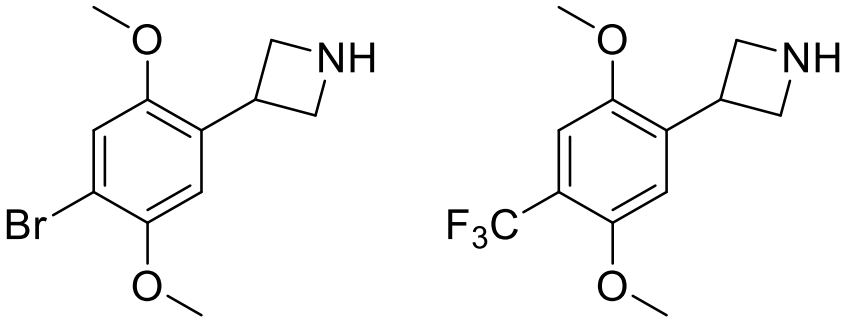
Synthesis of Conformationally Restrained Serotonin 2A Agonists

Probing for Functional Selectivity



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Preface

This thesis represents work done in the Kristensen research group at the Department of Drug Design and Pharmacology in University of Copenhagen from September 2017 to June 2018. The work was done under the supervison of Professor Jesper Langgaard Kristensen and co-supervisor, PhD student Emil Märcher-Rørsted and was part of an exchange student program from University of Gothenburg

Abstract

Over the last two decades an increasing amount of studies have investigated the use of hallucinogens for treating mental disorders with promising results. Some of the psychopharmacological effects of these hallucinogens can be attributed to agonism at the serotonin receptor 2A (5-HT_{2A}), a receptor that plays a key role in a variety of mental conditions such as depression.

Depending on molecular features of the 5-HT_{2A} agonist different intracellular signaling pathways may take place. It is hypothesized that specific signaling pathways can be attributed to certain pharmacological responses such as anti-depressant effects. Gaining more insight into these pathways would not only allow us to learn more about the mechanisms of action behind mental disorders but could possibly also pave the way for the development of novel highly selective drugs with few unwanted side effects. One way of studying different signaling pathways of the 5-HT_{2A} receptor could be to develop functionally selective agonists that only activate certain intracellular signaling pathways.

A newly emerged class of conformationally restricted phenethylamines has shown promising selectivity between 5-HT_2 receptor subtypes. It is hoped that these compounds can be used to probe for functional selectivity by the introduction of small structural changes.

The aim of this project was to develop a viable efficient way of synthesizing these compounds and obtain enough material to use in functional whole-cell assays to determine functional selectivity. A series of trifluoromethylated N-benzyl substituted phenethylamines were also to be synthesized and assayed in order to evalute the influence of the trifluoromethyl substituent on the 5-HT_{2A} scaffold.

It was found that a boronic acid sulfonyl hydrazone coupling reaction could successfully be employed to construct these conformationally restricted phenethylamines, albeit in low yields. Moreover, a novel one-pot method for reducing nitrostyrenes to phenethylamines utilizing cheap and safe reagents was developed.

Abbreviations

5-HT	Serotonin
AcOH	Acetic acid
Akt	Protein kinase B
$B(OiPr)_3$	Triisopropyl borate
Cimbi-36	2-(4-Bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl) methyl]ethanamine
CNS	Central nervous system
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IP3	Inositol triphosphate
IPA	2-Propanol
LSD	Lysergic acid diethylamide
MsCl	Methanesulfonyl chloride
n-BuLi	n-Butyllithium
NMR	Nuclear magnetic resonance
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PLA2	Phospholipase A2
PLC	Phospholipase C
Src	Proto-oncogene tyrosine-protein kinase Src
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran

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1 Background

1.1 The Serotonergic System

The neurotransmitter serotonin (5-HT) and its interaction with 5-HT receptors regulates a broad range of neuropsychological processes and neural activity in the brain such as mood, sleep, memory, sexual behavior, pain and appetite.[1,2] The 5-HT receptors can be divided into seven different subfamilies depending on their structural and operational properties. One of them is the 5-HT_2 receptor family which can be further divided into three different subtypes, the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}.[3] Research suggests that the 5-HT_{2A} receptor plays a key role in a variety of conditions such as schizophrenia,[4] depression[5] and obsessive compulsive disorder.[6]

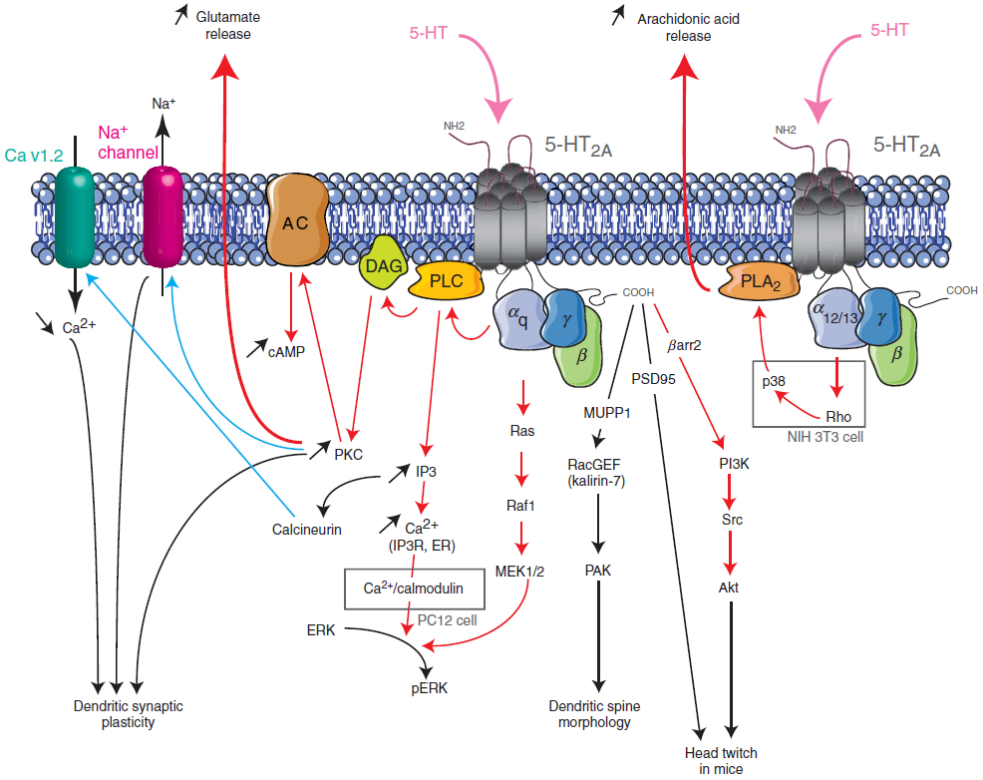


Figure 1. *5-HT_{2A} receptor signaling pathways. Red arrows indicates stimulation and blue arrows, inhibition.*[a]

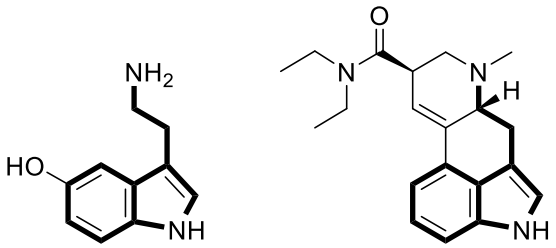
[a] Figure adapted with the authors permission.[7]

Most of the 5-HT receptors including the 5-HT_{2A} receptor are transmembrane G-protein coupled receptors meaning that they consist of seven transmembrane helices holding a small-molecule binding site for 5-HT in its extracellular part and an intracellular part with binding sites for different intracellular protein complexes (Figure 1). Upon activation of the receptor by 5-HT or other 5-HT_{2A} receptor agonists different signaling cascades can be initiated within the cell depending on the nature of the ligand. One of them occurs via the G-protein $G\alpha_q$, which stimulates phospholipase C (PLC) causing an increase of inositol triphosphate (IP3). IP3 thereafter induces a release of Ca^{2+} from the endoplasmic reticulum. The Ca^{2+} then activates protein kinase C (PKC) leading to an extracellular release of the neurotransmitter glutamate.[7,8] The glutamate may then cause further cell signaling between synapses in the brain.[9]

Other possible signaling pathways include the $G\alpha_{12/13}$ activation of phospholipase A2 (PLA2) which stimulates the release of arachidonic acid.[10] Or the more recently discovered β-arrestin-2/PI3K/Src/Akt cascade pathway.[11,12] This agonist-dependent selectivity in initiating different signaling pathways is commonly referred to as biased agonism or functional selectivity. Functional selective ligands could potentially be used to provide insights regarding what signaling pathways that corresponds to downstream effects. Are there for instance certain pathways that affects depression in particular? Can we in that case develop drugs targeting these pathways selectively and thus develop more efficient drugs with reduced side effects?

What is known though is that some of the psychopharmacological effects of hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin can be attributed to agonism of the 5-HT_{2A} receptors.[13] Hallucinogenic agonists and partial agonists of 5-HT_{2A} receptors in the brain are generally referred to as psychedelics. During the last decades there has been a surge in investigating psychedelics in hopes of finding new treatments for mental disorders.[14]

1.2 History of Psychedelic Research



5-HT LSD

Figure 2. *Molecular structures of 5-HT and LSD. With their mutual tryptamine core structure in bold.*

The modern scientific field of psychedelics started in 1943 when the Swiss chemist Albert Hofmann accidentally exposed himself to a chemical compound he had synthesized a few years prior when attempting to find medically useful ergot derivatives. Upon the exposure he experienced "a remarkable but not unpleasant state of intoxication", the compound was LSD (Figure 2). He later reproduced these effects intentionally and concluded that LSD was a highly potent psychoactive substance.[15]

It was later realized that the psychoactive effects of LSD had the ability to promote some symptoms resembling those in schizophrenia.[16] Moreover, in 1953 serotonins presence in the brain was discovered.[17] This knowledge coupled with the realization that the tryptamine core structure of serotonin could be recognized within the LSD molecular structure (Figure 2) contributed to the first hypotheses suggesting that brain chemistry may play a significant role in mental illness. Thus the field of psychopharmacology was born.[13]

During the 1950s to mid-1970s psychedelics received a lot of publicity and a large amount of clinical studies were performed.[13] These studies mainly investigated their psychotomimetic effects but also their use in therapy such as treating addictions like alcoholism.[16] However, most of these early studies suffered from low quality by modern day standards often lacking adequate controls. In the late 1960s hallucinogenic drugs became increasingly controversial leading to restrictions on their use causing some of its research being brought to a stand-still after the mid-1970s.[18]

1.3 Clinical Relevance

In later years there has been a resurgence of interest in these compounds from the scientific community. In one prominent pilot study from 2016 by Carhart-Harris et al.[19] a group of 12 subjects suffering from treatment-resistant depression were administered the psychedelic compound psilocybin. These subjects had suffered from depression on an average of 18 years and did not respond to any conventional anti-depression treatments such as psychiatric drugs, therapy or counselling. One week after the administration, 67% of the participants claimed they were symptom free of depression and in a follow-up after six months 30% of the participants stated they were still free from depression. 75% of the participants stated after six months that the treatment had given them reductions in their depressive symptoms of varying degree. It should be noted however, that this study lacked a placebo control group.

In another study from 2016 Griffiths et al.[20] investigated whether psilocybin could be used to reduce near end-of-life anxiety in cancer patients. The study was performed on a group of 51 cancer patients, some of which suffered from depression, and some from anxiety. They were divided into two groups, one receiving a high dose of psilocybin and a control group receiving a very low dose of psilocybin as an active placebo. Five weeks after the administration 92% of the patients suffering from depression stated that there were significant improvements in their symptoms as opposed to 32% of those who had received the placebo. For the patients suffering from anxiety these numbers were 76% and 24% respectively.

These results are interesting not only because of the large amount of participants stating improvements in their symptoms but also because it suggests that the antidepressant effects of psilocybin is long lasting after only a one-time administration. Where some of the subjects reported effects lasting for at least 6 months. This is unheard of for traditional antidepressant drugs, which often require continuous daily administration to reduce symptoms. The results of these and other recent studies[21-24] suggest that this field is undoubtedly worth investigating further. One way of obtaining more information on the mechanisms of action behind these drugs is by studying the 5-HT_{2A} receptor and its agonists. Not only could this provide more insight regarding mental illness but it might also aid in the development of new more effective drugs targeting CNS (central nervous system) disorders.

1.4 5-HT$_{2A}$ Agonists

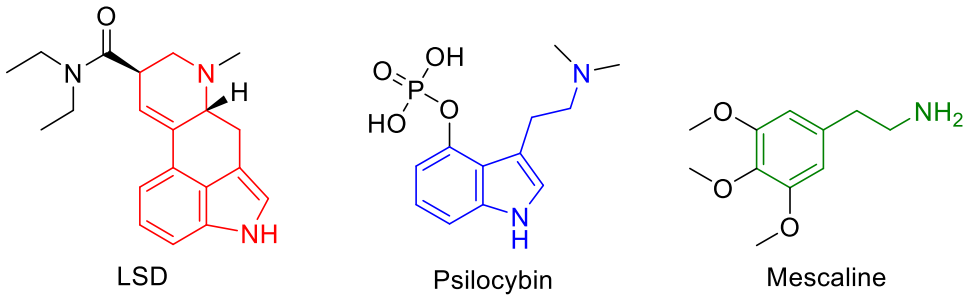


Figure 3. *Molecular structures of LSD, psilocybin and mescaline. The ergoline core structure is marked in red, the tryptamine in blue and the phenethylamine in green.*

Traditionally 5-HT$_{2A}$ agonists have been divided into three main classes, ergolines, tryptamines and phenethylamines (Figure 3). Some of the ergolines such as LSD are highly potent 5-HT$_{2A}$ agonists but suffers from poor receptor selectivity having high affinities for other targets such as dopamine receptors and various 5-HT subtypes.[25] The second class is the tryptamines where psilocybin is a notable example (Figure 3). In general the tryptamines also suffers from poor receptor selectivity, where in addition to being agonists of the different 5-HT$_2$ subtypes, this class often shows high affinity for 5-HT$_{1A}$ as well.[26] The phenethylamine class on the other hand has in general shown higher selectivity for the 5-HT$_2$ subtype and has therefore often been used as starting point in the pursuit of selective 5-HT$_{2A}$ agonists.[27-29]

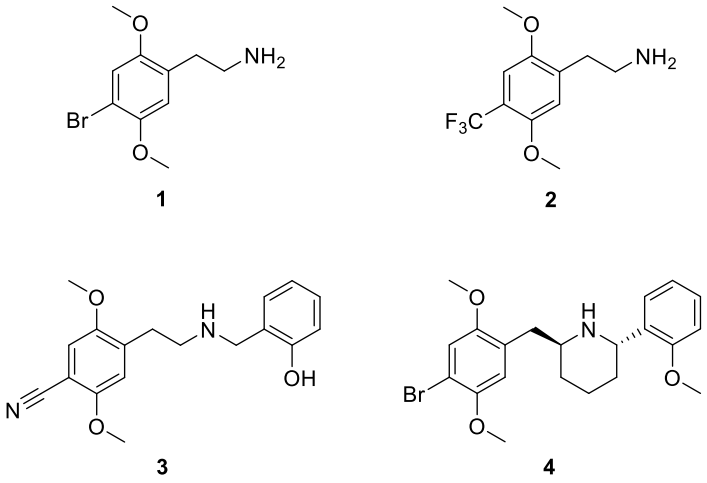


Figure 4. *Phenethylamines **1** (2C-B), **2** (2C-TFM) and the highly selective N-benzyl substituted phenethylamines **3** and **4**.*

The naturally occurring hallucinogenic phenethylamine mescaline (Figure 3) is a 5-HT_{2A} agonist of low potency, but has served as a lead molecule for the development of several highly potent hallucinogenic phenethylamines.[26] The perhaps most prominent work in this field was done by Alexander Shulgin during the 1970s and 1980s.[30] Shulgin synthesized and established oral dosages of approximately 180 different phenethylamines most of which can be described as mescaline derivatives. In doing so Shulgin established a relationship between molecular structure and hallucinogenic activity.

