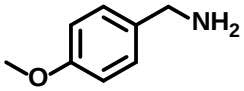
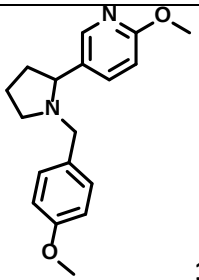
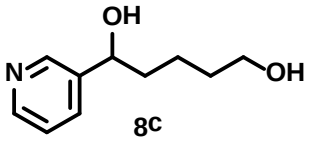
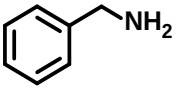
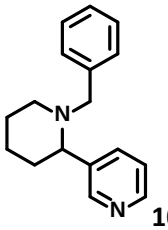
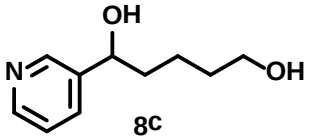
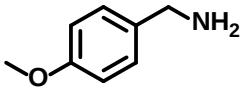
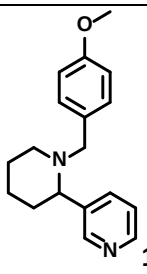
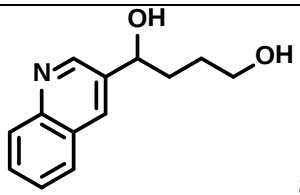
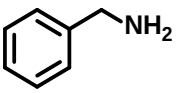
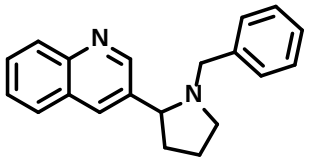
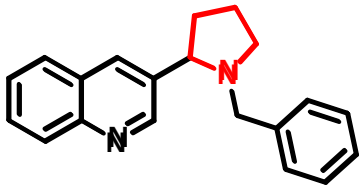
| Diol | Amine | Product | Yield (%)* |
|---|---|---|---|
|  8a |  9c |  10d | 78 |
|  8b |  9c |  10e | 75 |
|  8c |  9b |  10f | 70 |
|  8c |  9c |  10g | 75 |
|  8d |  9b |  10h | 78 |

**Table 3.2.** Synthesis of nor-nicotine derivatives, *Yields of isolated product

To check scope and limitations of the developed method, we performed N-heterocyclization of 1, 4-butandiols and 1, 5-pentandiols under optimized aqueous conditions to prepare series of nicotine and anabasine derivatives. As provided in **Table 3.2,** the reaction of 1, 4-butandiols with methylamine gave a modest yield of nicotine. The lower than expected yield is believed to be due to the high volatililty of methylamine in water at elevated temperatures of the microwave conditions. The reaction of benzyl amine and 4-methoxy amine with 1, 4-diol and 1, 5-diol provided good yields of the corresponding cyclization products.

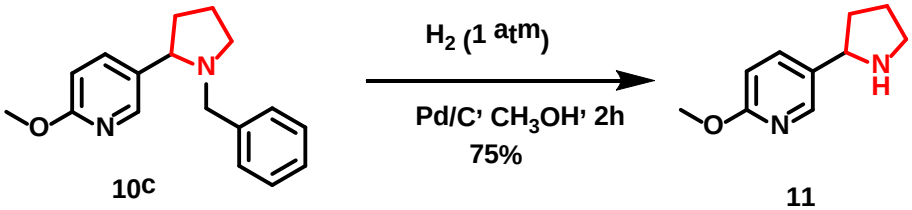
We also synthesized quinoline derivative in good yields using developed N-heterocyclization method from it corresponding diol (**Figure 3.3**).



**10h**

**Figure 3.3.** Quinoline analogue of Benzyl-nornicotine[13]

Further, to demonstrate utility of this approach, we performed transformation of one of the benzyl nor-nicotine derivative to its debenzylated analogue. The hydrogenolysis was performed using palladium on carbon at 55$^{o}$C afforded in 75% yield (**Scheme 3.7**).[13]




**Scheme 3.7.** Synthesis of Nicotine from its N-benzyl derivative

## 3.6 Conclusion

To conclude this chapter, we have devised an efficient three step methodology for the synthesis of nicotine and anabasine derivatives from readily available starting materials. The key step involves the aqueous microwave assisted, iridium-catalyzed N-heterocyclization reaction of 1, 4-diols and 1, 5-diols with various amines.

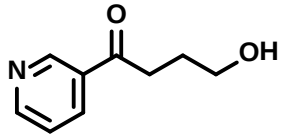
## 3.7. Experimental

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Microwave-assisted N-heterocyclization reactions were carried out using a StartSYNTH multicavity instrument with start rotor from Milestone. The maximum microwave power was 1200 W and the reaction temperature was monitored by an internal infrared sensor. All the reactions were performed in glass reactor tubes with a maximum working pressure of 15 bars and maximum temperature of 230 °C. Thin-layer chromatography (TLC) was performed on silica gel plates (250 mm) purchased from Sorbent Technologies. Compounds were made visual with UV light, iodine or phosphomolybdic acid. Chromatography was accomplished with silica gel 60 Å (230–400 mesh) purchased from Sorbent Technologies. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian 400 MHz NMR spectrometer at ambient temperature in $CDCl_3$. $^{1}$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 $CDCl_3$ (77.0 ppm). Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

**Hydroxy Ketones: General Procedure**

Under an $N_2$ atm, bromopyridine (**5b)** (1 equiv) was added to anhyd $Et_2O$ (20 mL) and cooled to –78 °C. A soln of *n*-BuLi (2.5 M in hexane, 1.2 equiv) was added dropwise, and the mixture was stirred for 15 min. A solution of gamma-butyrolactone (**6a)** or delta-valerolactone (**6b)** (1.1 equiv) in $Et_2O$ (5 mL) was added and the mixture was stirred for 2 h. The mixture was allowed to warm to R.T. and brine (20 mL) was added. The mixture was extracted with $Et_2O$ (3 × 20 mL) and the combined organic layers dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$–MeOH, 92:8) to afford the hydroxy ketones as oils.

**4-Hydroxy-1-(pyridine-3-yl) butan-1-one (7a)**

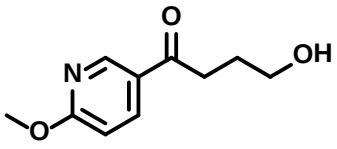



The title product was prepared from 3-bromopyridine **(5b)** (2 g, 12.5 mmol), gamma-butyrolactone **(6a)** (1.2 g, 13.9 mmol) and *n*-BuLi (6 mL, 15 mmol, 2.5 M in hexane) in anhyd $Et_2O$ (30 mL). Purification by flash chromatography afforded the product as yellow oil; Yield: 1.4 g (65%). The spectroscopic data were consistent with those reported previously for this compound.[10]

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 9.03 (s, 1 H), 8.61 (d, *J* = 3.6 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.34–7.30 (m, 1 H), 3.91 (br s, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 3.04 (t, *J* = 7.2 Hz, 2 H), 1.92–1.89 (m, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 199.3, 153.3, 149.5, 135.8, 132.4, 124.0, 61.5, 35.6, 26.8.

**4-Hydroxy-1-(6-methoxypyridin-3-yl) butan-1-one (7b)**

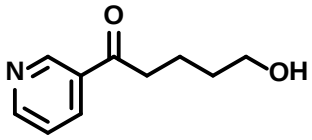



The title product was prepared from 5-bromo-2-methoxypyridine **(5a)** (2g, 10.6 mmol), gamma-butyrolactone **(6a)** (1g, 11.7 mmol) and *n*- BuLi (5.1 mL, 12.7 mmol, 2.5 M in hexane) in anhyd $Et_2O$ (30 mL). Purification by flash chromatography afforded the product as yellow oil; yield: 1.5 g (70%). The spectroscopic data were consistent with those reported previously for this compound.[10]

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.80 (d, *J* = 2.4 Hz, 1 H), 8.13 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 3.99 (s, 3 H), 3.74– 3.73 (m, 2 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 2.02–1.97 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 198.4, 166.4, 149.1, 138.3, 126.7, 111.1, 61.7, 54.1, 35.0, 27.0.

