Lead Optimization for Discovery of Potent and Selective Dopamine Receptor D_4 Antagonist

By

Andrea Lindsey McCollum

Thesis

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

in

Chemistry

December, 2015

Approved:

Craig Lindsey

Steve Townsend

ACKNOWLEDGEMENTS

The work in this manuscript would not have been possible without the contributions and support of many individuals. I would first like to thank my mentor, Craig Lindsley, to whom I owe a debt of gratitude for allowing me to train under his guidance. I would like to thank the members of the Lindsley lab, especially Kayla Temple, Pedro Garcia and Kellie Nance, for their intellectual guidance and happy memories throughout the last year. I would also like to thank my family for their everlasting love and support. Lastly, I would like to thank my committee: Craig Lindsley, Gary Sulikowski and Steve Townsend.

LIST OF TABLES

LIST OF FIGURES

Figure Page

LIST OF SCHEMES

Scheme Page

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Dopamine Receptors and Dopaminergic Signaling Pathways

In the late 1950's, Carlsson reported dopamine as a potential neurotransmitter associated with natural reward.[1,2] Shortly after, Parkinson's disease was found to be caused by deficient dopamine concentrations in two of the three regions of the basal ganglia (putamen and caudate nucleus). This lead to the treatment of Parkinson disease by replacement therapy using levadopa, a metabolic precursor to dopamine.[3] Dopamine is in a class of slow acting neurotransmitters meaning it induces a cascade of biochemical reactions making it vital to long lasting regulation.[4,5]

Dopamine modulates the signaling pathway of target neurons by changes in the various neuronal processing mechanisms and alteration of synaptic plasticity, which is a synapse's ability to strengthen or weaken from changes in activity. Voltage-gated ion channels are regulated by dopamine through phosphorylation by protein kinase A (PKA) of these channels or proteins of interest. Dopamine increases the phosphorylation of certain transcription factors which in turn, increases activity and expression of immediate early genes activating the expression of late genes. These late genes are believed to be key in long term modulation of synaptic plasticity induced by dopamine.[6] It was known that dopamine receptors were targets of neuroleptic agents; however, two distinctive types of dopamine receptors were classified once was revealed that neuroleptic compounds were acting as antagonists towards certain dopamine receptors.[5] The two classes are D_1 and D_2 which respectively stimulate and inhibit adenylyl cyclase. When these receptors were cloned, further subtypes of dopamine receptors were identified: D_1-like receptors (D_1 and D_5) and D_2 like receptors (D_2, D_3, and D_4).[6]

D_1 like receptors are coupled to $G\alpha_{s/olf}$ proteins and can increase the production of cyclic AMP. D2 like receptors have the opposite effect; they too are associated with $G\alpha_{i/o}$ proteins, but inhibit the production of cAMP. Dopamine receptor modulate cAMP production, therefore regulating proteins activated by cAMP e.g. PKA.[7]