One of the more important findings was the 2,4,5-substitution pattern on the benzene ring where methoxy groups at the 2- and 5-position proved highly beneficial for hallucinogenic activity (Figure 4). Potent substituents at the 4-position in terms of hallucinogenic activity proved to be short alkyl and alkylthio groups or the halogens Cl, Br and I.[30-33] Where **1** (Figure 4) is one of the more well-known creations of Shulgin. Later studies showed that the introduction of a trifluoromethyl group at the 4-position such as compound **2** (Figure 3) gave compounds with the highest *in vivo* potency observed so far.[34]

Although several highly potent phenethylamines have been made, selectivity between the 5-HT_{2A} and the 5-HT_{2C} subtype receptors have traditionally been difficult to achieve due to similar homology sequence.[35,36] However, in 2003 Ralf Heim discovered that N-benzyl substitution of phenethylamine 5-HT_{2A} receptor agonists lead to a dramatic increase in binding affinity to the 5-HT_{2A} receptor.[37] This discovery paved the way for the development of the first truly selective ligands. Where the most noteworthy ones are compound **3** which exhibited a 100-fold selectivity for 5-HT_{2A} over 5-HT_{2C} and the rigid analogue **4** which displayed a 124-fold greater binding affinity towards 5-HT_{2A} over 5-HT_{2C} (Figure 4).[28,29]

Unfortunately many of the N-benzyl substituted phenethylamines turned out to be metabolically unstable[38] and have been reported to have adverse toxic effects where their recreational use has resulted in several deaths and hospitalizations.[39] This class of compounds is still being researched however and continue to serve as important tool compounds.[29]

1.5 A New Chemotype Emerges

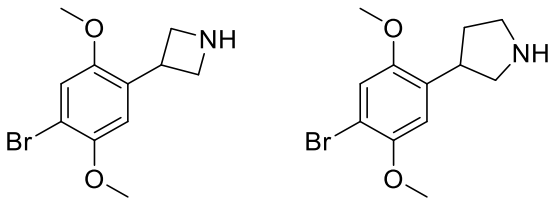


Figure 5. *Two compounds part of a series of rigid phenethylamines synthesized by the Kristensen group utilizing a new chemotype in 5-HT$_{2A}$ research.*

Discovering potent, selective and metabolically stable 5-HT$_{2A}$ agonists would undoubtedly provide valuable tools for elucidating the mechanism of action of hallucinogens and possibly pave the way for new therapeutical drugs targeting mental illnesses.

Continuing the efforts of finding such compounds the Kristensen group synthesized a series of rigid analogues of **1** having its amines in a heterocycle adjacent to its aromatic moiety, a chemotype not yet explored in 5-HT$_{2A}$ research (Figure 5). These compounds were screened in a preliminary ^{3}[H]Cimbi-36 competition binding assay[40] where the results hinted towards promising selectivity profiles between the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor subtypes. It was therefore decided to further investigate this new class of compounds.

One of the major goals was to examine if the small structural differences in these compounds could induce different signaling pathways upon activation of the 5-HT$_{2A}$ receptor. To do this the compounds would undergo two different functional assays. One being a Ca^{2+} assay[40] that shows at what extent the ligand activates a G-protein signaling pathway and the other one being a recently developed β-arrestin-2 pathway assay. In addition to this, the compounds were to be tested in a mouse head-twitch response assay[41] in order to investigate their pharmacokinetic properties. Such as their ability to survive the first-pass effect and whether they are able to cross the blood-brain barrier in order to reach the target 5-HT$_{2A}$ receptors.

Unfortunately a lengthy and impractical synthetic route to the azetidine and pyrrolidine analogues halted these ambitions. In order to get sufficient amounts of product for thorough *in vitro* and *in vivo* testing a new more efficient synthetic route was in high demand.

2 Project aim

2.1 Conformationally Restricted Phenethylamines

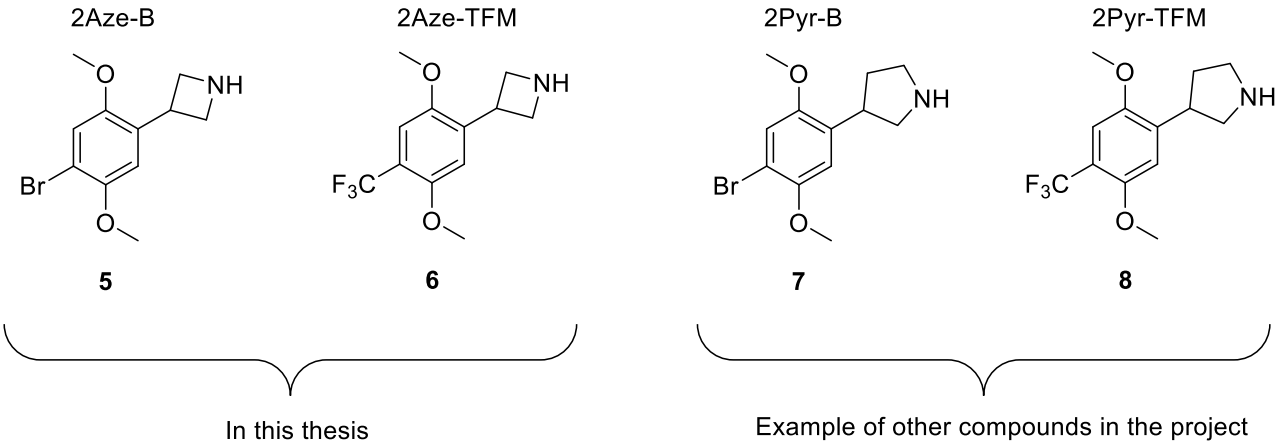


Figure 6. *Molecular structures of the target phenyl azetidines **5** and **6** including two other compounds part of the overall project.*

The main goal of this thesis project was to continue on the Kristensen groups work on the rigid phenethylamines. With focus lying in developing a new more efficient synthetic route to the phenyl azetidines **5** (2Aze-B) and **6** (2Aze-TFM) (Figure 6) in order to obtain enough product for extensive *in vitro* and *in vivo* testing.

Although the preliminary ^{3}[H]Cimbi-36 competition binding assays were only performed on the bromo analogues it was decided to extend the scope and investigate the trifluoromethyl substituted compounds as well since this 4-position substituent has shown to induce elevated *in vivo* potency in its non-rigid parent compound **2** (Figure 4).[34]

The pyrrolidine derivates **7** and **8** (Figure 6) including a series of other compounds were also part of the overall research project but their synthesis was performed by PhD student Emil Märcher-Rørsted and will therefore not be included in this thesis.

2.2 N-Benzyl Substituted Phenethylamines

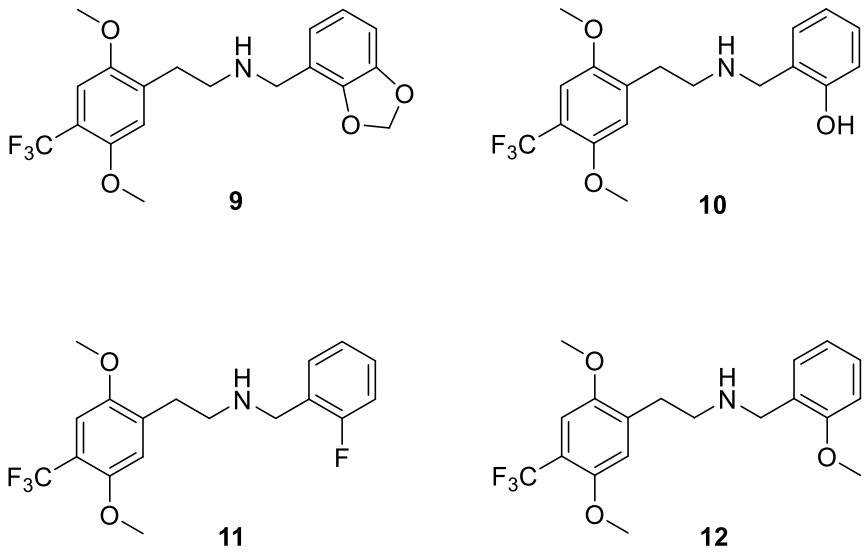


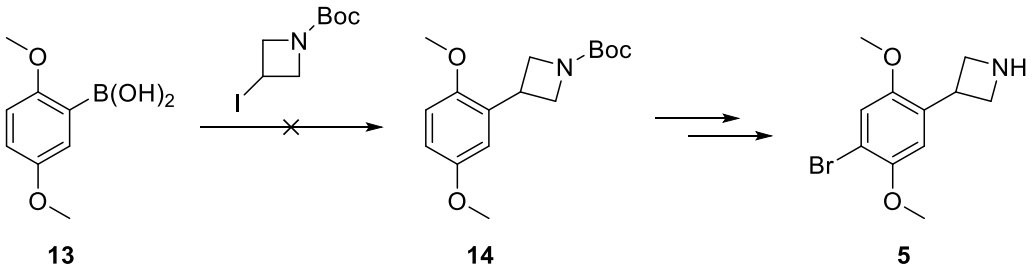
Figure 7. *Molecular structures of the target N-benzyl substituted phenethylamines.*

To further evaluate the influence of the triflouromethyl group on $5HT_{2A}$ agonists it was decided to prepare a set of four different N-benzyl substituted phenethylamines (Figure 7). These compounds would be assessed pharmacologically as part of a larger study together with a range of different N-benzyl substituted phenethylamines. It was hoped that the pharmacological profiles of these compounds would serve as useful data points for developing more accurate computational models of the 5-HT_{2A} receptor. As well as shedding more light on the effects of the trifluoromethyl group substitution on the 5-HT_{2A} scaffold.

3 Chemistry

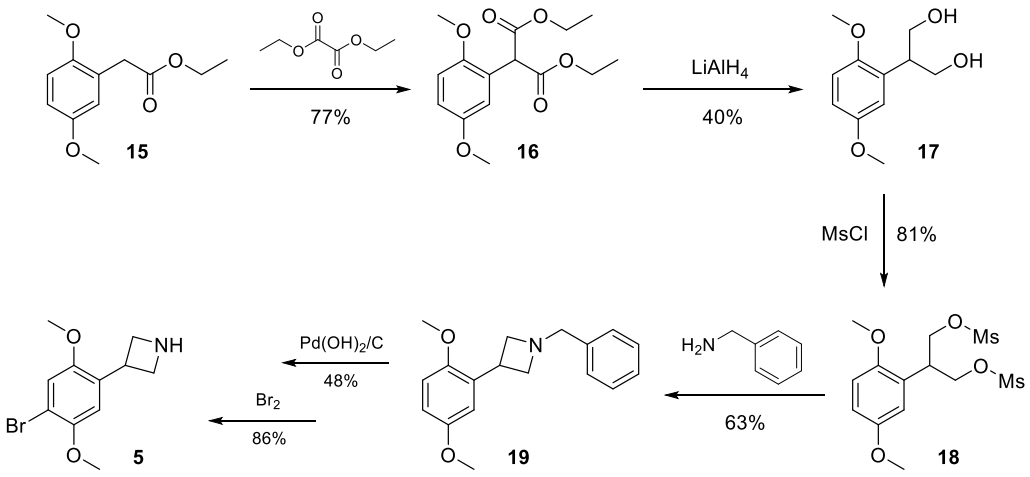
3.1 Synthesis of Phenyl Azetidines

3.1.1 Previous Trials



Scheme 1. *Failed attempt of synthesizing **5** via a Suzuki type coupling reaction.*

An initial attempt at making **5** performed previously in the group utilized commercially available 1-Boc-3-Iodoazetidine and boronic acid **13** in a Suzuki type coupling (Scheme 1).[42] It was hoped that the coupling reaction would provide protected azetidine **14** which could thereafter be brominated and deprotected to give **5**. However, despite several attempts this coupling reaction failed to give any product.

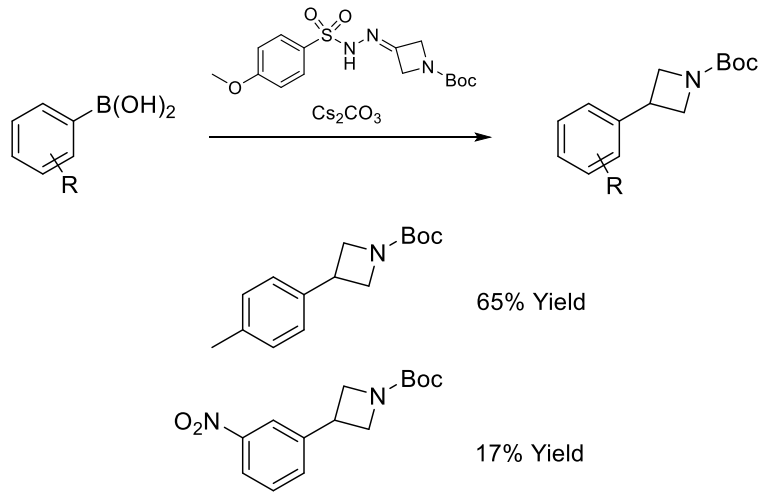


Scheme 2. *Overview of the first successful route to **5** with an overall yield of 6.5% over six steps.*

The first successful route by the Kristensen group to make **5** started from commercially available **15** (Scheme 2). Diethyl oxalate and **15** were reacted in a Claisen type condensation to give intermediate **16**. The ethyl esters of **16** were thereafter reduced using $LiAlH_4$ giving diol **17** in modest yields followed by a mesylation giving intermediate **18**. Dimesyl **18** was then reacted with benzylamine to form the four-membered azetidine ring of **19**. Azetidine **19** was thereafter debenzylated by a palladium-catalyzed hydrogenation followed by a bromination to give **5**. The presented route gave **5** in an overall yield of 6.5% over six steps.