**5-Hydroxy-1-(pyridin-3-yl) pentan-1-one (7c)**




The title product was prepared from 3-bromopyridine **(5b)** (2g, 12.5 mmol), delta-valerolactone **(6b)** (1.4 g, 13.9 mmol) and *n*-BuLi (6 mL, 15 mmol, 2.5 M in hexane) in anhyd $Et_2O$ (30 mL). Purification by flash chromatography afforded the product as yellow oil; yield: 1.7 g (65%). The spectroscopic data were consistent with those reported previously for this compound.[10]

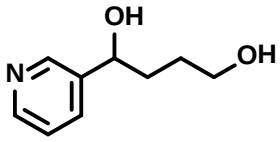
**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 9.14 (d, *J* = 4.0 Hz, 1 H), 8.73 (dd, *J* = 8.0, 4.0 Hz, 1 H), 8.22 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.41–7.39 (m, 1 H), 3.67 (t, *J* = 4.8 Hz, 2 H), 3.05–3.01 (m, 2 H), 1.87–1.82 (m, 2 H), 1.67–1.63 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 199.2, 153.2, 149.4, 135.7, 132.3, 123.9, 61.9, 38.6, 32.1, 20.3.

**Diols 6a, b and 7; General Procedure**

Powdered $NaBH_4$ (1.5 equiv) was added to a well stirred soln of hydroxy ketone **7a, 7b** or **7c** (1 equiv) in anhyd MeOH at 0 °C. After 2 h, $NaHCO_3$ was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford the diols **8a, 8b** or **8c** as viscous oils.

**1-(Pyridin-3-yl) butane-1, 4-diol (8a)**

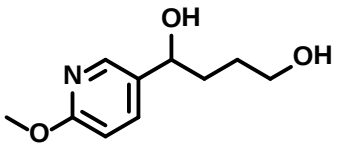



The title product was prepared from **(7a)** (1g, 6.0 mmol) and $NaBH_4$ (0.34 g, 9 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography ($CH_2Cl_2$–MeOH, 92:8) afforded colorless oil; yield: 0.96 g (95%). The spectroscopic data were consistent with those reported previously for this compound.[14]

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 8.47 (d, *J* = 4.0 Hz, 1 H), 8.38 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.24 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.95 (brs, 1 H), 4.73 (t, *J* = 6.4 Hz, 1 H), 3.69 (br s, 1 H), 3.68–3.64 (m, 2 H), 1.87–1.82 (m, 2 H), 1.68–1.62 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 148.3, 147.6, 140.8, 134.2, 123.8, 71.8, 62.6, 36.7, 29.1

**1-(6-Methoxypyridin-3-yl) butane-1, 4-diol (8b)**



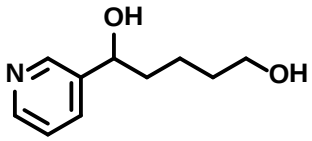
The title product was prepared from **(7b)** (1g, 5.2 mmol) and $NaBH_4$ (0.30 g, 7.77 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography afforded colorless oil; yield: 0.9 g (90%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 7.89 (s, 1 H), 7.46 (d, *J* = 0.8 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 5.06 (br s, 1 H), 4.48 (t, *J* = 6.4 Hz, 1 H), 4.43 (br s, 1 H), 3.76 (s, 3 H), 3.47–3.43 (m, 2 H), 1.70–1.61 (m, 2 H), 1.52–1.43 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 163.7, 144.5, 137.1, 133.3, 110.8, 71.4, 62.2, 53.7, 36.0, 29.0.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.55; N, 6.99.

**1-(pyridine-3-yl) pentane-1, 5-diol (8c)**



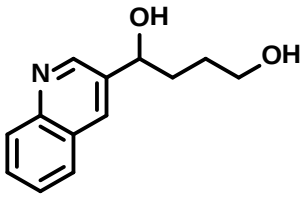

The title product was prepared from **(7c)** (1g, 5.2 mmol) and $NaBH_4$ (0.3g, 7.8 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography afforded colorless oil; yield: 0.9g (95%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.44 (d, *J* = 1.6 Hz, 1 H), 8.38 (dd, *J* = 6.4, 1.2 Hz, 1 H), 7.70–7.69 (m, 1 H), 7.26–7.23 (m, 1 H), 4.68 (t, *J* = 5.6 Hz, 1 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 1.82–1.70 (m, 2 H), 1.71–1.65 (m, 2 H), 1.45–1.36 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 148.3, 147.6, 141.0, 134.27, 123.8, 71.8, 62.6, 38.8, 32.4, 22.1.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.22; H, 8.45; N, 7.67.

**1-(Quinolin-3-yl) butane-1, 4-diol (8d)**




Under an $N_2$ atm, 3-bromoquinoline **(5c)** (2.0 g, 9.6 mmol) was added to anhydrous $Et_2O$ (30 mL) and the resulting soln cooled to –78 °C. A solution of *n*-BuLi (4.6 mL, 11.4 mmol, 2.5 M in hexane) was added dropwise and the mixture stirred for 15 min. A solution of gamma-butyrolactone **(6a)** (0.95 g, 10.5 mmol) in $Et_2O$ (5 mL) was added and the mixture was stirred for 2 h. The mixture was allowed to warm to RT and brine (20 mL) was added. The mixture was extracted with $Et_2O$ (3 × 20 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to furnish ketone **(7d)** as light yellow oil. The crude ketone **8** was dissolved in anhydrous MeOH (20 mL) and cooled to 0 °C. Powdered $NaBH_4$ (0.52 g, 14.22 mmol) was added in one portion and the mixture was stirred for 2 h. Purification by flash chromatography (10% MeOH– $CH_2Cl_2$) afforded as yellow oil; overall yield over two steps: 1.1g (50%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.77 (d, *J* = 2.0 Hz, 1 H), 8.06 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.63–7.57 (m, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 4.87 (t, *J* = 6.0 Hz, 1 H), 3.69– 3.60 (m, 3 H), 1.92–1.87 (m, 2 H), 1.71–1.01 (m, 2 H).

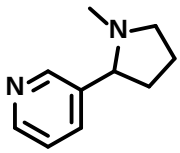
**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 149.5, 147.2, 138.0, 133.1, 129.6, 128.7, 128.1, 127.1, 110.5, 72.0, 62.5, 36.7, 29.2.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.59; H, 7.03; N, 6.11.

**Microwave-Assisted N-Heterocyclization; General Procedure**

The diol (1 equiv) was added to a well stirred soln of $[Cp^*IrCl_2]_2$ (5 mol%) and Na2CO3 (1.1 equiv), in $H_2O$ (5 mL), in a microwave reactor tube under an $N_2$ atm. The amine (1 equiv) was added to the soln and the mixture was irradiated at 110 °C for 2 h. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH–$CH_2Cl_2$) to afford the cyclic amine.

**(±)-Nicotine (10a)**

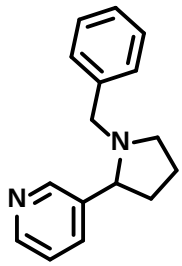


The title product was prepared from **6a** (100 mg, 0.6 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.015 mmol), $Na_2CO_3$ (1.3 mg, 0.015 mmol) and 40% aq. $MeNH_2$ soln **(9a)** (0.050 mL, 0.6 mmol). Purification by flash chromatography afforded brown oil; yield: 48 mg (50%). The spectroscopic data were consistent with a commercial sample and those reported previously for this compound.[15]

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.52 (d, *J* = 2.0 Hz, 1 H), 8.49 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 6.8 Hz, 1 H), 3.25 (t, *J* = 7.6 Hz, 1 H), 3.09 (t, *J* = 8.0 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.24–2.16 (m, 4 H), 2.00–1.74 (m, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 153.5, 149.7, 135.8, 124.0, 75.8, 61.9, 35.7, 29.9, 26.8.