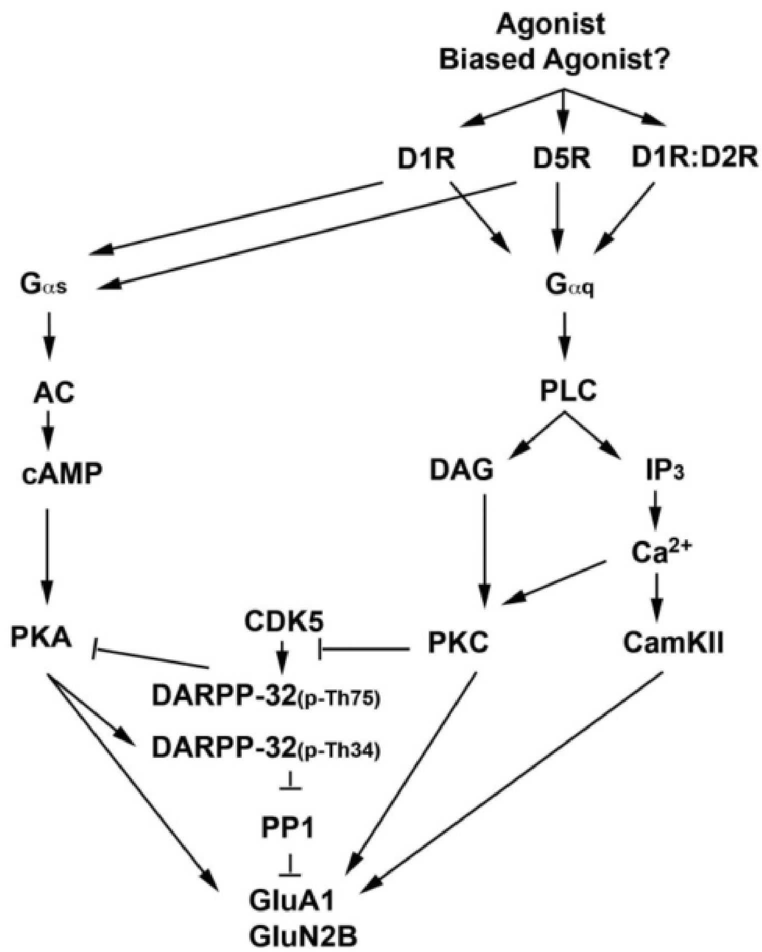


Figure 1. Dopamine D_1 receptor (D1R) activation of signaling cascades inducing production of cAMP. D5R and D1R: D2R are dopamine D_5 receptor and dopamine D1-D2 receptor heteromer respectively [8]

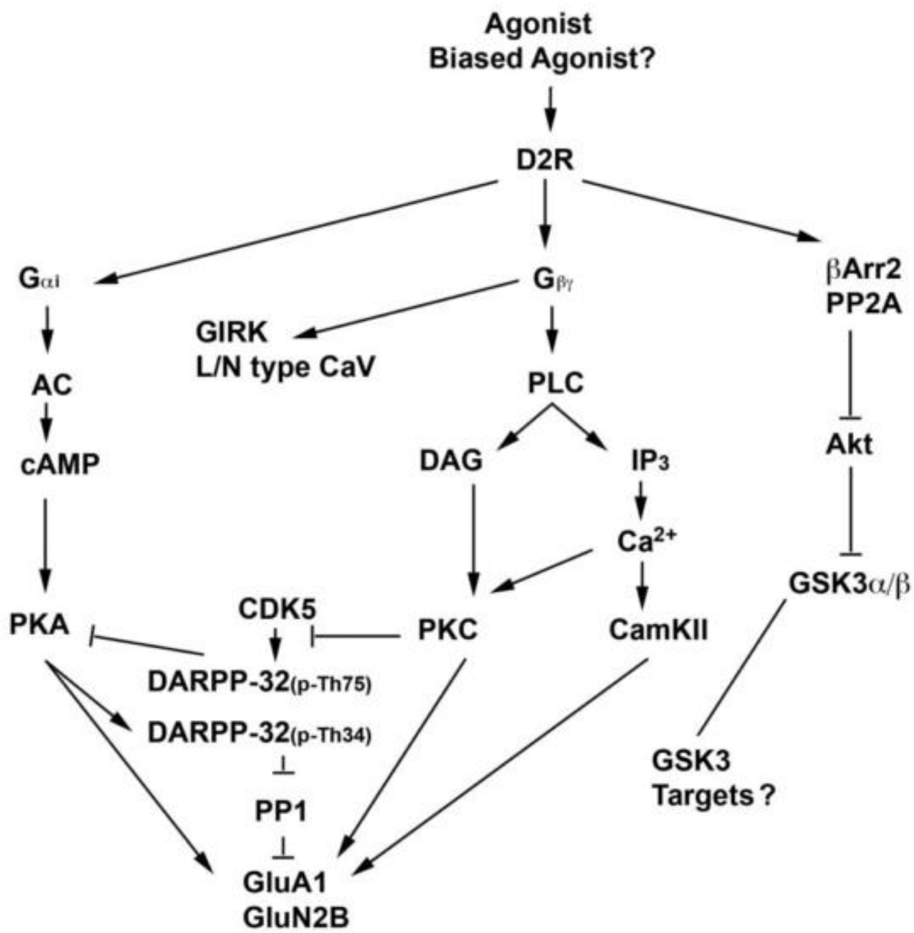


Figure 2. Dopamine D_2 receptor (D2R) activation of signaling cascades inducing inhibition of cAMP.[8]