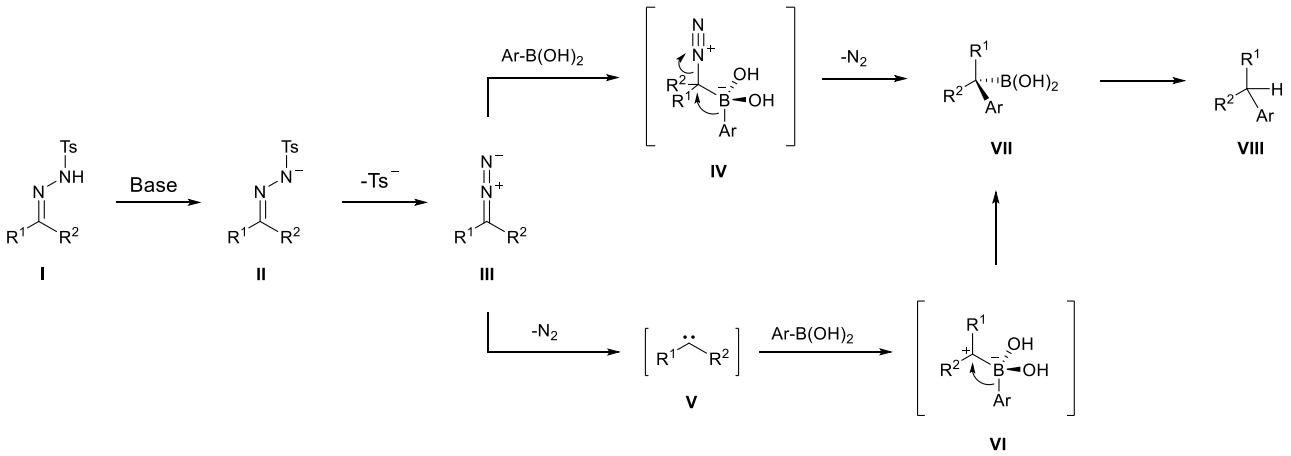
While this was a decent albeit somewhat lengthy method for synthesizing **5**, it was not an appealing route for the trifluoromethyl analogue **6** due to the lack of suitable commercially available starting material. This combined with the difficulties associated with introducing trifluoromethyl groups in later stages of the synthesis limited the scope of this route and made a compelling argument to find a new more efficient synthetic route.

3.1.2 The Boronic Acid Sulfonyl Hydrazone Coupling Reaction



Scheme 3. *Overview of the boronic acid sulfonyl hydrazone coupling reaction reported by Allwood et al.*

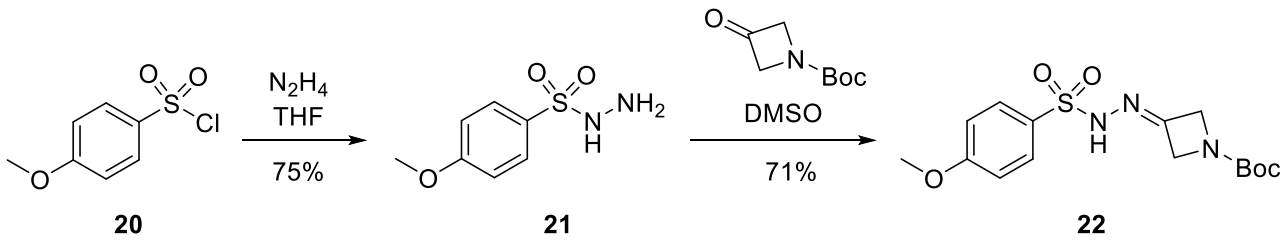
In search for a new synthetic method to make **5** and **6** it was decided to try the boronic acid sulfonyl hydrazone coupling reaction reported by Allwood et al.[43] (Scheme 3). The article reported yields in the range of 17-65% for phenyl azetidines and it was hoped that this method would allow the target compounds **5** and **6** to be obtained using only a few synthetic steps.



Scheme 4. *Proposed mechanistic pathways for the sulfonyl hydrazone boronic acid coupling reaction by Barluenga et al.[44]*

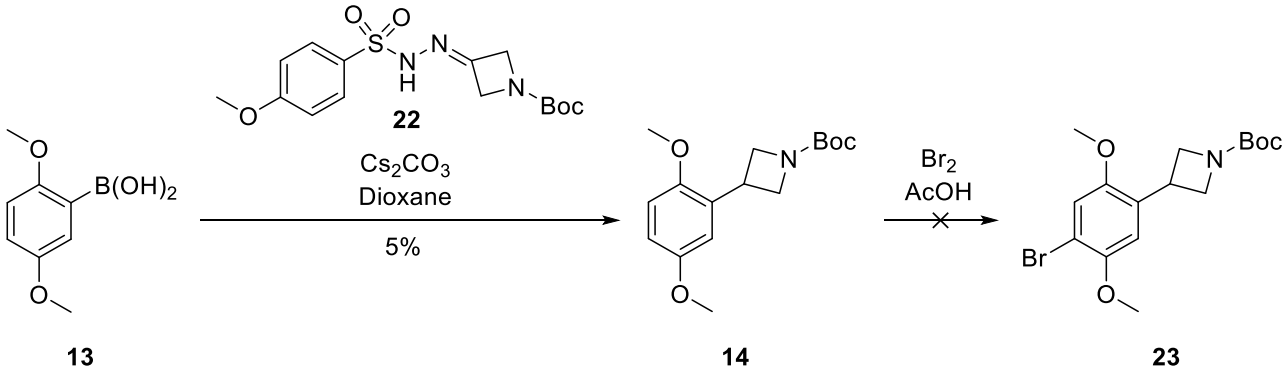
Two possible mechanistic pathways of the sulfonyl hydrazone boronic acid coupling reaction has been suggested by Barluenga et al.[44] (Scheme 4). In this proposal the reaction starts by the base deprotonation of **I** forming the hydrazone salt **II** which is then thermally decomposed to form the diazo compound **III**. Following this step two different mechanistic pathways were suggested. One forming intermediate **IV** after a nucleophilic attack of the boronic acid on **III**. **IV** then eliminates nitrogen in an aryl migration forming **VII**. Another suggested pathway proposes that nitrogen is eliminated from species **III** forming intermediate carbene **V** which then adds to the boronic acid forming intermediate **VI** which then undergoes an aryl migration to give **VII**. Upon protodeboronation of **VII** coupled product **VIII** is obtained.

3.1.3 Synthesis of 2Aze-B



Scheme 5. *Synthetic route to sulfonyl hydrazone **22**.*

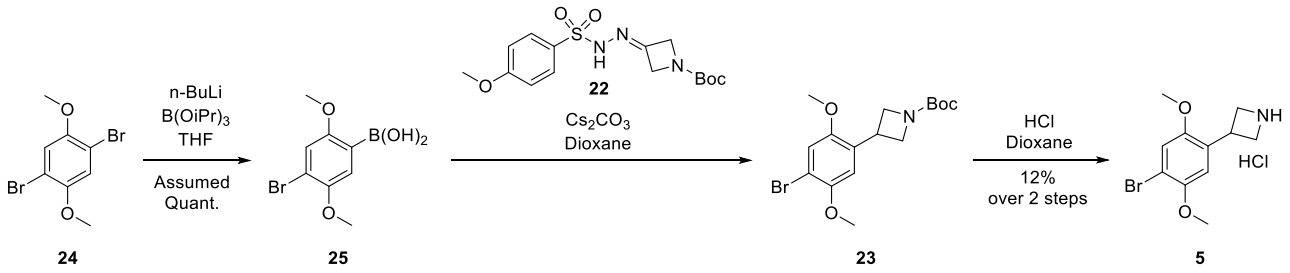
In order to attempt the coupling reaction the first goal was to prepare sulfonyl hydrazone **22** (Scheme 5). The synthesis of **22** followed the procedure reported by Allwood et al.[43] starting with the preparation of sulfonyl hydrazide **21** which was readily obtained in good yields from the reaction between **20** and hydrazine. Sulfonyl hydrazide **21** was then reacted with commercially available 1-Boc-3-azetidinone forming sulfonyl hydrazone **22**. During this preparation it was noted that **22** was fairly unstable with decomposition occurring at room temperature. The subsequent coupling reaction should therefore be performed shortly after the preparation of **22**.



Scheme 6. *Failed bromination of coupling product **14**.*

With the sulfonyl hydrazone **22** and commercially available **13** at hand the coupling reaction could be attempted. The reaction however, turned out to be low yielding giving only around 5% of product **14** despite several attempts (Scheme 6). Due to the low yields and the fact that the reaction did not scale well only miniscule amounts of **14** could be obtained. The amounts were so

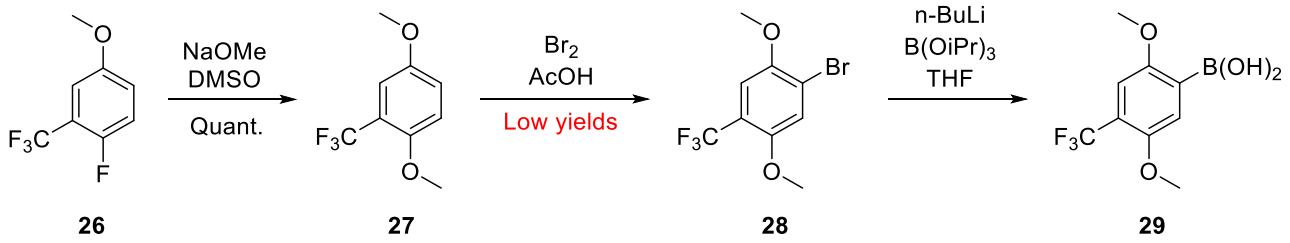
small that the following bromination could not be carried out in a satisfactory manner. Although conversion to aryl bromide **23** was detected, virtually no product could be obtained.



Scheme 7. *Synthetic route to target compound **5**.*

To tackle this problem it was decided to prepare and use aryl bromo boronic acid **25** in the coupling reaction instead (Scheme 7). Having the bromo substituent already installed on the boronic acid building block would mean that the precious coupling product **23** would only have to be deprotected in order to reach target compound **5**. Aryl bromo boronic acid **25** was easily prepared from dibromobenzene **24** following a procedure reported by Moy et al.[45] The following coupling reaction between **25** and **22** gave the expected product **23** which was deprotected to give target compound **5** as the hydrochloride salt in 12% yield over two steps.

3.1.4 Synthesis of 2Aze-TFM



Scheme 8. *Early method by the Kristensen group for synthesizing boronic acid **29**.*

In order to make **6** via the same route as for **5** the boronic acid **29** had to be obtained (Scheme 8). This compound had previously been made in the research group by a route starting from commercially available **26**. In a quantitative yielding nucleophilic aromatic substitution reaction

the aryl fluoride was exchanged for a methoxy group to give compound **27**. The following bromination however suffered from low yields with poor regioselectivity, likely due to the electron deficient nature of **27** caused by the electron withdrawing trifluoromethyl group

It was essential that compound **28** could be made in an efficient manner since it was a key intermediate not only in the synthesis of **6** but also in the synthesis of the five-membered analogue **8** as well as other target compounds in the project. After a screening of a few different bromination procedures one method published by Eguchi et al.[46] stood out in terms of starting material conversion. In this method DBH was utilized as a brominating agent with TfOH as an additive.

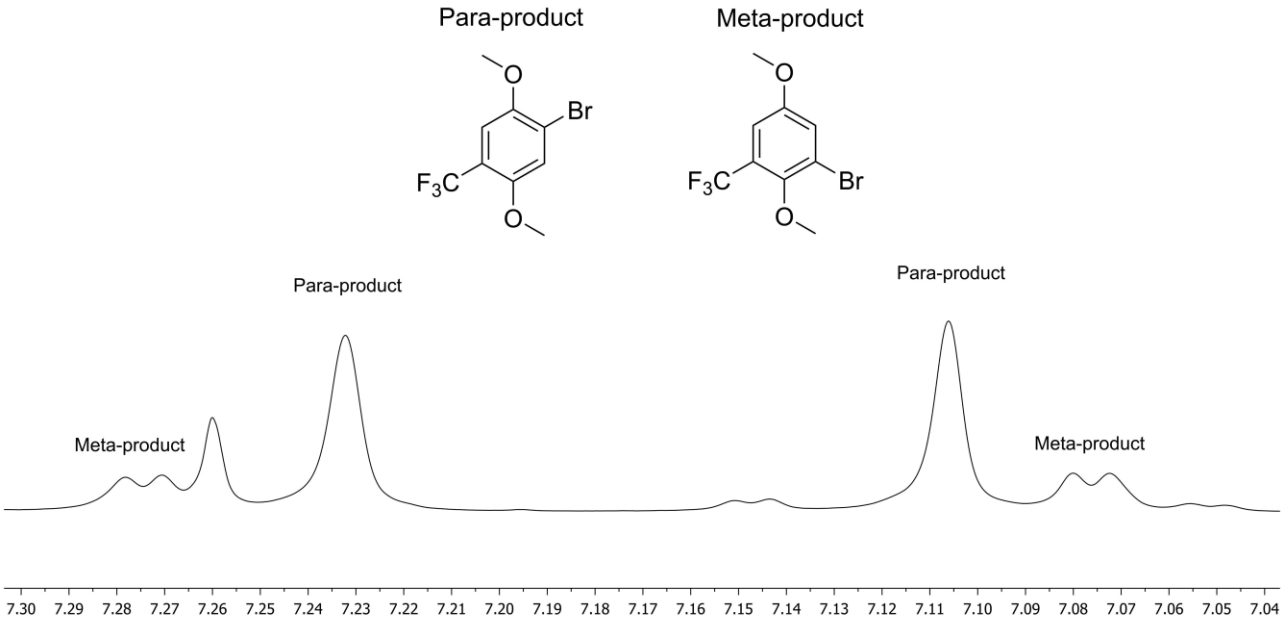


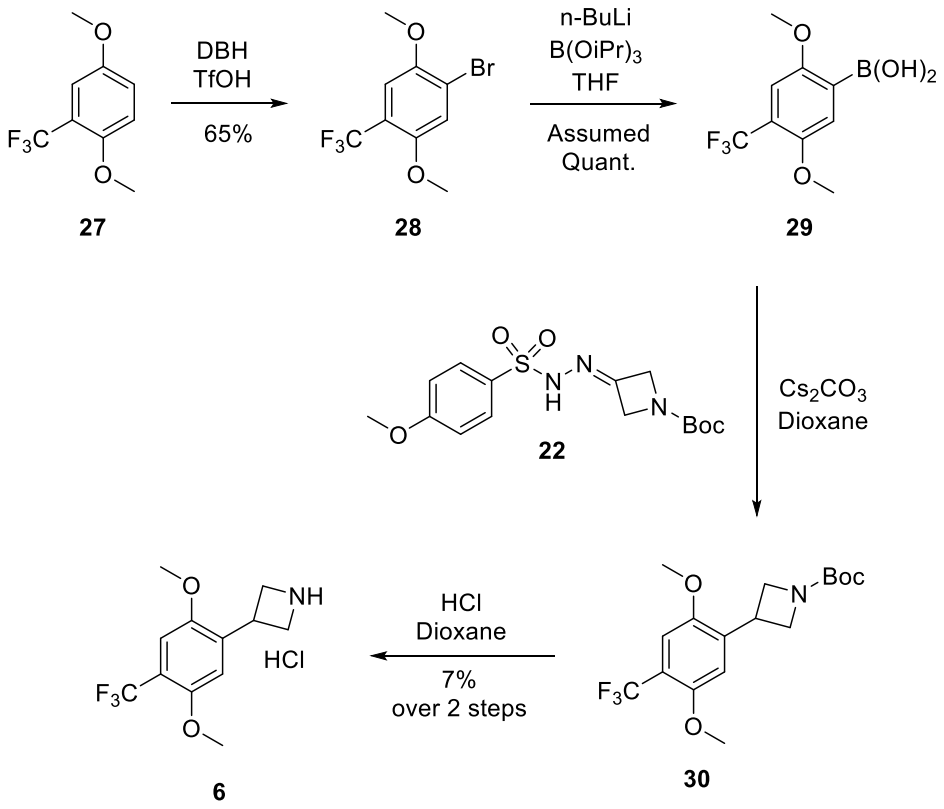
Figure 8. *^{1}H-NMR of a crude post-reaction mixture in the bromination of **27** by DBH and TfOH. Integration of the peaks was used to estimate proportions of formed products at different conditions.*

By analyzing the crude reaction mixture by ^{1}H-NMR it was noted that two major products were formed. One presumably being the desired para-product giving single peaks in the aromatic area and the other one being the meta-product giving splitted peaks in the aromatic area caused by meta-coupling between the aromatic protons (Figure 8).