**3-(1-Benzylpyrrolidin-2-yl) pyridine (10b)**

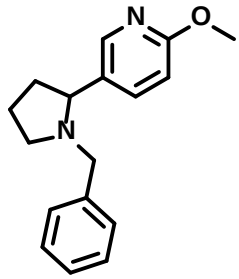


The title product was prepared from **8a** (100 mg, 0.6 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.015 mmol), $Na_2CO_3$ (1.3 mg, 0.015 mmol) and $BnNH_2$ (64 mg, 0.60 mmol) **(9b)** in $H_2O$ (5 mL). Purification by Flash chromatography afforded colorless oil; yield: 105 mg, (75%). The spectroscopic data were consistent with those reported previously for this compound.[16]

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.63 (s, 1 H), 8.48 (d, *J* = 3.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.33–7.18 (m, 6 H), 3.81 (d, *J* = 13.2 Hz, 1 H), 3.44–3.40 (m, 1 H), 3.13–3.09 (m, 2 H), 2.28–2.18 (m, 2 H), 1.89–1.68 (m, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 149.9, 148.8, 135.2, 128.8, 128.7, 128.4, 127.2, 123.9, 67.2, 58.3, 53.7, 35.5, 22.7.

**5-(1-Benzylpyrrolidin-2-yl)-2-methoxypyridine (10c)**



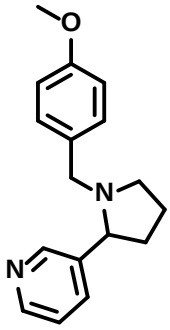
The title product was prepared from **(8b)** (100 mg, 0.5 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.012 mmol), $Na_2CO_3$ (1.1 mg, 0.012 mmol) and $BnNH_2$ **(9b)** (0.053 g, 0.5 mmol). Purification by flash chromatography afforded colorless oil; yield: 100 mg (78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 8.15–8.14 (d, *J* = 2.4 Hz, 1 H), 7.75 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.29–7.20 (m, 5 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 3.94 (s, 3 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 3.33–3.31 (m, 1 H), 3.08–3.06 (m, 2 H), 2.19–2.14 (m, 2 H), 1.89–1.86 (m, 1 H), 1.80–1.69 (m, 2 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 163.9, 146.3, 139.7, 138.2, 132.0, 128.4, 127.0, 111.3, 66.6, 58.1, 53.5, 35.1, 22.5.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.00; H, 7.73; N, 10.28.

**3-[1-(4-Methoxybenzyl) pyrrolidin-2-yl] pyridine (10d)**



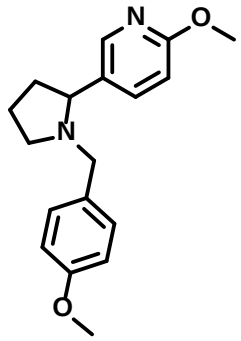

The title product was prepared from (**8a)** (100 mg, 0.6 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.015 mmol), $Na_2CO_3$ (1.3 mg, 0.015 mmol) and 4-methoxybenzylamine **(9c)** (82 mg, 0.6 mmol). Purification by flash chromatography afforded colorless oil; yield: 110 mg (73%).

The spectroscopic data were consistent with those reported previously for this compound.[16]

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 8.63 (d, *J* = 1.6 Hz, 1 H), 8.49 (dd, *J* = 4.4, 1.6 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.25 (dd, *J* = 8.0 Hz, 1 H), 7.25 (dd, *J* = 8.0, 4.4 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 3.78 (s, 3 H), 3.73 (d, *J* = 12.8 Hz, 2 H), 3.38 (t, *J* = 8.0 Hz, 1 H), 3.10–3.02 (m, 2 H), 2.64–2.19 (m, 2 H), 1.77–1.67 (m, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 158.8, 149.8, 148.8, 139.7, 135.2, 129.6, 123.8, 114.0, 113.8, 67.0, 57.6, 55.4, 53.5, 35.5, 22.7.

**2-Methoxy-5–[1-(4-methoxybenzyl) pyrrolidin-2-yl] pyridine (10e)**



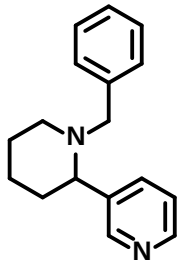
The title product was prepared from **(8b)** (100 mg, 0.5 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.012 mmol), $Na_2CO_3$ (1.1 mg, 0.012 mmol) and 4-methoxybenzylamine **(9c)** (69 mg, 0.5 mmol). Purification by flash chromatography afforded colorless oil; yield: 110 mg (75%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.13 (d, *J* = 1.6 Hz, 1 H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 3.93 (s, 3 H), 3.77 (s, 3 H), 3.73 (d, *J* = 12.8 Hz, 1 H), 3.28 (t, *J* = 8.0 Hz, 1 H), 3.05 (t, *J* = 8.0 Hz, 1 H), 2.98 (d, *J* = 12.8 Hz, 1 H), 2.22–2.10 (m, 2 H), 1.89–1.65 (m, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)**: δ = 163.9, 158.7, 146.2, 138.2, 132.0, 131.7, 130.0, 113.7, 111.3, 66.4, 57.3, 55.4, 53.6, 53.4, 35.1, 22.4.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.40; H, 7.52; N, 9.11.

**3-(1-Benzylpiperidin-2-yl) pyridine (10f)[17]**



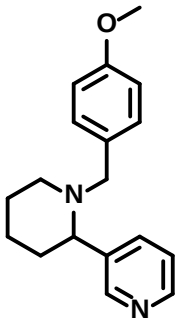
The title product was prepared from **(8c)** (100 mg, 0.55 mmol), $[Cp^*IrCl_2]_2$ (14 mg, 0.013 mmol), $Na_2CO_3$ (1.2 mg, 0.013 mmol) and $BnNH_2$ **(5b)** (55 mg, 0.55 mmol). Purification by flash chromatography afforded colorless oil; yield: 100 mg, (70%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.65 (d, *J* = 1.6 Hz, 1 H), 8.48 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.34–7.18 (m, 6 H), 3.70 (d, *J* = 13.6 Hz, 1 H), 3.16 (dd, *J* = 11.2, 2.8 Hz, 1 H), 2.99 (d, *J* = 11.6 Hz, 1 H), 2.85 (d, *J* = 13.6 Hz, 1 H), 1.99–1.92 (m, 2 H), 1.81–1.75 (m, 2 H), 1.65–1.42 (m, 2 H), 1.42–1.37 (m, 1 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 149.7, 148.9, 141.2, 139.5, 135.1, 128.8, 128.4, 127.1, 124.0, 66.7, 60.3, 53.5, 37.2, 26.0, 25.2.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.77; H, 8.21; N, 11.00.

**3-[1-(4-Methoxybenzyl) piperidin-2-yl) pyridine (12b)**



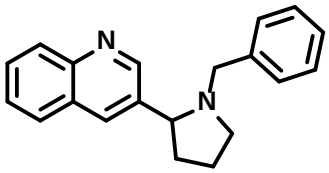

The title product was prepared from **(8c)** (100 mg, 0.55 mmol), $[Cp^*IrCl_2]_2$ (14 mg, 0.013 mmol), $Na_2CO_3$ (1.2 mg, 0.013 mmol) and 4-methoxybenzylamine **(5c)** (75 mg, 0.55 mmol). Purification by flash chromatography afforded colorless oil; yield: 129 mg (75%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ = 8.63 (s, 1 H), 8.48 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.26–7.24 (m, 1 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 3.78 (s, 3 H), 3.61 (d, *J* = 13.6 Hz, 1 H), 3.15 (dd, *J* = 7.2, 2.4 Hz, 1 H), 2.98 (d, *J* = 11.6 Hz, 1 H), 2.79 (d, *J* = 13.6 Hz, 1 H), 1.96 1.89 (m, 1 H), 1.80–1.72 (m, 2 H), 1.63–1.50 (m, 3 H), 1.41–1.30 (m, 1 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 158.7, 149.7, 148.8, 141.3, 135.1, 131.3, 130.0, 123.9, 113.7, 66.6, 59.3, 55.4, 53.3, 37.3, 26.0, 25.2.

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.50; H, 7.91; N, 9.78.

**3-(1-Benzylpyrrolidin-2-yl) quinoline (13)**



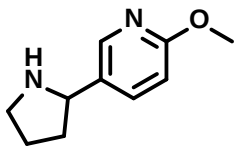
The title product was prepared from **(8d)** (100 mg, 0.5 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.012 mmol), $Na_2CO_3$ (1.1 mg, 0.012 mmol) and $BnNH_2$ **(5b)** (53 mg, 0.5 mmol). Purification by flash chromatography afforded colorless oil; yield: 100 mg (78%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 9.05 (s, 1 H), 8.17 (s, 1 H), 8.12 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.2 Hz, 1 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.34–7.19 (m, 5 H), 3.85 (d, *J* = 12.8 Hz, 1 H), 3.59 (t, *J* = 7.6 Hz, 1 H), 3.15 (d, *J* = 12.8 Hz, 1 H), 2.34– 2.27 (m, 2 H), 2.01–1.81 (m, 4 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 151.6, 148.1, 139.5, 137.0, 134.4, 129.5, 129.2, 129.0, 128.6, 128.4, 127.8, 127.1, 126.8, 67.5, 58.5, 53.7, 35.5, 22.9.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.29; H, 7.08; N, 9.53.

**2-Methoxy-5-(pyrrolidin-2-yl) pyridine (11)**



5-(1-Benzylpyrrolidin-2-yl)-2-methoxypyridine (**10c**) (100 mg, 0.37 mmol),) and 10% Pd/C (10 mg) were stirred in EtOH under $H_2$ (1 atm) for 2 h at 55 °C. After the reaction was complete

(TLC), the mixture was filtered through Celite. The solvent was removed under reduced pressure to afford the nornicotine derivative as a light yellow oil; yield: 51 mg (75%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 8.19 (d, *J* = 4.0 Hz, 1 H), 7.79 (dd, *J* = 4.8, 2.4 Hz, 1 H), 6.72 (d, *J* = 4.8 Hz, 1 H), 5.73 (br s, 1 H, NH), 4.37 (t, *J* = 6.8 Hz, 1 H), 3.88 (s, 3 H), 3.36–3.34 (m, 1 H), 3.21– 3.16 (m, 1 H), 2.16–2.14 (m, 1 H), 2.10–2.01 (m, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 164.8, 147.0, 138.4, 123.8, 111.5, 60.8, 53.8, 45.1, 31.6, 24.0.

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.12; H, 8.15; N, 15.67.

## 3.8. References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**Chapter 4: Solvent free, base free microwave mediated iridium catalyzed N-alkylation of amides with alcohols**

## 4.1. Abstract

Solvent-free, base-free microwave mediated $(Cp^*IrCl_2)_2$ catalyzed conditions for the N-alkylation of amides with alcohols have been developed. A series of primary and secondary alcohols have been shown to produce high yields of N-alkyl arylamides and N-alkyl alkylamides.

## 4.2. Introduction

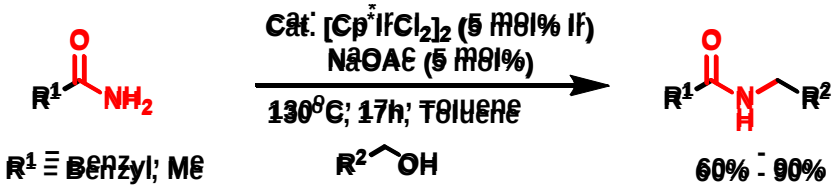
### Importance of N-substituted amides

The N-substituted amide is an important functional group found in natural products as well as non-natural compounds and materials. The N-substituted amide also plays important role in synthetic chemistry as a protecting group for amines and carboxylic acid derivatives.[1] There has been variety of reports that describe methods for the preparation of N-substituted amides.[2, 3]

Recently, transition metals have been used to catalyze the formation of C-N bonds using alcohols as environmentally benign equivalents of alkyl halides.[4-7] These reactions work on the hydrogen borrowing concept which involves generation of only water as a by-product. Previous reports on N-alkylation of amides with alcohols have been shown that high reaction temperatures (>180 °C) are required.[8,9].

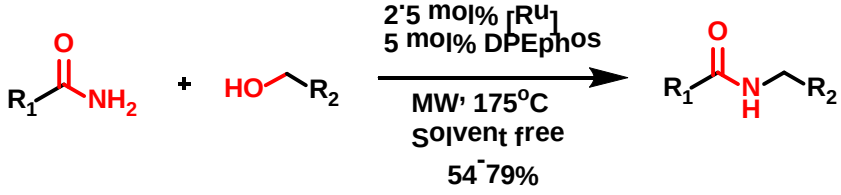
### Literature report of N-alkylation of primary amide

The first example of N-alkylation of amides with alcohols using an iridium complex was reported by Fujita coworkers.[10] This process required refluxing toluene for 17 h in the presence of base (**Scheme 4.1**).




**Scheme 4.1.** N-alkylation of primary amides with primary alcohol using iridium catalysis

Subsequent studies by Xu and co-workers had demonstrated that solvent-free conditions could be employed for N-alkylation of amides with primary alcohols using a variety of transition metal catalyst systems (Rh, Ru, Ir).[11] However, these systems typically required long reaction times and high reaction temperatures. Williams and coworkers reported the use of ruthenium catalysis under solvent-free microwave mediated conditions to affect N-alkylation of amides with alcohols(**Scheme 4.2**).[12]




**Scheme 4.2.** N-alkylation of primary amides using primary alcohol with Ruthenium catalysis

However, despite the success of the metal catalyzed N-alkylation of amides, these reports were limited to use of only primary alcohols as alkylation agents.

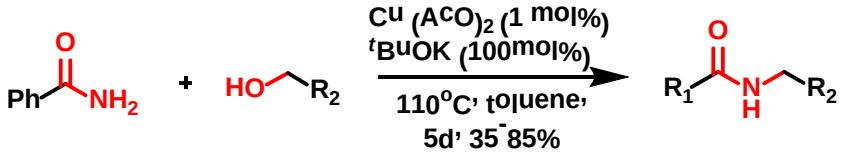



**Figure 4.3.** N-alkylation of primary amides using primary alcohol with copper catalysis

Consequently, there has remained a need for the development of a suitable method with wide substrate tolerance that exploited solvent-free microwave mediated conditions. Our interest in

iridium-based catalytic systems for the formation of C-N bonds prompted us to investigate the potential application of iridium catalyzed amide alkylation under solvent-free and microwave conditions.[13] Herein we wish to report the first solvent-free, base-free microwave mediated iridium catalyzed N-alkylation of amides with both primary and secondary alcohols.

The developed method under microwave condition for synthesis of nicotine and anabasine derivatives prompted us to investigate the use of iridium catalyzed N-alkylation of amides under microwave conditions. [14]The microwave approach would provide N-alkylated product in shorter time period than the conventional reflux times for these reactions.