#	Eq. acid	Solvent	Ratio P:M
1	0.5	$CHCl_3$	0.77
2	1.0	$CHCl_3$	1.04
3	2.0	$CHCl_3$	1.43
4	0.5	DCM	1.17
5	1.0	DCM	2.01
6	**2.0**	**DCM**	**2.74**
7	3.0	DCM	0.68

Table 1. *Results from bromination condition screening. All reactions were performed at 0.5 mmol scale with 0.5 eq DBH. Measured after 30 min. P = para-product, M = meta-product. Optimized conditions in bold.*

In order to estimate the proportions between the two formed regioisomers, aromatic peaks from the ^{1}H-NMR spectras were integrated and compared. Using the same conditions as the original article[46] gave roughly the same ratio of the two regioisomers (Table 1, Entry 2). During a screening of different conditions, it was noted that solvent type and amount of TfOH seemed to have a significant impact on the ratio between the two formed products. Using DCM as a solvent instead of chloroform seemed to favor the formation of para-product. In the conditions tested, DCM combined with two equivalents of TfOH gave the highest ratio of the desired para-product (Table 1, Entry 6). Interestingly 0.5 and 3.0 equivalents of TfOH favored formation of the undesired meta-product.

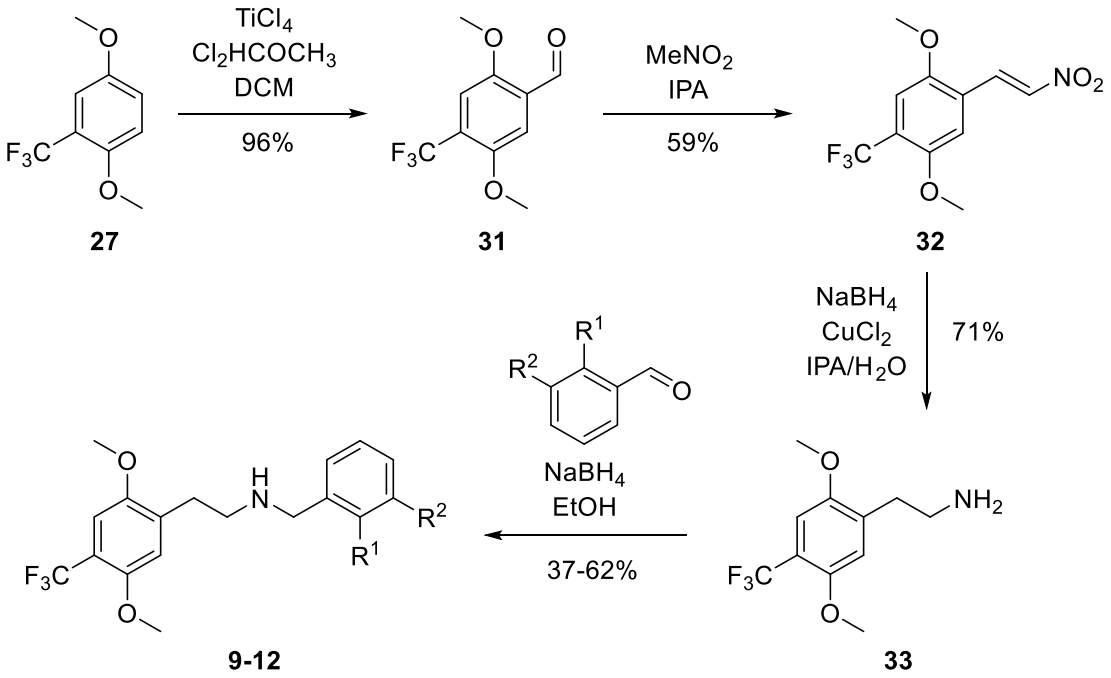


Scheme 9. *Synthetic route to target compound **6**.*

Using the optimized conditions, the bromination reaction was scaled up to gram-scale and successfully gave compound **28** in 65% yields (Scheme 9). Bromobenzene **28** could then be converted to boronic acid **29**. With boronic acid **29** and sulfonyl hydrazone **22** at hand, the stage was set to attempt the hydrazone coupling. Using the same conditions as in the preparation of **5** the final product **6** was obtained in 7% yield over two steps.

The presented route to make **5** and **6** using a sulfonyl hydrazone boronic acid coupling turned out to be low yielding and unfortunately did not scale well. However, the route proved viable for preparing small amounts of product in a few synthetic steps. This route was also successfully employed in the synthesis of the five membered pyrrolidine derivatives **7** and **8** (Figure 6) albeit with similar low yields.

3.2 Synthesis of N-Benzyl Substituted Phenethylamines



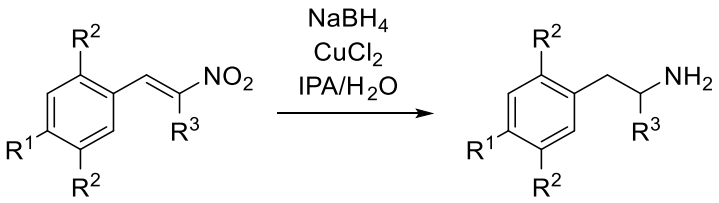
Scheme 10. *Synthetic route used for preparing N-benzyl substituted phenethylamines.*

The synthesis of the N-benzyl substituted phenethylamines **9**-**12** followed the synthetic route depicted in Scheme 10. The synthesis started with a Rieche formylation of compound **27** previously obtained during the synthesis of **6**.[47] This type of formylation which gave benzaldehyde **31** in high yields utilizes dichloromethyl methyl ether and $TiCl_4$ and has shown to be effective in formylating electron deficient substrates.[48] Benzaldehyde **31** was then reacted with nitromethane in a classic nitroaldol condensation to give nitrostyrene **32** in moderate yields.

The reduction of nitrostyrenes to phenethylamines are often performed using $LiAlH_4$.[30] However, $LiAlH_4$ is highly sensitive to moisture, fairly expensive and has some serious safety issues when scaling up and often involves cumbersome workups. Another method that has been used is to perform the reduction in two separate steps where the double bond is first reduced by $NaBH_4$ followed by a reduction of the aliphatic nitro group using a combination of $NiCl_2$ and $NaBH_4$.[49]

In the light of this, it was realized that a new method utilizing cheap and easier to handle reagents, that can perform the reduction in one pot would be highly desirable. In a procedure reported by

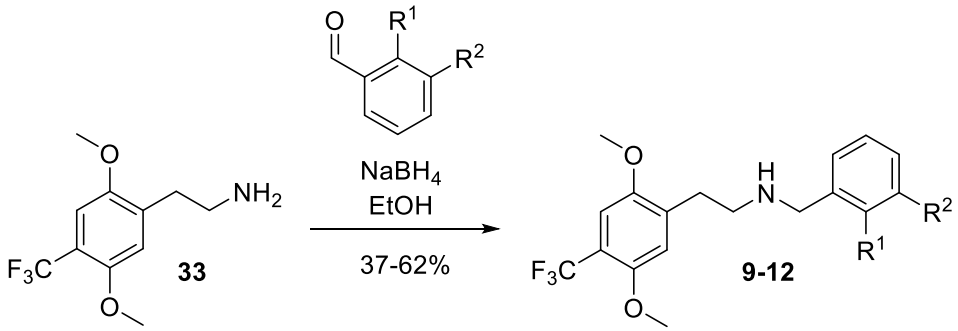
Sung-eun et al.[50] The authors showed that aliphatic nitro groups can be efficiently reduced by a combination of $CuSO_4$ and $NaBH_4$. This combined with the knowledge that $NaBH_4$ alone can reduce the double bond of nitrostyrenes,[49] it was realized that it should be possible to develop a modified procedure where the double bond and the nitro group is reduced in one-pot using a combination of $NaBH_4$ and a Cu(II)-salt.



#	Compound	R^1 =	R^2 =	R^3 =	Yield (%)
1	33	CF_3	OCH_3	H	71
2	34	H	H	H	83
3	35	H	OCH_3	H	72
4	36	CH_3	OCH_3	H	65
5	37	H	OCH_3	CH_3	62

Table 2. *Results of the $CuCl_2$-$NaBH_4$ one-pot reduction on five different nitroalkenes.*

To test this hypothesis, unsubstituted nitrostyrene was used to probe for suitable reaction conditions. The main challenge turned out to be solubility issues where finding a solvent system that would keep both the nitrostyrene and the $NaBH_4$ in solution at a sufficiently high concentration to give decent yields proved difficult. After extensive screening it was discovered that a mixture of IPA and water worked to satisfaction. Further optimization eventually gave a synthetic procedure where nitrostyrene could be reduced to phenethylamine in 83% yields (Table 2, Entry 2). In this optimized route, the nitrostyrene was added in portions to a suspension of 7.5 equivalents of $NaBH_4$ in isopropanol and water followed by the addition of 0.1 equivalents of $CuCl_2$. The suspension was then heated and stirred vigorously for 30 minutes. Encouraged by the success of this method, nitrostyrene **32** and three other similiar substrates were treated using the optimized conditions giving phenethylamines in moderate to high yields (Table 2).



#	Compound	R^1 =	R^2 =	Yield (%)
1	9	O-CH_2-O		62
2	10	OH	H	42
3	11	F	H	46
4	12	OCH_3	H	37

Table 3. *Results of the reductive amination reactions forming N-benzyl substituted phenethylamines.*

With phenethylamine **33** at hand the reductive aminations with four different benzaldehydes could be performed in a straightforward manner using $NaBH_4$ in EtOH to give the target N-benzyl phenethylamines **9**-**12** in moderate yields (Table 3).

4 Conclusions

During the finalization of writing this thesis the results from the *in vitro* and *in vivo* assays of both the azetidines and the N-Benzyl phenethylamines had unfortunately not yet arrived and could therefore not be included in this work. What can be concluded however is that the sulfonyl hydrazone boronic acid coupling reaction is a viable albeit low yielding synthetic route to **5** and **6**. If the results from the pending *in vitro* and *in vivo* assays turns out to be promising in terms of functional selectivity and potency, more material of these and similar substances will be desired and thus the efforts of finding an efficient synthetic route will likely continue.

Although the objective of finding an efficient route to **5** and **6** failed within the given time constraints the efforts did however lead to the findings of an efficient way to brominate the electron deficient trifluoromethyl benzene **29** to give compound **30**. The synthesis of compound **30** had previously been a bottleneck in the synthesis of other targets in the project. Moreover, in the synthesis of the N-benzyl substituted phenethylamines a new facile and effective way to reduce nitroalkenes to phenethylamines in a $CuCl_2$-$NaBH_4$ one-pot reduction was developed. This novel method utilizes cheaper, safer and easier to handle reagents compared to conventional methods for reducing nitroalkenes.

The efforts of developing accurate structure-activity relationship models of the 5-HT_{2A} receptor in order to learn more about its mechanism of action will continue and hopefully lead to the discovery of new more effective therapeutical drugs targeting mental disorders.

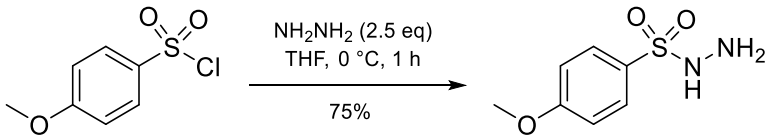
5 Experimental

5.1 General information

Reactions requiring anhydrous conditions were performed under inert atmosphere using flame-dried glassware. Commercially available reagents were used without further purification. DCM and THF were dried using a SG water purification system. DMSO, dioxane and EtOH were dried over molecular sieves (3Å). NMR spectras were recorded on a Bruker Avance 400 MHz or a Bruker Avance III 600 MHz. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} plates. Flash column chromatography was carried out using silica gel 60 (40-63 µm).

5.2 Synthesis Experimental

4-methoxybenzenesulfonohydrazide (21)

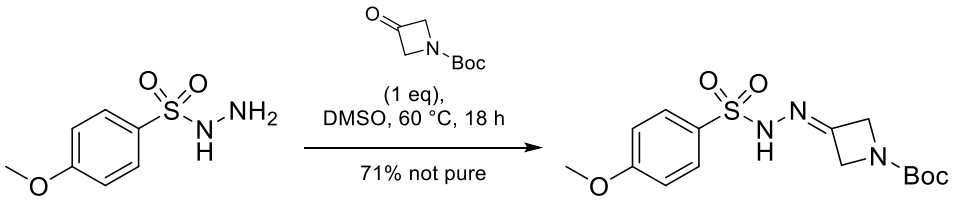


20 **21**

Sulfonyl chloride **20** (5.17 g, 25 mmol) was dissolved in THF (125 ml) and cooled on an ice-bath. Thereafter a 50% aqueous solution of hydrazine (3.90 ml, 62.5 mmol) was added dropwise. The mixture was then stirred at 0°C for 1 h. The volatiles were removed by rotary evaporation followed by the addition of water (50 ml). The mixture was then extracted with EtOAc (3x100 ml). The extractions were combined and washed with water (50 ml), brine (50 ml), dried over Na_2SO_4, filtrated and evaporated to yield **21** as a colorless amorphous solid (3.79 g, 75%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 5.55 (s, 1H), 3.89 (s, 3H), 3.59 (s, 2H); **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 163.86, 130.63, 127.64, 114.68, 55.86.