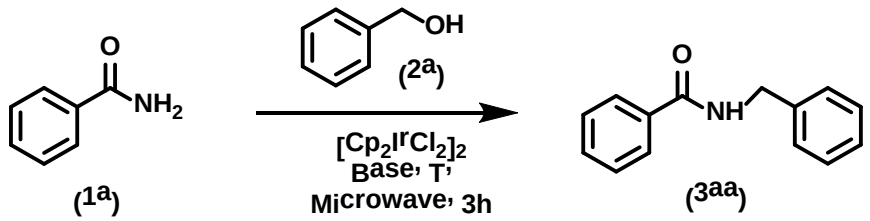
## 4.3. Result and discussion

### Optimization of conditions

Initially, we examined the conditions for N-alkylation of benzyl alcohol with benzamide with microwave irradiation to heat the reaction mixture. We found that the solvent free system using 1 equiv. of alcohol and sodium acetate afforded a modest yield of N-benzylbenzamide (Table 1, Entry1). Further, we found that use of potassium carbonate showed slight improvement of yield, while switching to stronger base diminished the yield to only trace amount of product (Table 1, entry 2).[15]

Serendipitously, it was discovered that if the base was omitted from the reactant mixture, the reaction still gave N-alkylation products, albeit in low yield (Table 1, entry 4). However, this result was encouraging since it revealed that a base was not essential to the catalytic cycle in order to affect the N-alkylation of amides. It was subsequently determined that by increasing the quantity of the alcohol **2a** to three equivalents (Table 1, entry 6) and raising the reaction temperature to 160 °C (Table 1, entry 8) the yield of **3aa** (85%) under base-free conditions could be significantly improved. It was determined that the solvent-free, base-free microwave mediated

conditions furnished amide yields equivalent to yields reported using conventional methods (**Scheme 4.4, Table 4.1**).[10]




**Scheme 4.4.** Development of methodology for N-alkylation of amides using microwave stratergy

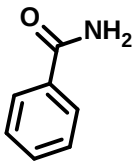
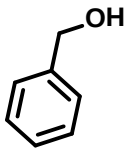
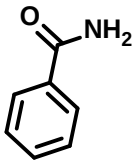
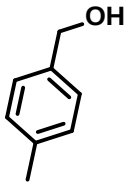
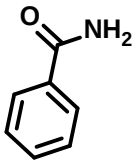
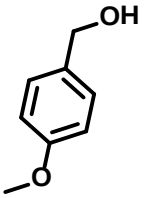
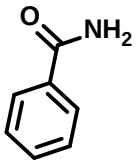
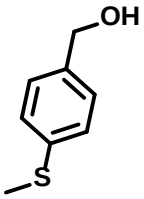
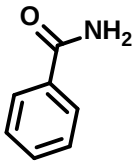
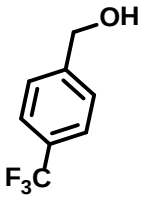
| Entry | 2a (equiv) | $(Cp^*IrCl_2)_2$ (mol %) | Base | T (°C) | Yield [%] |
|---|---|---|---|---|---|
| 1 | 1 | 5 | NaOAc | 160 | 40 |
| 2 | 1 | 5 | $K_2CO_3$ | 160 | 51 |
| 3 | 1 | 5 | KOtBu | 160 | <10 |
| 4 | 1 | 5 | - | 140 | 10 |
| 5 | 2 | 5 | - | 140 | 25 |
| 6 | 3 | 5 | - | 140 | 50 |
| 7 | 3 | 5 | - | 150 | 80 |
| 8 | 3 | 5 | - | 160 | 85 |
| 9 | 3 | 5 | - | 165 | 84 |
| 10 | 3 | 2.5 | - | 160 | 60 |
| 11 | 3 | 1.25 | - | 160 | 35 |

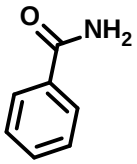
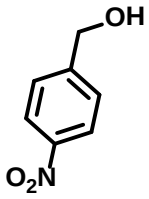
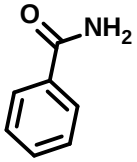
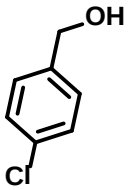
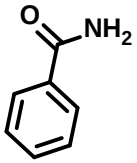
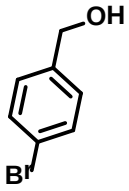
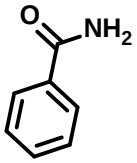
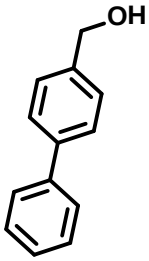
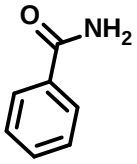
**Table 4.1.** Reaction optimization for N-alkylation of benzamide with benzyl alcohol

Further evaluation of the solvent-free base-free microwave mediated conditions revealed that there was no improvement in yields with an increase of reaction temperature above 160 °C (Table 4.1, entry 9), while a decrease in yield was observed with a reduction in catalyst loading below 5 mol% (Table 4.1, entries 10-11). Having established optimized conditions for the N-alkylation of benzamide (**1a,** Table 4.1, entry 8) it was of interest to explore the scope and limitations of the method.[15]

**Examination of scope of developed method**

As summarized in **Table 4.2**, substituted benzyl alcohols afforded good yields of the corresponding N-substituted benzyl amides (**3aa–3ai)**. Benzyl alcohols substituted with electron-donating groups, electron-withdrawing groups and halogen were equally tolerant of the solvent-free, base-free reaction conditions. Only the 4-nitrobenzyl alcohol (**2f**) failed to give a good yield of the amide **3f,** affording only an intractable mixture of material. In addition to benzyl alcohols, the primary alkanols, 1- pentanol (**2j**) and 1-hexanol (**2k**) furnished the N-alkyl amides **3aj** and **3ak** in 70% yield and 72% yield, respectively. Acetamide (**1b**) and the substituted benzamides (**1c-1f**) also gave good yields of the corresponding N-benzyl benzamide derivatives (**3ba-3fa**) under the solvent-free, base-free conditions.

| Entry[a] | Amide | Alcohol | Product, Yield **3** (%)[b] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | **3aa**, 85 |
| 2 |  **1a** |  **2b** | **3ab**, 85 |
| 3 |  **1a** |  **2c** | **3ac**, 72 |
| 4 |  **1a** |  **2d** | **3ad**, 75 |
| 5 |  **1a** |  **2e** | **3ae**, 77 |

| Entry[a] | Amide | Alcohol | Product, Yield **3** (%)[b] |
|---|---|---|---|
| 6 |  **1a** |  **2f** | **3af,** IM[c] |
| 7 |  **1a** |  **2g** | **3ag**, 65 |
| 8 |  **1a** |  **2h** | **3ah**, 68 |
| 9 |  **1a** |  **2i** | **3ai**, 60 |
| 10 |  **1a** | **$CH_3(CH_2)_4$-OH** **2j** | **3aj**, 72 |

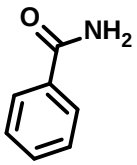
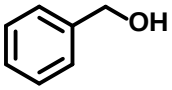
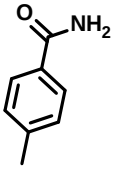
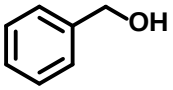
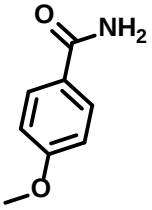
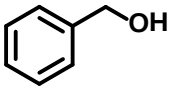
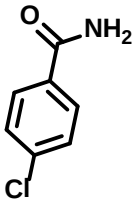
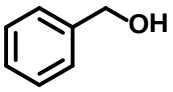
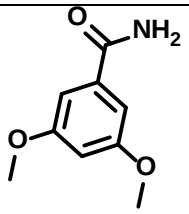
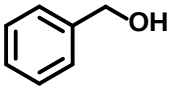
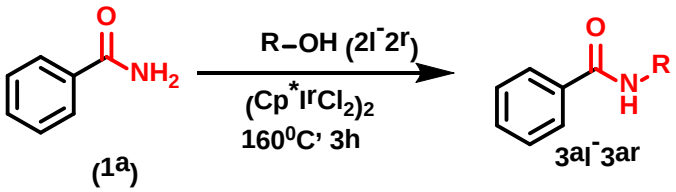
| Entry[a] | Amide | Alcohol | Product, Yield **3** (%)[b] |
|---|---|---|---|
| 11 |  **1a** | **$CH_3(CH_2)_5$-OH** **2k** | **3ak**, 70 |
| 12 | **$CH_3$-$NH_2$** **1b** |  **2a** | **3ba**, 68 |
| 13 |  **1c** |  **2a** | **3ca**, 76 |
| 14 |  **1d** |  **2a** | **3da**, 75 |
| 15 |  **1e** |  **2a** | **3ea** 70 |
| 16 |  **1f** |  **2a** | **3fa**, 78 |

**Table 4.2.** Reaction of variety of amides with various substituted primary alcohols

As summarized in Table 4.2, substituted benzyl alcohols afforded good yields of the corresponding N-substituted benzyl amides **3aa – 3fa**. Benzyl alcohols substituted with electron-donating groups, electron-withdrawing groups and halogen were equally tolerant of the solvent-free, base-free reaction conditions. Only the 4-nitrobenzyl alcohol (**2f**, entry 6) failed to give a good yield of the amide **3af,** affording only an intractable mixture of material. However, the poor yield obtained with **2f** was consistent with the sluggish reactivity previously reported for the nitro derivative in other systems.[16, 17]

In addition to benzyl alcohols, the primary alkanols, 1- pentanol (**2j**, Table 4.2, entry 10) and 1-hexanol (**2k**, Table 4.3, entry 11) furnished the N-alkyl amides **3aj** and **3ak** in 70% yield and 72% yield, respectively. Acetamide (**1b**, entry 12) and the substituted benzamides (**1c-1f**, entries 13-16) also gave good yields of the corresponding N-benzyl benzamide derivatives (**3ba-3fa**) under the solvent-free, base-free conditions.[15]

The success of the solvent-free, base-free microwave mediated conditions with primary alcohols prompted a further investigation of the suitability of the reaction conditions for the N-alkylation of benzamide (**1a**) with secondary alcohols. A variety of acyclic and cyclic secondary alcohols (**4**) were investigated as substrates for the N-alkylation reaction.[15]




**Scheme 4.6.** Reaction of benzamide with secondary alcohols

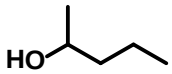
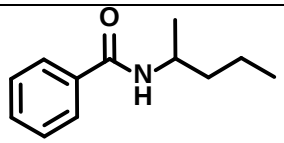
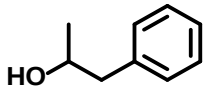
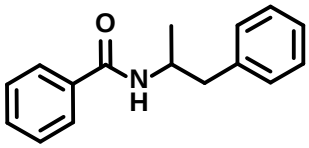
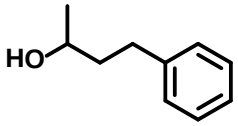
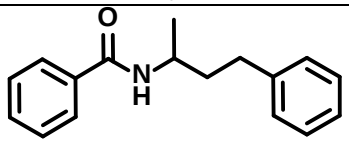
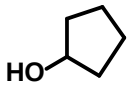
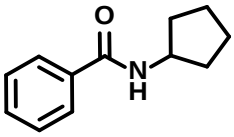
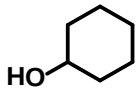
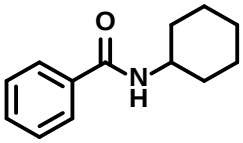
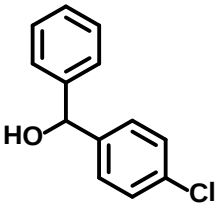
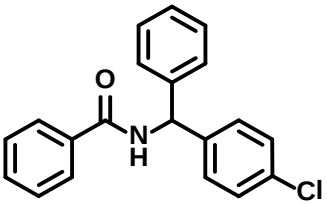
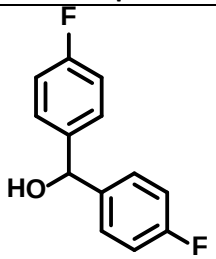
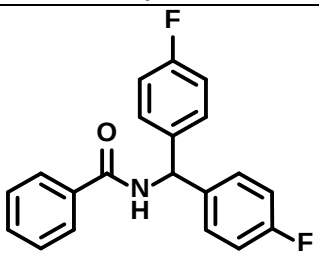
| Entry | Alcohol | Product, Yield (%) |
|---|---|---|
| 1 |  **2l** |  **3al, 68%** |
| 2 |  **2m** |  **3am, 72%** |
| 3 |  **2n** |  **3an, 65%** |
| 4 |  **2o** |  **3ao, 78%** |
| 5 |  **2p** |  **3ap, 76%** |
| 6 |  **2q** |  **3aq, 65%** |
| 7 |  **2r** |  **3ar, 65%** |

**Table 4.3.** Reaction of benzamide with secondary alcohols

It was satisfying to observe that the solvent free, base-free microwave mediated reaction conditions developed for the primary alcohols were applicable to secondary alcohols as well. The acyclic alcohols (entries 1-3) and cyclic alcohols (entries 4-5) coupled with benzamide to furnish the N-alkyated products in 65-78% yield. Even the sterically hindered benzhydrol derivatives (entry 6 and 7) afforded the N-benzhydryl amides **3aq** and **3ar** in good yield.[15]

## 4.4. Conclusion

In summary, we have devised a solvent-free, base free, micro-wave mediated process for the iridium-catalyzed alkylation of amides with alcohols. This environmentally benign method furnished a variety of structurally diverse N-alkyl and N-arylalkyl amides from both primary and secondary alcohols. The reaction conditions were tolerant of a variety of functional groups, employed short reaction times and provided good to high yields of the corresponding highly functionalized N-alkylated amides.[15]

## 4.5. Experimental

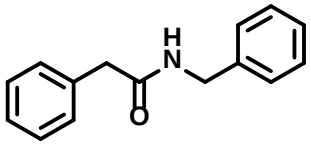
All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Microwave-assisted N-alkylation of amides were carried out using a StartSYNTH multicavity instrument with start rotor from Milestone. The maximum microwave power was 1200 W and the reaction temperature was monitored by an internal infrared sensor. Thin layer chromatography (TLC): silica gel (250 m). Visualization with UV light, iodine or phosphomolybdic acid, Chromatography: silica gel 60 Å (230-400 mesh). $^{1}$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 $CDCl_3$. $^1H$ 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 chloroform-*d* (77.0 ppm). Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

**N-Alkylation of Amides with Alcohols**

**General Procedure** The amide (100 mg, 1 equiv), alcohol (3 equiv.) and $(Cp^*IrCl_2)_2$ (2.5 mol %) were added to a microwave reactor tube. The reaction mixture was microwaved at 160ºC for 3h. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added. The mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified using flash silica gel chromatography with DCM: $CH_3OH$ (95:5) to furnish the N-alkyl amide.

**N-Benzylbenzamide (3aa) [18]**

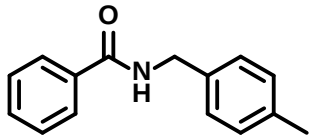


The title product was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and benzyl alcohol (270 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 149 mg (85%); mp 105-106ºC [Lit. 103-104ºC].

**$^1H$ NMR (400 MHz, $CDCl_3$):** δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.52-7.30 (m, 8H), 6.39 (brs, 1H), 4.65 (d, *J* = 5.6 Hz, 2H).