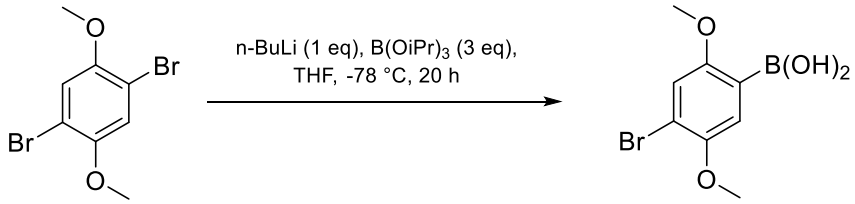
tert-butyl 3-(2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)azetidine-1-carboxylate (22)



21 **22**

Hydrazide **21** (3.83 g, 18.91 mmol) and tert-butyl 3-oxoazetidine-1-carboxylate (3.24 g, 18.93 mmol) were dissolved in dry DMSO (13 ml) in a vial. The vial was capped and heated at 60°C for 18 h. The reaction mixture was then poured into water (350 ml) and extracted with Et_2O (3x100 ml). The extractions were combined and washed with water (5x50 ml), brine (50 ml), dried over Na_2SO_4, filtrated and evaporated to give **22** (4.77 g, 71%) as a crude slightly off-white solid that was used in the subsequent reactions without further purification.

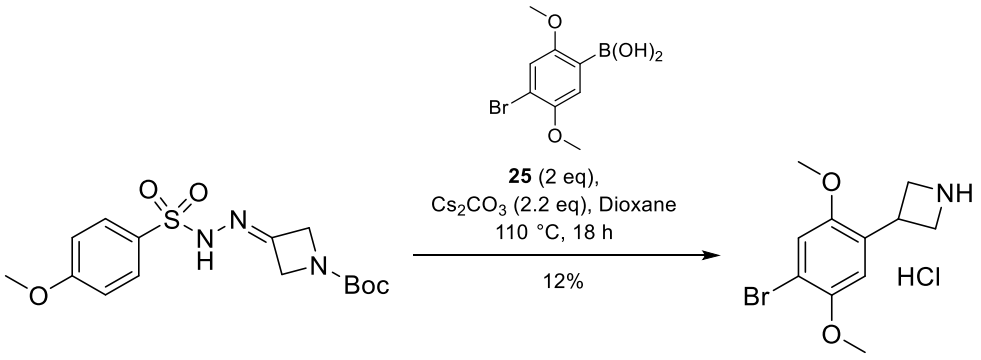
(4-bromo-2,5-dimethoxyphenyl)boronic acid (25)



24 **25**

Dibromobenzene **24** (2.22 g, 7.5 mmol) was dissolved in dry THF (75 ml) and cooled to -78°C. Thereafter n-BuLi (2.17 M, 7.5 mmol) was added dropwise and stirred for 20 minutes. Triisopropyl borate (5.19 ml, 22.5 mmol) was then added and the dry ice bath was removed allowing the reaction to reach r.t. After stirring the reaction for 20 h at r.t it was quenched by careful addition of 2 M HCl (15 ml). The mixture was then extracted with Et_2O (3x100 ml). The extractions were combined and washed with water water (50 ml), dried over Na_2SO_4, filtrated through a silica plug and evaporated to give **25** as a crude white solid (2.22 g, 98%) that was used in the subsequent step without further purification.

3-(4-bromo-2,5-dimethoxyphenyl)azetidine hydrochloride (5)

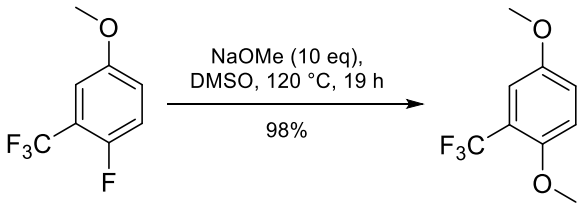


22 **5**

Sulfonyl hydrazone **22** (249 mg, 0.70 mmol), boronic acid **25** (365 mg, 1.40 mmol) and dry Cs_2CO_3 (502 mg, 1.54 mmol) were placed in a vial that was kept under high vacuum for 2 h. The vial was then backfilled with argon followed by the addition of dry dioxane (5.7 ml). The suspension was then degassed 4 times under stirring by applying vacuum and then backfilling the vial with argon through a needle inserted into the reaction mixture. The suspension was then heated at 110°C for 18 h under heavy stirring. After reaching r.t the mixture was filtered through celite, evaporated and purified with flash column chromatography (R_f = 0.50, 1:2 EtOAc/Heptane) to give the boc-protected intermediate as a clear oil which was then deprotected by dissolving it in 4M HCl in dioxane (1 ml) and stirring it for 24 h. The mixture was then diluted with Et_2O (25 ml) and kept in a freezer overnight causing product to crystallize. The solids were isolated by careful removal of the supernatant by pipetting and washing it repeatedly with Et_2O to give **5** as a colorless crystalline solid (26 mg, 12%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.22 (s, 1H), 6.91 (s, 1H), 4.35 (d, J = 3.3 Hz, 2H), 4.33 (s, 2H), 4.30 – 4.25 (m, 1H), 3.85 (s, 6H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 153.17, 151.74, 127.91, 117.33, 113.85, 112.06, 57.57, 56.69, 52.50, 34.73; **HRMS** *m/z* (MALDI-TOF) cald. for $C_{11}H_{15}BrNO_2$ $[M+H]^+$ 272.0281; found: 272.0282.

1,4-dimethoxy-2-(trifluoromethyl)benzene (27)

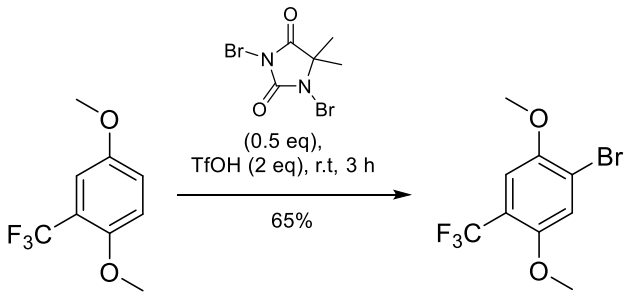


26 **27**

Fluorobenzene **26** (14.56 g, 75 mmol) and sodium methoxide (40.52 g, 750 mmol) were suspended in DMSO (150 ml) and heated at 120 °C for 19 h in a round-bottom flask fitted with a condenser. The mixture was then poured into water (700 ml) and extracted with Et_2O (3x200 ml). The extractions were combined and washed with water (3x200 ml), dried over $MgSO_4$, filtered and evaporated to yield **27** as a colorless oil (15.21 g, 98%) which crystallized into a solid over the course of several days.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (d, *J* = 3.0 Hz, 1H), 7.02 (dd, *J* = 9.2, 3.1 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 152.98, 151.55, 124.77, 118.12, 113.63, 112.87, 112.81, 56.60, 55.91.

1-bromo-2,5-dimethoxy-4-(trifluoromethyl)benzene (28)



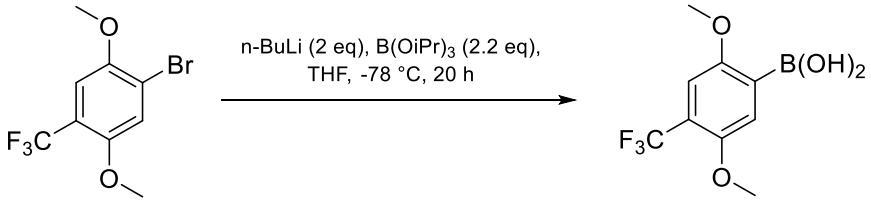
27 **28**

Trifluoromethylbenzene **27** (5.15 g, 25 mmol) was dissolved in anhydrous DCM (50 ml) in a round-bottom flask shielded from light. The flask was cooled on an ice-bath and TfOH (4.43 ml, 50 mmol) was added and the contents allowed to stir for 2 minutes. Thereafter 1,3-Dibromo-5,5-dimethylhydantoin (3.57 g, 12.5 mmol) was added in one portion and the suspension was stirred

for an additional 5 minutes. Thereafter the ice-bath was removed and the suspension was stirred for 3 h at r.t. The reaction was then quenched by careful addition of saturated sodium bisulfite (7 ml) followed by saturated $NaHCO_3$ (30 ml). The phases were separated and the aqueous phase was extracted with DCM (2x50 ml). The extractions were combined, washed with brine (50 ml), dried over Na_2SO_4, filtered and evaporated to give a crude off-white solid that was recrystallized repeatedly with IPA and Et_2O to give **28** (4.63 g, 65%) as a colorless crystalline solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (s, 1H), 7.09 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 151.79, 149.88, 121.97, 118.25, 116.38, 110.91, 110.85, 57.16, 56.95.

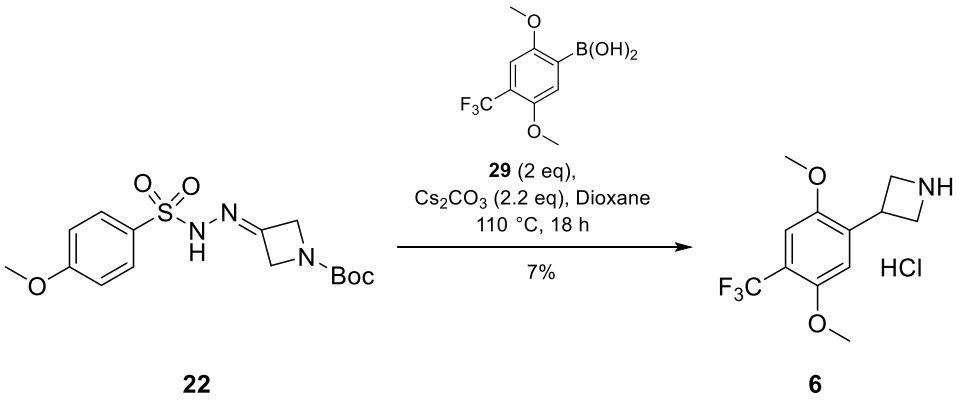
(2,5-dimethoxy-4-(trifluoromethyl)phenyl)boronic acid (29)



28 **29**

Bromobenzene **28** (1.00 g, 3.52 mmol) was dissolved in dry THF (50 ml) and cooled to -78°C. Thereafter n-BuLi (2.3 M, 7.04 mmol) was added dropwise and stirred for 1 h. Triisopropyl borate (1.79 ml, 7.74 mmol) was then added and the dry ice bath was removed allowing the reaction to reach r.t. After stirring the reaction for 20 h at r.t it was quenched by careful addition of 0.5 M HCl (25 ml) followed by water (50 ml). The THF was removed by rotary evaporation and the mixture was extracted with DCM (3x50 ml). The extractions were combined and washed with water (50 ml), brine (50 ml), dried over $MgSO_4$, filtrated and evaporated to give **29** as a crude off-white solid (896 mg, 102%) that was used in the subsequent step without further purification.

3-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)azetidine hydrochloride (6)

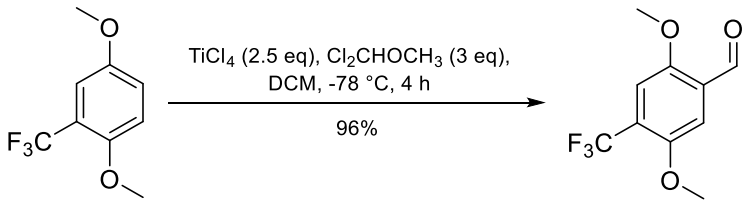


22 **6**

This compound was synthesized following the same procedure as for **5** but instead using boronic acid **29** as reactant. **6** were isolated as a colorless crystalline solid (15.3 mg, 7%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.19 (s, 1H), 7.04 (s, 1H), 4.39 – 4.34 (m, 5H), 3.89 (s, 6H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 151.61, 150.72, 131.66, 124.36, 112.79, 109.08, 109.04, 55.81, 55.20, 51.00, 33.38; **HRMS** *m/z* (MALDI-TOF) cald. for $C_{12}H_{15}F_3NO_2$ $[M+H]^+$ 262.1049; found: 262.1051.

2,5-dimethoxy-4-(trifluoromethyl)benzaldehyde (31)



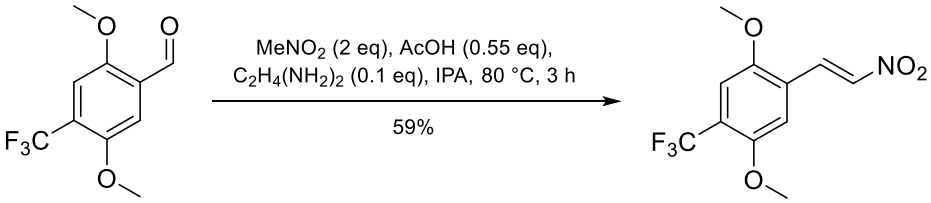
27 **31**

Trifluoromethylbenzene **27** (6.19 g, 30 mmol) was dissolved in DCM (100 ml) and cooled to -78°C on a dry-ice bath. Thereafter $TiCl_4$ (8.24 ml, 75 mmol) was added dropwise followed by dichloromethyl methyl ether (8.13 ml, 90 mmol). The reaction was then allowed to slowly reach r.t over the course of 4 h. The mixture was then poured into ice water (400 ml) and extracted with DCM (3x100 ml). The extractions were combined and washed with water (100 ml), saturated

$NaHCO_3$ (100 ml), brine (100 ml) and then dried over $MgSO_4$, filtered and evaporated to give **31** as an off-white solid (6.75 g, 96 %).

^{1}H NMR (400 MHz, Chloroform-d) δ 10.48 (s, 1H), 7.45 (s, 1H), 7.23 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H); **^{13}C NMR** (101 MHz, Chloroform-d) δ 188.76, 155.32, 151.39, 127.37, 124.94, 124.15, 111.46, 110.96, 56.55, 56.39.