**$^{13}C$ NMR (100 MHz, $CDCl_3$):** δ 44.3, 127.2, 127.8, 128.1, 128.8, 129.0, 131.7, 134.6, 138.4, 167.6.

**N-(4-Methylbenzyl) benzamide (3ab)** [19]

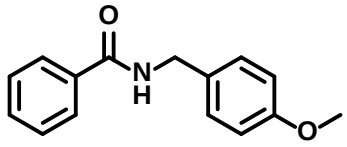


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2b** (305 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 159 mg (85%); mp 138-140 °C [Lit. 137 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.41 (brs, 1H), 4.59 (d, *J* = 5.6 Hz, 2H), 2.34 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 44.1, 127.3, 128.2, 128.8, 129.7, 131.7, 134.6, 135.3, 137.6, 167.5.

**N-(4-Methoxybenzyl) benzamide (3ac)** [18]

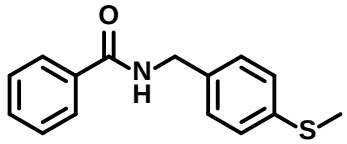


The final compound was prepared according to the general method using **1d** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2c** (350 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 144 mg (72%); mp 94-96 °C [Lit. 97-98 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4, 2H), 6.40 (brs, 1H), 4.57 (d, *J* = 5.2 Hz, 2H), 3.79 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 43.8, 55.5, 114.3, 127.1, 128.8, 129.5, 130.4, 131.7, 134.6, 159.3, 167.4.

**N-4-Methylthiobenzyl benzamide (3ad)**



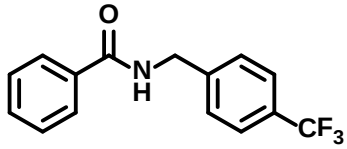
The final compound was Prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2d** (390 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 160 mg (75%); mp 109-110 °C.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.21-7.28 (m, *J* = 7.2 Hz, 2H), 6.47 (brs, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 2.46 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 16.1, 43.8, 127.1, 127.2, 128.7, 128.8, 131.8, 134.5, 135.2, 128.0, 167.6.

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44. Found: 69.88; H, 5.71; 5.20.

**N-4-Trifluoromethylbenzyl benzamide (3ae)**.[20]

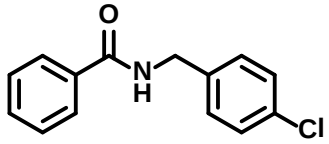


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2e** (440 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid 179 mg (77%); mp 134-135 °C [Lit.131-134 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.48-7.52 (m, 1H), 7.41 (d, *J* = 6.4 Hz, 2H), 7.37-7.38 (m, 2H), 6.91 (brs, 1H), 4.64 (d, *J* = 5.6 Hz, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 43.6, 125.8, 125.9, 127.2, 128.1, 128.8, 132.0, 134.2, 142.6, 167.9.

**N-4-Chlorobenzyl benzamide (3ag)** [13]

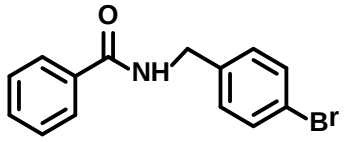



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2g** (350 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 132 mg, (65%); mp 140-142 °C [Lit. 140-143 °C];

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.22-7.28 (m, 4H), 6.78 (brs, 1H), 4.55 (d, *J* = 6.0 Hz, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 43.5, 127.2, 128.8, 129.0, 129.3, 131.9, 133.5, 134.3, 137.0, 167.7.

**N-(4-Bromobenzyl) benzamide (3ah)** [21]

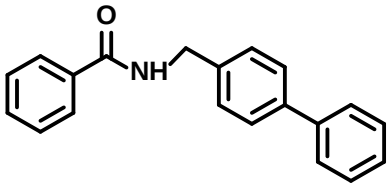



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2h** (470 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 163 mg (68%); mp 140-142 °C [Lit. 144-145 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 6.8 Hz, 1H), 7.36-7.42 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.88 (brs, 1H), 4.51 (d, *J* = 6.0 Hz, 2H).

**$^{13}$C NMR (400 MHz, $CDCl_3$):** δ 43.5, 115.5, 121.5, 127.2, 128.8, 129.6, 131.9, 134.3, 137.6, 167.8

***N*-(4-Phenylbenzyl) benzamide (3ai)** [22]

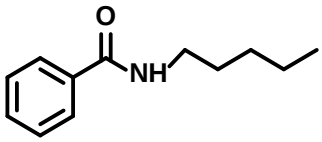



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2i** (220 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 143 mg (60%); mp 166-167 °C [Lit. 166.9 – 168.3 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 6.8 Hz, 2H), 7.59 – 7.52 (m, 4H), 7.49 – 7.35 (m, 6H), 7.33 (d, *J* = 7.2 Hz, 2H), 6.57 (s, 1H), 4.68 (d, *J* = 5.6 Hz, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 44.1, 127.2, 127.3, 127.6, 127.8, 128.6, 128.8, 129.1, 131.8, 134.6, 137.5, 140.9, 141.0, 167.7.

**N-Pentylbenzamide (3aj)** [21]

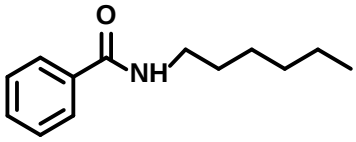



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2j** (220 mg, 2.5 mmol). Purification by flash chromatography afforded a colorless liquid; yield: 114 mg (72%).

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 6.64 (brs, 1H), 3.35-3.40 (m, 2H), 1.53-1.60 (m, 2H), 1.26-1.31 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 14.2, 22.6, 29.3, 29.5, 40.3, 127.1, 128.6, 131.4, 135.0, 167.8.

**N-Hexylbenzamide (3ak)** [23]

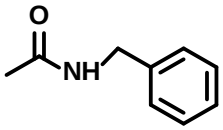


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2k** (260 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 119 mg (70%); mp 44-45 °C.

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 6.0 Hz, 1H), 7.33-7.41 (m, 2H), 6.64 (brs, 1H), 3.35-3.40 (m, 2H), 1.52-1.59 (m, 2H), 1.26-1.33 (m, 6H), 0.83 (t, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 14.2, 22.7, 26.9, 29.8, 31.7, 40.3, 127.1, 128.6, 131.4, 135.0, 167.8.

**N-Benzylacetamide (3ba)** [24]

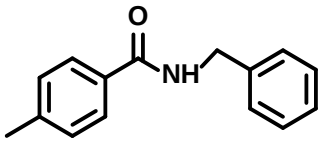


The final compound was prepared according to the general method using **1b** (100 mg, 1.7 mmol), $(Cp^*IrCl_2)_2$ (32 mg, 0.041 mmol) and **2a** (550 mg, 5.1 mmol). Purification by flash chroma-tography afforded a white solid; yield: 172 mg (68%); mp 58-60 °C [Lit. 61°C].

**$^1$ H NMR (400 MHz, $CDCl_3$):** δ 7.23-7.32 (m, 5H), 6.27 (brs, 1H), 4.35 (d, *J* = 5.6 Hz, 2H), 1.95 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 23.3, 43.8, 127.6, 128.0, 128.8, 138.5, 170.4.

**N-Benzyl 4-methylbenzamide (3ca)** [25]

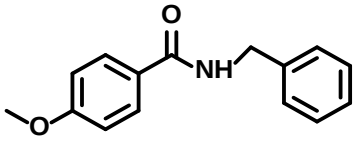


The final compound was prepared according to the general method using **1c** (100 mg, 0.74 mmol), $(Cp^*IrCl_2)_2$ (14 mg, 0.019 mmol) and **2a** (240 mg, 2.2 mmol). Purification by flash chromatography afforded a white solid; yield: 133 mg (80%); mp 133-135 °C [Lit. 133-135 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.25-7.35 (m, 5H), 7.18 (d, *J* = 7.6 Hz, 2H), 6.71 (brs, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 2.37 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.6, 44.21, 127.2, 127.7, 128.0, 128.9, 129.4, 131.7, 138.6, 142.1, 167.6.