1,4-dimethoxy-2-(2-nitrovinyl)-5-(trifluoromethyl)benzene (32)

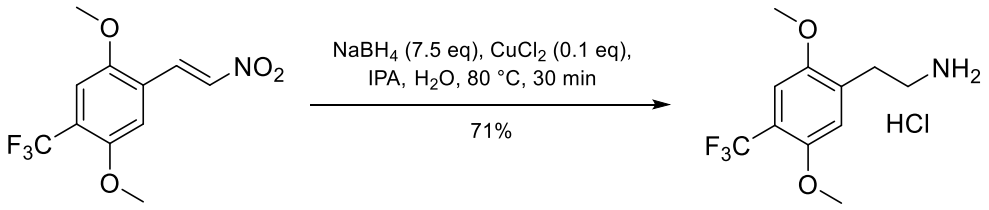


31 **32**

Benzaldehyde **31** (5.85g, 25 mmol) was dissolved in IPA (32 ml) at 80°C. Thereafter nitromethane (2.68 ml, 50 mmol), acetic acid (0.79 ml, 13.8 mmol) and ethylene diamine (0.167 ml, 2.5 mmol) were added in the stated order and the reaction were kept at 80°C with stirring for 3 h. The mixture was then kept in a fridge overnight causing crystallization. The solids were filtered and washed with cold IPA yielding **32** as a crystalline yellow solid (3.47 g, 59%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 13.7 Hz, 1H), 7.89 (d, *J* = 13.6 Hz, 1H), 7.17 (s, 1H), 7.05 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H).

2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride (33)

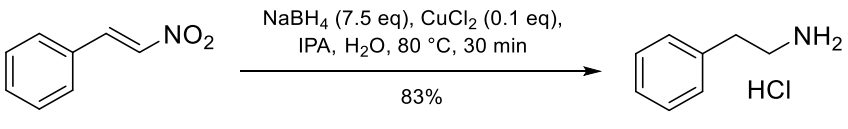


32 **33**

Nitrostyrene **32** (2.77 g, 10 mmol) was added carefully in portions to a stirred suspension of $NaBH_4$ (2.84 g, 75 mmol) in IPA (32 ml) and water (16 ml) causing an exothermic reaction increasing the temperature of the mixture to 50-60°C. Thereafter a 2M solution of $CuCl_2$ (0.5 ml, 1 mmol) was added carefully dropwise causing further exothermicity. The reaction was then held at 80°C for 30 minutes using external heating. After reaching r.t, a 25% solution of NaOH (20 ml) was added under stirring and the phases were separated. The aqueous phase was thereafter extracted with IPA (3x30 ml). The extractions were combined, dried over $MgSO_4$ and filtered. A stoichiometric amount of 4M HCl in dioxane was added to the filtrate under stirring. The mixture was evaporated yielding a greyish sludge that was suspended in dry acetone and stirred for 1 h. The suspension was thereafter filtered and washed with dry acetone to yield **33** as a colorless amorphous solid (2.02 g, 71%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.16 (s, 1H), 7.10 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.18 (t, J = 7.4 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 152.98, 152.41, 131.62, 125.88, 124.08, 116.83, 110.40, 57.10, 56.57, 40.45, 29.85.

2-phenylethan-1-amine hydrochloride (34)

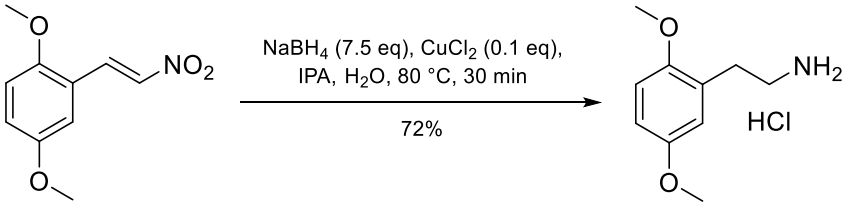


34

This compound was synthesized following the same procedure as for **33** but instead using nitrostyrene **34** as reactant. **38** was isolated as a colorless amorphous solid (1.308 g, 83%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.37 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.27 (m, 3H), 3.20 (t, *J* = 7.9, 2H), 3.01 – 2.97 (m, 2H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 136.54, 128.60, 128.39, 126.87, 40.60, 33.16.

2-(2,5-dimethoxyphenyl)ethan-1-amine hydrochloride (35)

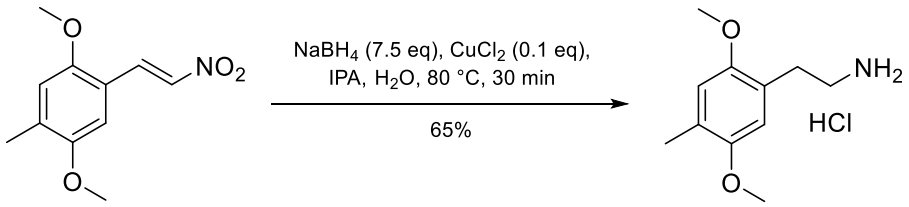


35

This compound was synthesized following the same procedure as for **33** but instead using nitrostyrene **35** as reactant. **39** was isolated as a colorless amorphous solid (1.567 g, 72%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 6.94 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.82 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.15 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 153.84, 151.75, 125.44, 116.59, 112.48, 111.34, 54.87, 54.71, 39.45, 28.56.

2-(2,5-dimethoxy-4-methylphenyl)ethan-1-amine hydrochloride (36)

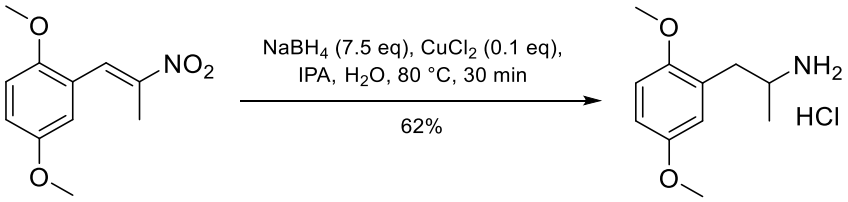


36

This compound was synthesized following the same procedure as for **33** but instead using nitrostyrene **36** as reactant. **40** was isolated as a colorless amorphous solid (151 mg, 65%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 6.83 (s, 1H), 6.78 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.20 (s, 3H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 151.81, 151.25, 126.32, 121.97, 113.56, 112.83, 55.08, 54.93, 39.66, 28.40, 14.87.

1-(2,5-dimethoxyphenyl)propan-2-amine hydrochloride (37)

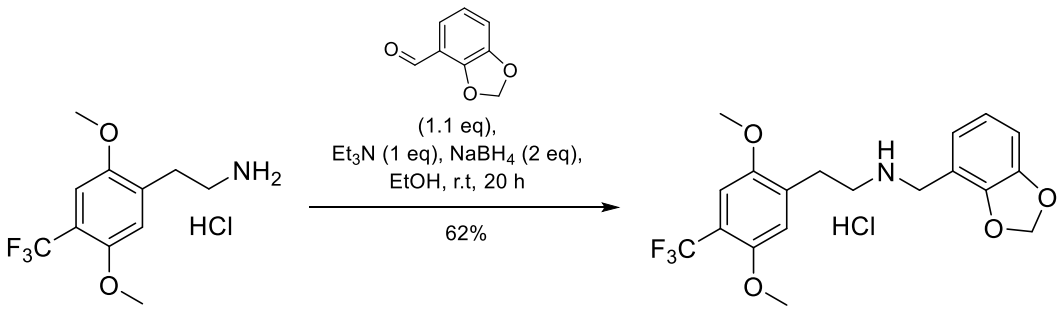


37

This compound was synthesized following the same procedure as for **33** but instead using nitroalkene **37** as reactant. **41** was isolated as a colorless amorphous solid (1.437 g, 62%).

^{1}H NMR (600 MHz, Methanol-d_4) δ 6.95 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.80 (t, *J* = 3.2 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.59 (quint, *J* = 6.8 Hz, 1H), 2.99 - 294 (m, 1H), 2.84 (dd, *J* = 13.4, 7.3 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 153.75, 151.77, 124.85, 117.23, 112.67, 111.41, 54.85, 54.73, 47.82, 35.46, 17.17.

N-(benzo[d][1,3]dioxol-4-ylmethyl)-2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride (9)

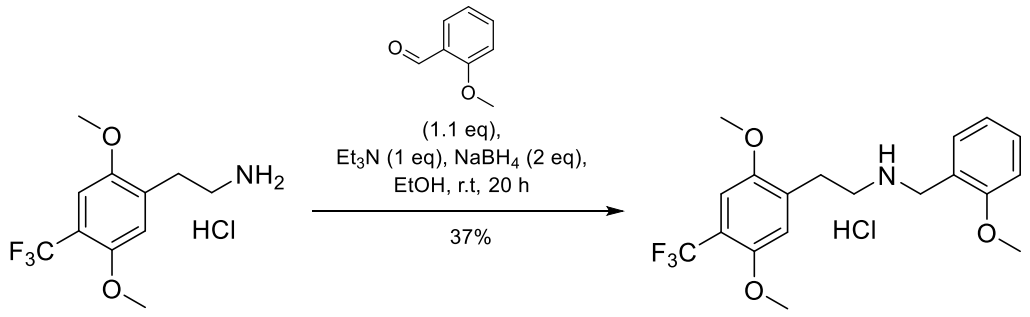


33 **9**

Phenethylamine **33** (214.3 mg, 0.75 mmol), 2,3-(Methylenedioxy)benzaldehyde (123.9 mg, 0.825 mmol) and triethylamine (0.105 ml, 0.75 mmol) were dissolved in dry EtOH (7.5 ml) and stirred for 19 h at r.t. $NaBH_4$ (56.7 mg, 1.5 mmol) was then added and the mixture was allowed to stir for an additional 30 minutes. The volatiles were thereafter evaporated followed by addition of water (10 ml). The mixture was extracted with DCM (3x10 ml). The extractions were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated to yield a crude product that was purified using flash column chromatography (98:2:0.4 DCM/MeOH/NH_3). The isolated freebase was then dissolved in EtOH (1 ml) and a stoichiometric amount of 4M HCl in dioxane was added followed by Et_2O (50 ml). The mixture was then kept in a fridge overnight causing product to crystallize. After filtration and washing with cold ether **9** was obtained as a colorless crystalline solid (194 mg, 62%).

TLC R_f = 0.16 (98:2:0.4 DCM/MeOH/NH3); **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.42 (s, 2H), 7.17 (s, 1H), 7.14 (s, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.07 (s, 2H), 4.12 (t, *J* = 5.4 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.19 – 3.15 (m, 2H), 3.06 – 3.02 (m, 2H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ 151.29, 151.03, 147.61, 146.77, 131.50, 124.50, 123.76, 122.68, 122.33, 116.20, 115.58, 113.52, 109.66, 101.70, 57.00, 56.66, 46.12, 44.09, 26.98.

2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-N-(2-methoxybenzyl)ethan-1-amine hydrochloride (12)



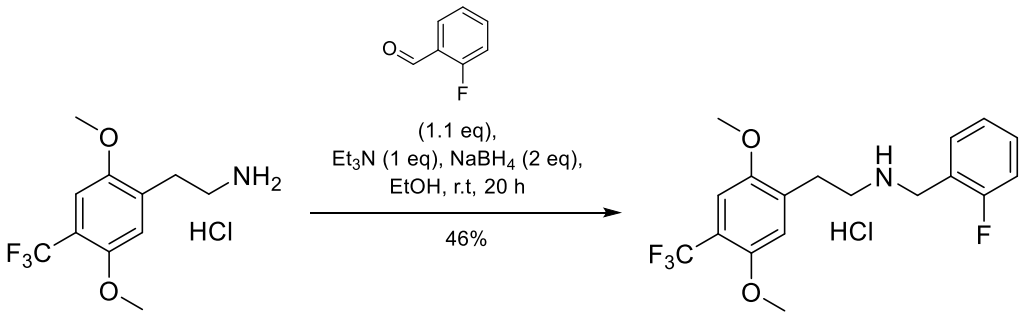
33 **12**

This compound was synthesized following the same procedure as for **9** but instead using 2-methoxybenzaldehyde as reactant. **12** was isolated as a colorless crystalline solid (75.3 mg, 37%).

TLC R_f = 0.25 (98:2:0.4 DCM/MeOH/NH3); **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.19 (s, 2H), 7.49 (d, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.00 (t, *J* = 7.4

Hz, 1H), 4.14 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.15 – 3.10 (m, 2H), 3.07 – 3.03 (m, 2H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ 157.48, 150.82, 150.52, 131.44, 131.15, 130.78, 124.51, 122.70, 120.37, 119.66, 115.67, 111.10, 109.19, 56.53, 56.16, 55.58, 45.57, 44.87, 26.40.

2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-N-(2-fluorobenzyl)ethan-1-amine hydrochloride (11)

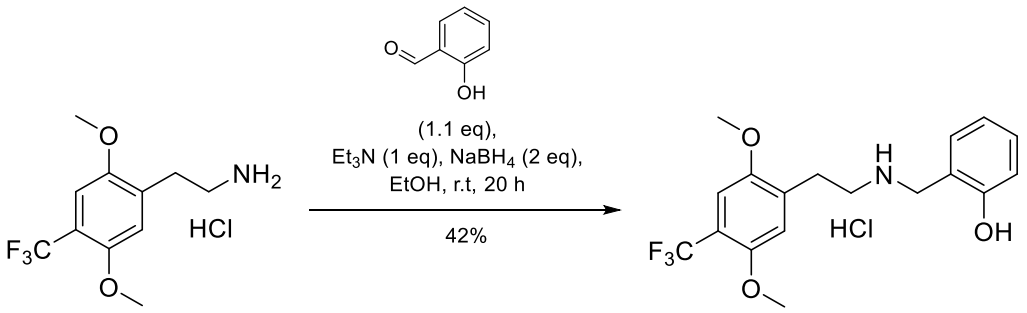


33 **11**

This compound was synthesized following the same procedure as for **9** but instead using 2-fluorobenzaldehyde as reactant. **11** were isolated as a colorless crystalline solid (137 mg, 46%).

TLC R_f = 0.30 (98:2:0.4 DCM/MeOH/NH3); **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.29 (s, 2H), 7.67 (td, J = 7.7, 1.8 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.31 – 7.28 (m, 2H), 7.17 (s, 1H), 7.15 (s, 1H), 4.24 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.20 (t, J = 7.8 Hz, 2H), 3.07 – 3.01 (m, 2H); **^{13}C NMR** (151 MHz, DMSO-d_6) δ 161.39, 150.79, 150.54, 132.37, 132.35, 131.59, 131.53, 130.94, 124.75, 124.73, 115.71, 115.56, 109.19, 56.52, 56.18, 45.91, 43.18, 26.52.

2-(((2,5-dimethoxy-4-(trifluoromethyl)phenethyl)amino)methyl)phenol hydrochloride (10)



33 **10**

This compound was synthesized following the same procedure as for **9** but instead using salicylaldehyde as reactant. **10** were isolated as a colorless crystalline solid (124 mg, 42%).

TLC R_f = 0.13 (98:2:0.4 DCM/MeOH/NH3); **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.32 – 7.27 (m, 2H), 7.15 (s, 1H), 7.10 (s, 1H), 6.91 (t, *J* = 7.4 Hz, 2H), 4.25 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.27 (dd, *J* = 8.8, 6.5 Hz, 2H), 3.09 (dd, *J* = 8.8, 6.5 Hz, 2H); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 157.49, 153.01, 152.26, 132.59, 132.40, 131.46, 125.85, 124.05, 121.05, 118.68, 116.75, 116.29, 110.42, 110.38, 57.08, 56.58, 47.69, 28.45.

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Big thanks to Emil Märcher-Rørsted for your support and encouragement throughout the project.

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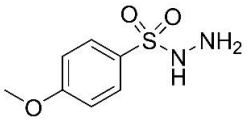
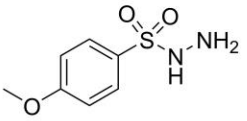
8 Appendix



^{1}H-NMR, 600 MHz, $CDCl_3$



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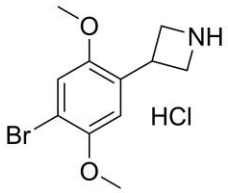

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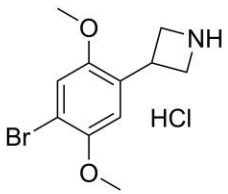

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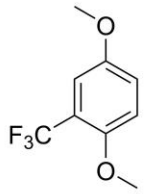

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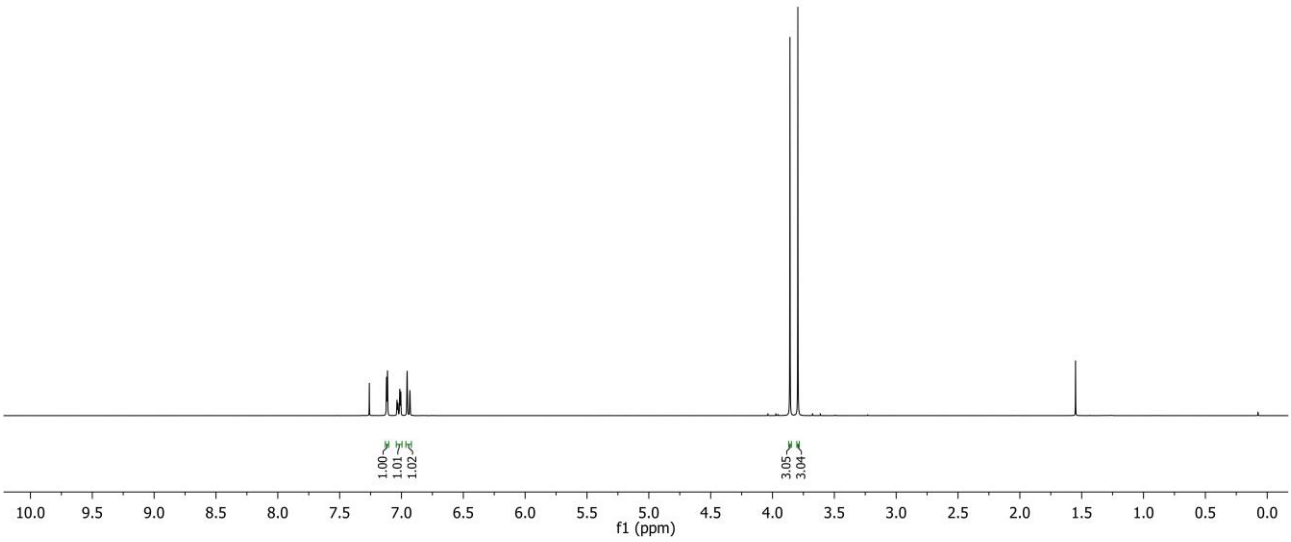
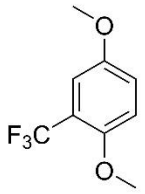
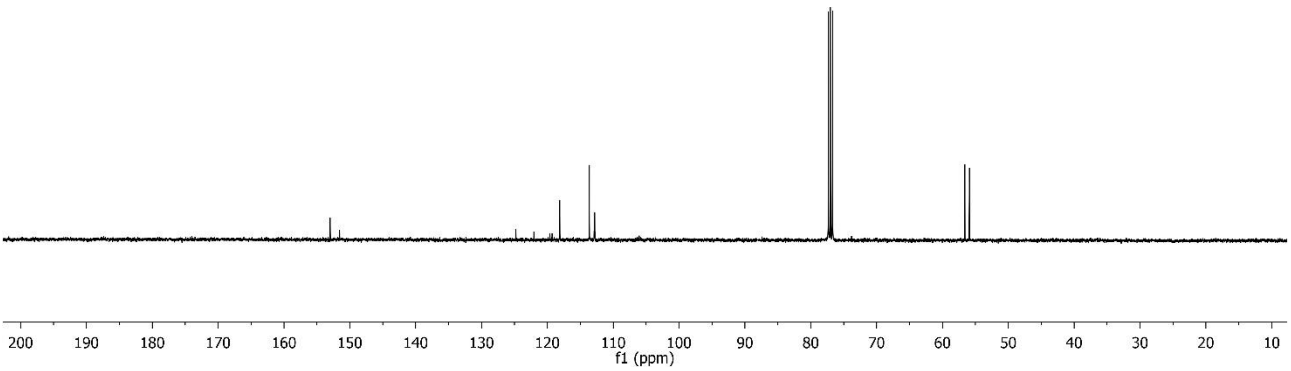
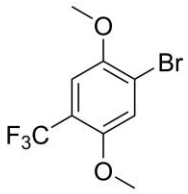