**N-Benzyl 4-methoxybenzamide (3da)** [26]

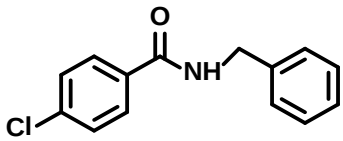


The final compound was prepared according to the general method using **1d** (100 mg, 0.66 mmol), $(Cp^*IrCl_2)_2$ (13 mg, 0.017 mmol) and **2a** (216 mg, 2.0 mmol). Purification by flash chromatography afforded a white solid; yield: 119 mg (75%); mp 126-128 °C [Lit. 126-128 °C].

**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.25-7.33 (m, 5H), 7.88 (d, *J* = 8.8 Hz, 2H), 6.52 (brs, 1H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.82 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 44.2, 55.6, 113.9, 126.8, 127.7, 128.1, 128.9, 129.0, 138.6, 162.4, 167.1.

**N-Benzyl-4-chlorobenzamide (3ea)** [25]

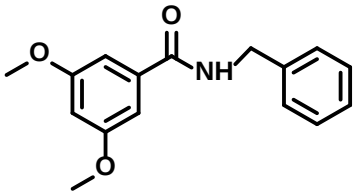


The final compound was prepared according to the general method using **1e** (100 mg, 0.65 mmol), (Cp*IrCl2)2 (12 mg, 0.016 mmol) and **2a** (216 mg, 2.0 mmol). Purification by flash chromatography afforded a white solid; yield: 121 mg (76%); mp 162-164 °C [Lit. 162 °C].

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.72 (dd, $J$ = 6.4 Hz, $J$ = 2.0 Hz, 2H), 7.27-7.40 (m, 7H), 6.47 (brs, 1H), 4.62 (d, $J$ = 5.6 Hz, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ 44.5, 127.9, 128.6, 129.0, 132.9, 138.0, 138.1, 166.5.

**N-Benzyl-3, 5-dimethoxybenzamide (3fa)** [26]

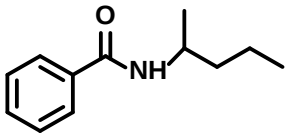



The final compound was prepared according to the general method using **1f** (100 mg, 0.55 mmol), $(Cp^*IrCl_2)_2$ (11 mg, 0.014 mmol) and **2a** (180 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 117 mg (78%); mp 125-126 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.25-7.33 (m, 5H), 6.91 (d, $J$ = 2.0 Hz, 2H) 6.59 (brs, 1H), 6.55 (t, $J$ = 2.0 Hz, 1H), 4.59 (d, $J$ = 6.0 Hz, 2H), 3.78 (s, 6H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 44.3, 55.7, 103.8, 105.1, 127.8, 128.1, 132.8, 136.8, 138.3, 161.1, 167.4.

**N-(Pentan-2-yl) benzamide (3al)** [27]

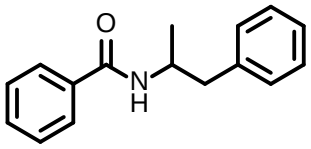



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2l** (220 mg, 2.5 mmol). Purification by flash chromatography afforded a colorless liquid; yield: 108 mg (68%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 2H), 6.58 (brs, 1H), 3.42 (q, *J* = 6.0 Hz, 2H), 1.59-1.64 (m, 1H), 1.45 (q, *J* = 6.4 Hz, 2H), 0.88-0.90 (m, 6H).

**$^{1}$H NMR (100 MHz, $CDCl_3$):** δ 22.7, 26.1, 38.6, 38.6, 127.1, 128.6, 131.4, 135.0, 167.8

**N-(1-Phenylpropan-2-yl) benzamide (3am) [29]**

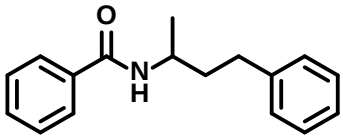


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2m** (340 mg, 2.5 mmol) Purification by flash chromatography afforded a white solid; yield: 143 mg (72%); mp 127-129 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 3H), 5.91 (brs, 1H), 4.46-4.49 (m, 1H), 2.83-2.97 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 20.2, 42.5, 46.6, 126.7, 126.9, 128.6, 128.7, 129.7, 131.5, 135.0, 138.0, 166.9.

**N-(1-Phenylbutan-3-yl) benzamide (3an) [31]**

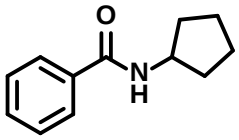


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2n** (375 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 136 mg (65%); mp 117-119 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.46-7.49 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 6.8 Hz, 3H), 5.93 (brs, 1H), 4.26-4.30 (m, 1H), 2.70-2.74 (m, 2H), 1.86-1.92 (m, 2H), 1.28 (d, *J* = 6.8 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 21.3, 32.7, 38.8, 45.9, 126.2, 127.0, 128.6, 128.7, 131.5, 135.1, 141.9, 167.0.

**N-(Cyclopentyl) benzamide (3ao) [28]**

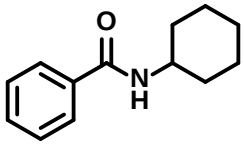


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2o** (215 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 122 mg (78%); mp 158-160°C [Lit. 160-162 °C].

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.53 (brs, 1H), 4.37-4.41 (m, 1H), 2.06-2.10 (m, 2H), 1.63-1.77 (m, 4H), 1.47-1.64 (m, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 24.0, 33.4, 51.9, 127.0, 128.7, 131.4, 135.1, 167.4.

**N-Cyclohexylbenzamide (5ap) [33]**

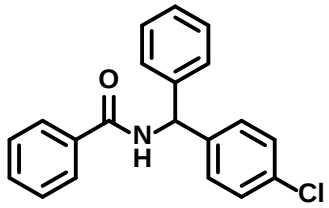


The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2p** (250 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 128 mg (76%); mp 152-154 °C [Lit. 152-154 °C].

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ = 7.74 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 2H), 5.98 (brs, 1H), 3.95-3.99 (m, 1H), 2.05-2.04 (m, 2H), 1.63-1.77 (m, 4H), 1.18-1.47 (m, 5H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ = 25.1, 25.7, 33.4, 48.9, 127.0, 128.7, 131.4, 135.3, 166.8.

**N-[(4-Chlorophenyl) (phenyl) methyl]-benzamide (3aq) [34]**

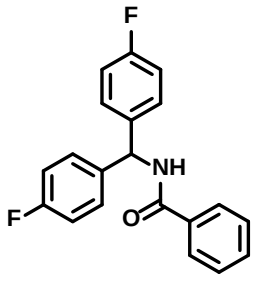



The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2q** (545 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 173 mg (65%)

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.21-7.35 (m, 8H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.38 (d, *J* = 7.6 Hz, 1H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 57.1, 115.5, 127.3, 127.8, 128.0, 128.8, 129.0, 129.0, 129.1, 132.0, 134.2, 140.2, 141.1, 166.8.

**N-Bis (4-fluorophenyl) methylbenzamide (3ar) [25]**




The final compound was prepared according to the general method using **1a** (100 mg, 0.83 mmol), $(Cp^*IrCl_2)_2$ (16 mg, 0.021 mmol) and **2r** (550 mg, 2.5 mmol). Purification by flash chromatography afforded a white solid; yield: 174 mg (65%); mp 177-179 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.22-7.05 (m, 4H), 7.02 (t, *J* = 8.4 Hz, 4H), 6.65 (brs, 1H), 6.39 (d, *J* = 7.6 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 56.4, 115.8, 116.0, 127.2, 128.9, 129.3, 129.3, 132.1, 134.1, 137.2, 137.2, 163.6

## 4.6. References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## VITA

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