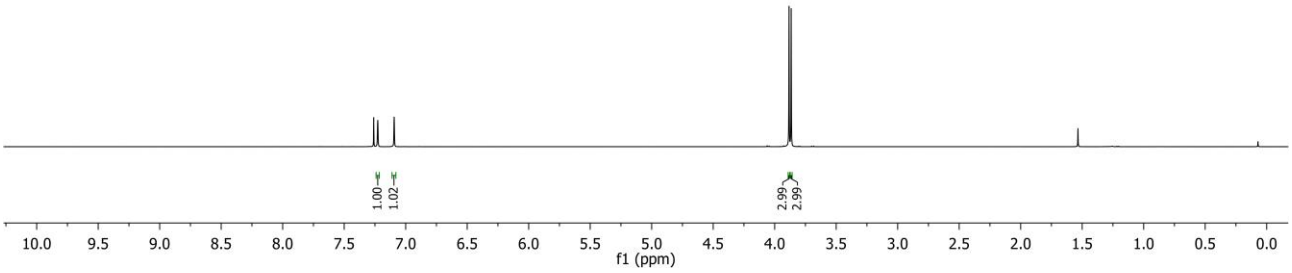


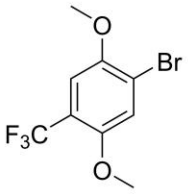
^{13}C-NMR, 101 MHz, $CDCl_3$



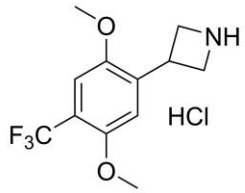


^{1}H-NMR, 400 MHz, $CDCl_3$

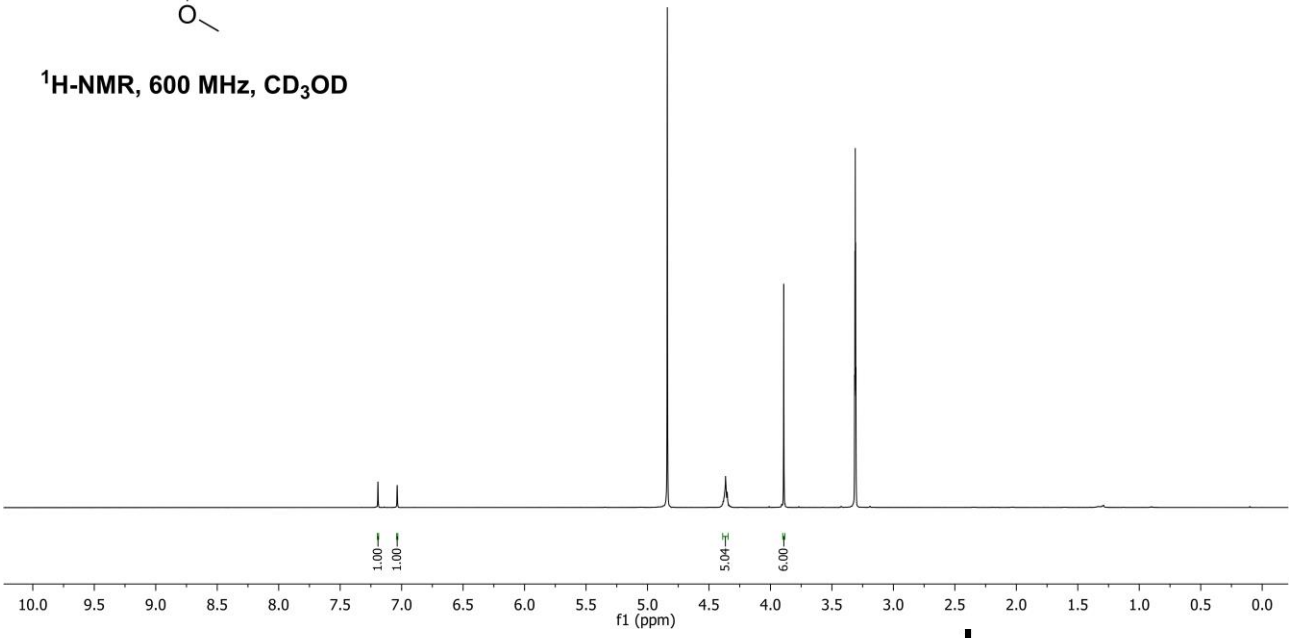


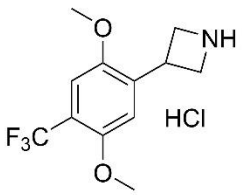


^{13}C-NMR, 101 MHz, $CDCl_3$

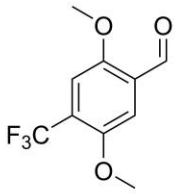


^{1}H-NMR, 600 MHz, CD_3OD

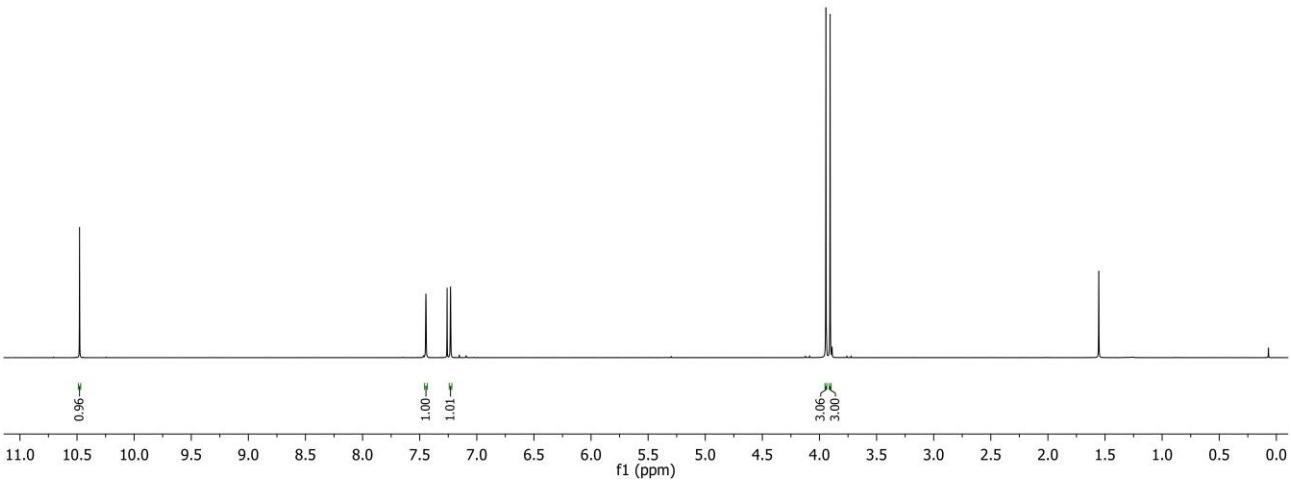


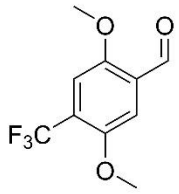


^{13}C-NMR, 151 MHz, CD_3OD

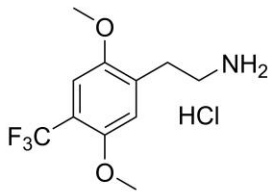


^{1}H-NMR, 400 MHz, $CDCl_3$

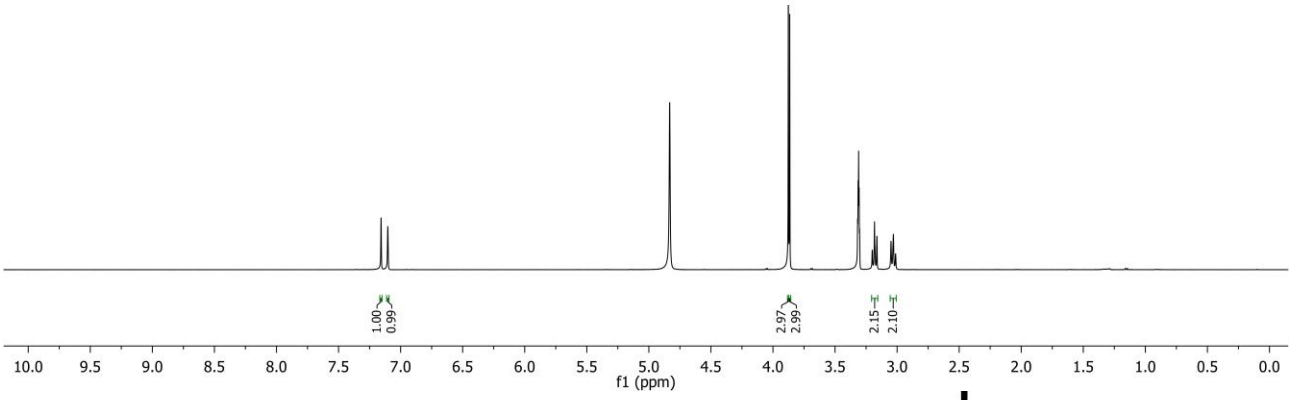


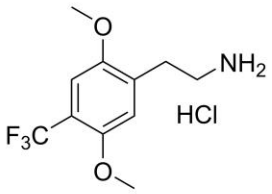


^{13}C-NMR, 101 MHz, $CDCl_3$

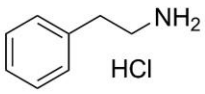


^{1}H-NMR, 400 MHz, CD_3OD

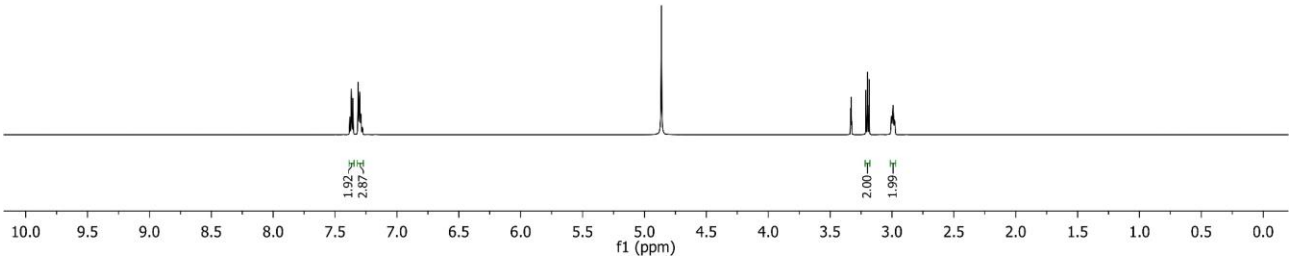


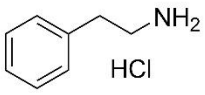


^{13}C-NMR, 151 MHz, CD_3OD

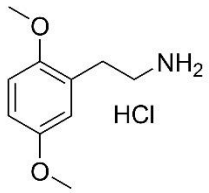


^{1}H-NMR, 600 MHz, CD_3OD

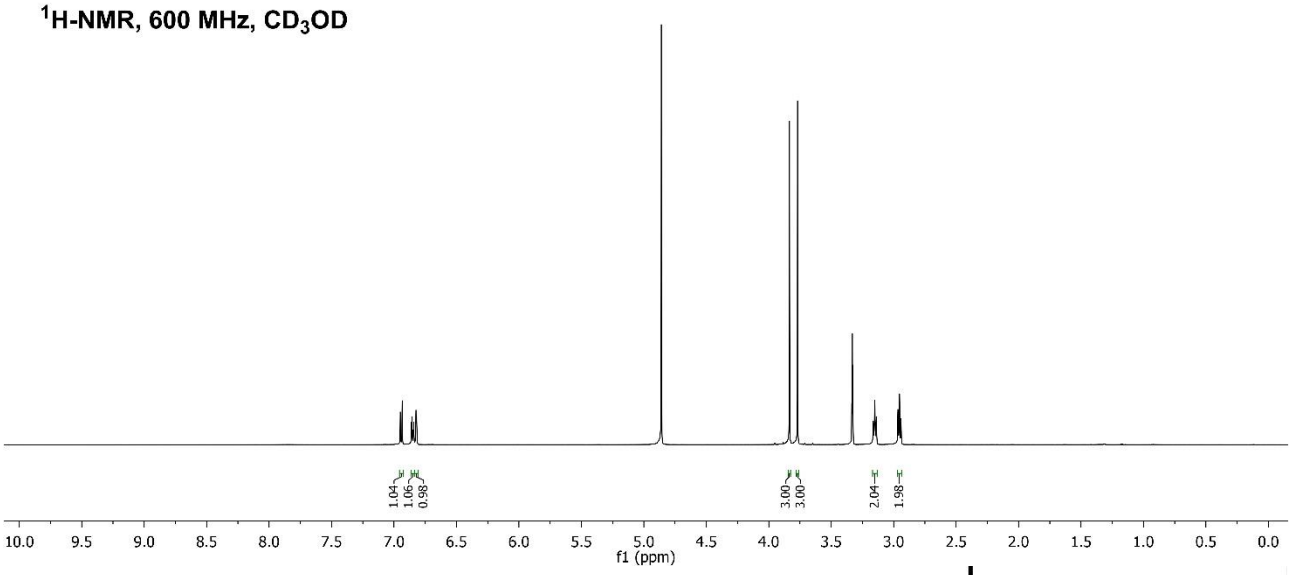


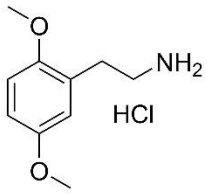


^{13}C-NMR, 151 MHz, CD_3OD

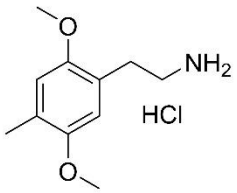


^{1}H-NMR, 600 MHz, CD_3OD

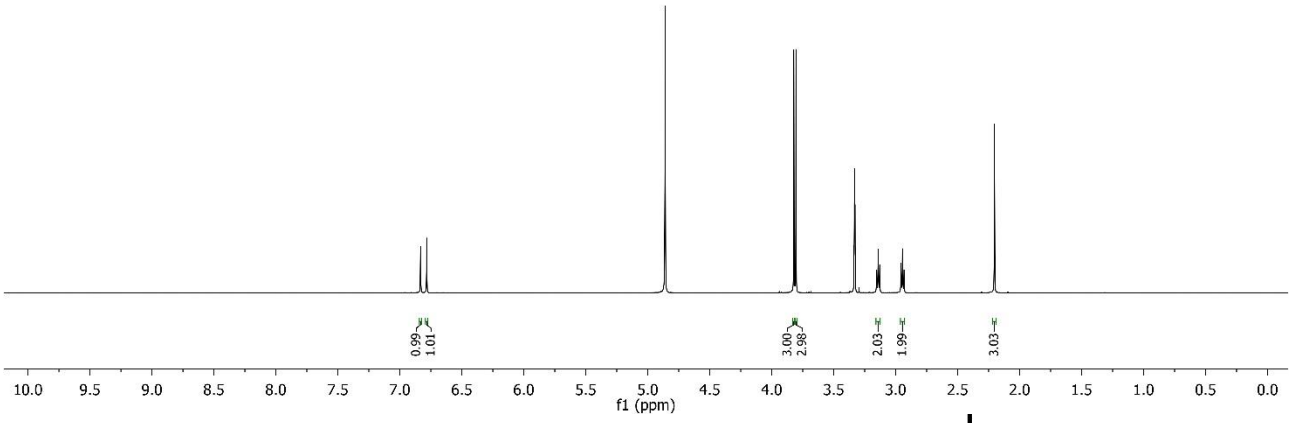


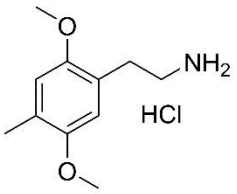


^{13}C-NMR, 151 MHz, CD_3OD

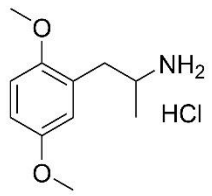


^{1}H-NMR, 600 MHz, CD_3OD

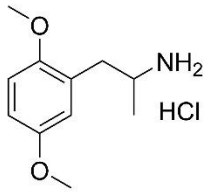




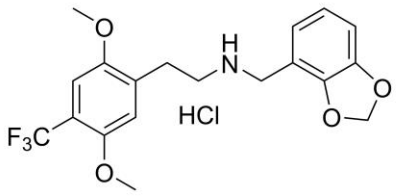
^{13}C-NMR, 151 MHz, CD_3OD



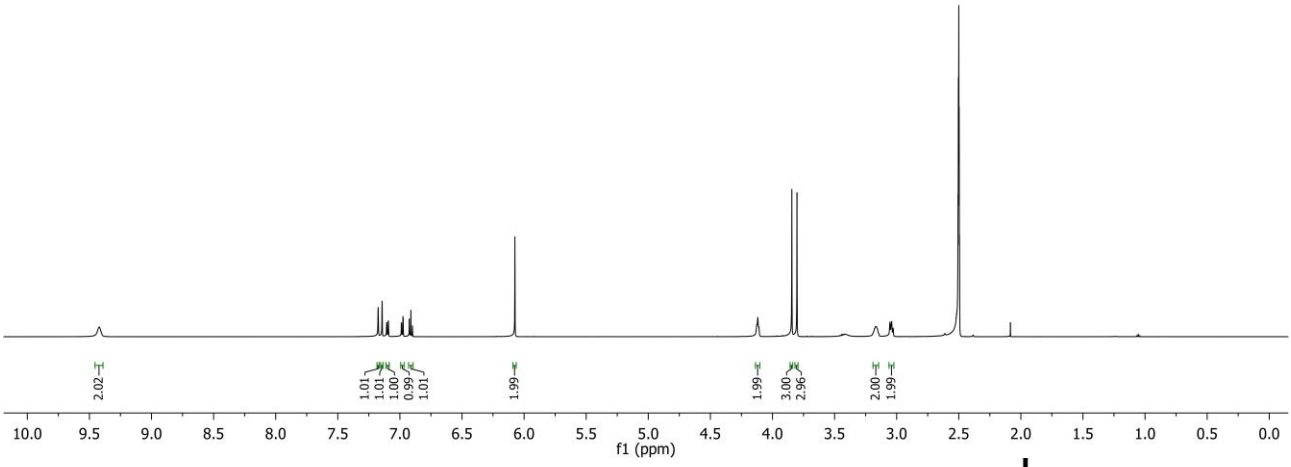
^{1}H-NMR, 600 MHz, CD_3OD

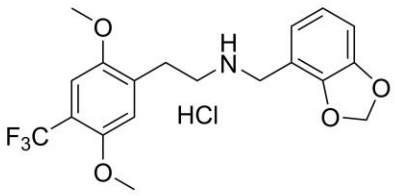


^{13}C-NMR, 151 MHz, CD_3OD

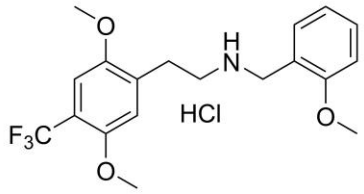


^{1}H-NMR, 600 MHz, DMSO

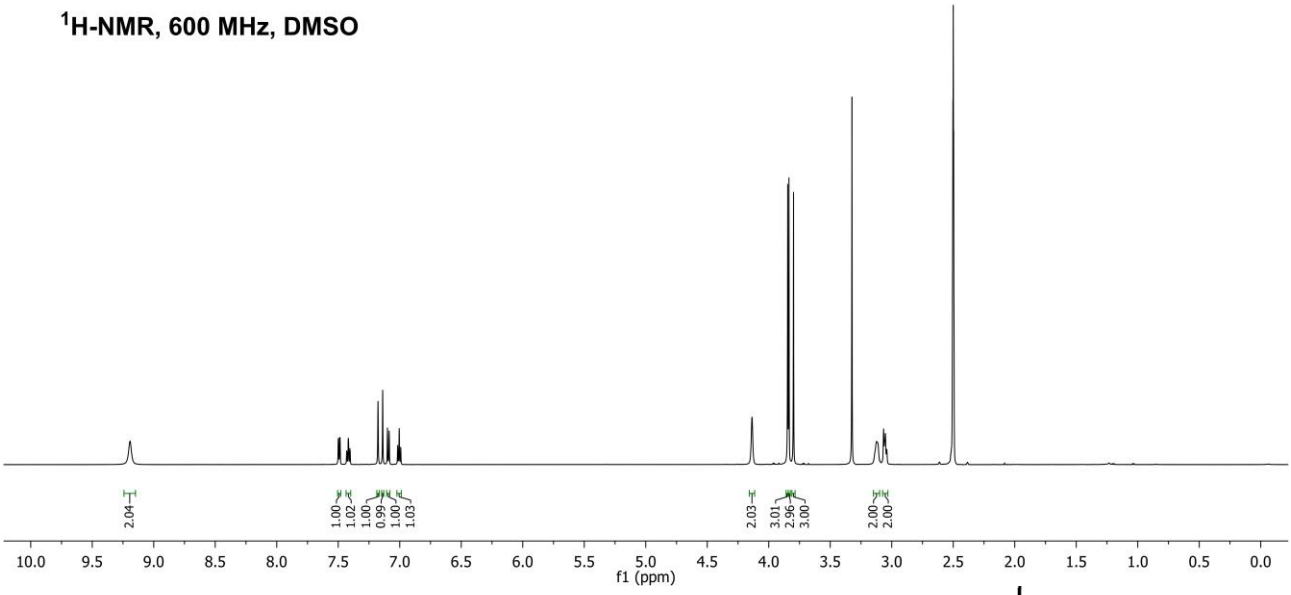


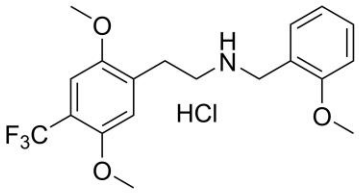


^{13}C-NMR, 151 MHz, DMSO

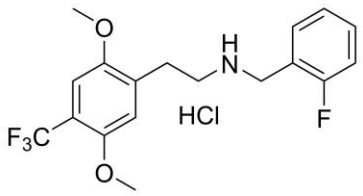


^{1}H-NMR, 600 MHz, DMSO

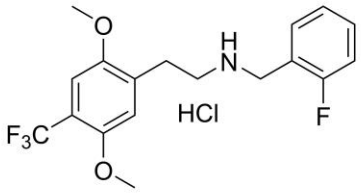




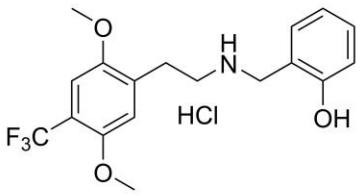
^{13}C-NMR, 151 MHz, DMSO



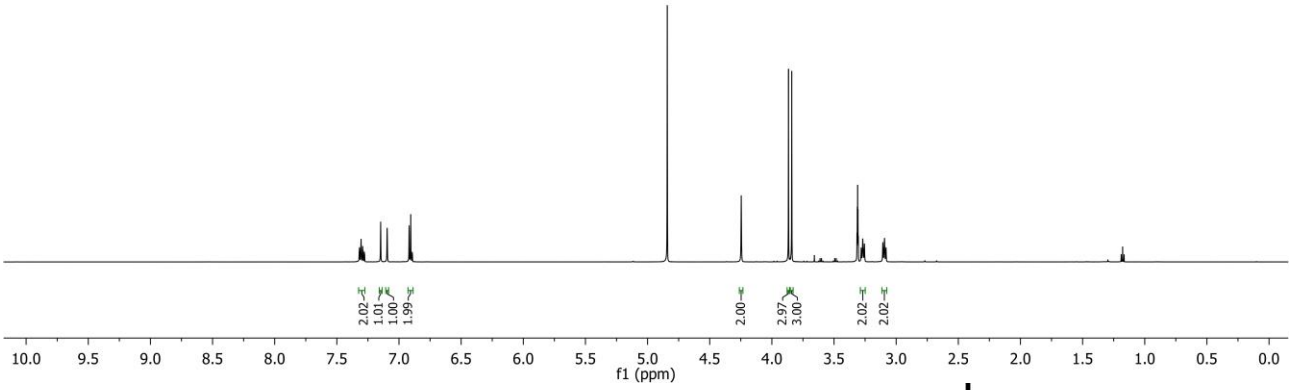
^{1}H-NMR, 600 MHz, DMSO

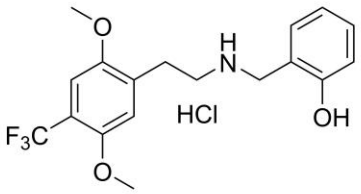


^{13}C-NMR, 151 MHz, DMSO



^{1}H-NMR, 600 MHz, CD_3OD





^{13}C-NMR, 151 MHz, CD_3OD