The multifunctional dopamine and cAMP-regulated phosphoprotein (DARPP-32/PPP1R1B) is one of many PKA substrates. Phosphorylation of this substrate by PKA results in DARPP-32 responding as a negative regulator of protein phosphatase 1 (PP1). Phosphorylation by cyclin-dependent kinase 5 (CDK5) inhibits PKA in a response to D1 receptor activation. (**Figure 1 and 2**).[8] PKA and DARPP-32 play important roles in dopaminergic signaling; evidence suggest contribution of PKA and DARPP-32 to dopamine receptor physiological function.[9,10]

1.2 Dopamine D_4 Receptor

D_4 is unique from other dopamine receptors in that it exhibits an atypical polymorphism in exon 3 consisting of an open reading frame with 48 base pairs that is repeated in tandem up to ten times per allele.[11,12] These polymorphisms can be translated producing receptors that differ from each other by as many as 128 amino acids.[13] These variable receptor proteins are responsible for and have unique effects on the coupling of G proteins. It was important to characterize pharmacological profile and identify second messenger coupling for D_4 as a putative G protein coupled receptor. Enough protein was produced from heterologous expression to demonstrate the G coupling and found that activation of D_4 receptor opens the kir3 potassium channel, activates kinases ERK1 and 2, and lowers functional γ-aminobutryic acid type A receptor levels along with inhibition of cyclic AMP production.[14]

1.3 Localization and Therapeutic Relevance

Clozapine, an antipsychotic used for the treatment of schizophrenia, has a high affinity for D_4 receptor which spurred the initial interest in development of compounds for D_4 modulation as a treatment for schizophrenia.[15] The issue with this lies in the highly polymorphic nature of the D_4 receptor. The variations in *DRD4* gene lead to a high number of proteins of differing pharmacological and signaling properties.[1] Understanding of the role dopamine has in neuronal response elucidates its purpose in various mental ailments such as Parkinson disease, attention deficit disorder, schizophrenia and drug dependence.[6]

The location of dopamine D_4 receptor in the brain is paralleled by its function in cognitive function and memory. D_4 receptors are distributed in the amygdala and hippocampus.[16] The amygdala especially is key in the connection between learning through emotional stimuli.[16,17] D_4 receptor agonists improve performance of cognitive task.[18] Drug seeking behavior is often brought on by external stimuli which is why the D_4 receptor is the focal point regarding drug dependence.[1]

Drd4 knockout mice were used in an effort to understand D_4 receptor role in locomotion activities. It was found that the mice lacking the receptor were highly sensitive to locomotor activity induced by ethanol, methamphetamine and cocaine. Compared to the wild type counterparts, the knockout mice had elevated levels of dopamine synthesis and turnover in dorsal striata of their basal ganglia. From this study, it was concluded that dopamine D_4 receptor modulates the locomotor activities in both normal and drug stimulated mice.[19]

Hypersensitivity of D_4 deficient mice to stimulant induced hyperlocomotion demonstrated that D_4 receptor may be responsible for predisposition to addiction.[20] D_4 knockout mice and wild type have similar response to cocaine.[21] In studies of self-administration of nicotine, a D_4 antagonist (L-745,840) was shown to have no effect; this may suggest that D_4 is not in fact responsible for drug dependence; however, this is not the case.[22] L-745,840 has an affinity to D_2, D_3 and D_4 with Ki respectively 0.43, 960 and 2300 with no binding to D_1 or D_5 receptors.[23] A known issue with D_2 antagonist is that when a drug dose is decreased, rats can compensate by increasing their response rate for the decreased dosage.[24,25] D_3 and D_4 receptors do not share in this problem.[26] In a larger context, Dopamine D_4 receptors should not be viewed as targets for drug dependence as they may actually induce drug usage. Combined results from the D_4 knockout mice and D_4 receptor antagonist show that D_4 antagonists do not increase drug usage and could potentially be a target for development of therapeutic for drug addiction.[1]

Stimulant drug dependence is a prolonged relapsing condition that can be exhibited by reinstatement animal models. Reinstatement is a reliable and highly predictive animal model for stimulant dependence.[27] For this model, the animal is trained to self- administer a drug with a response. The response is then extinguished by removing the self-administered drug with no consequences.

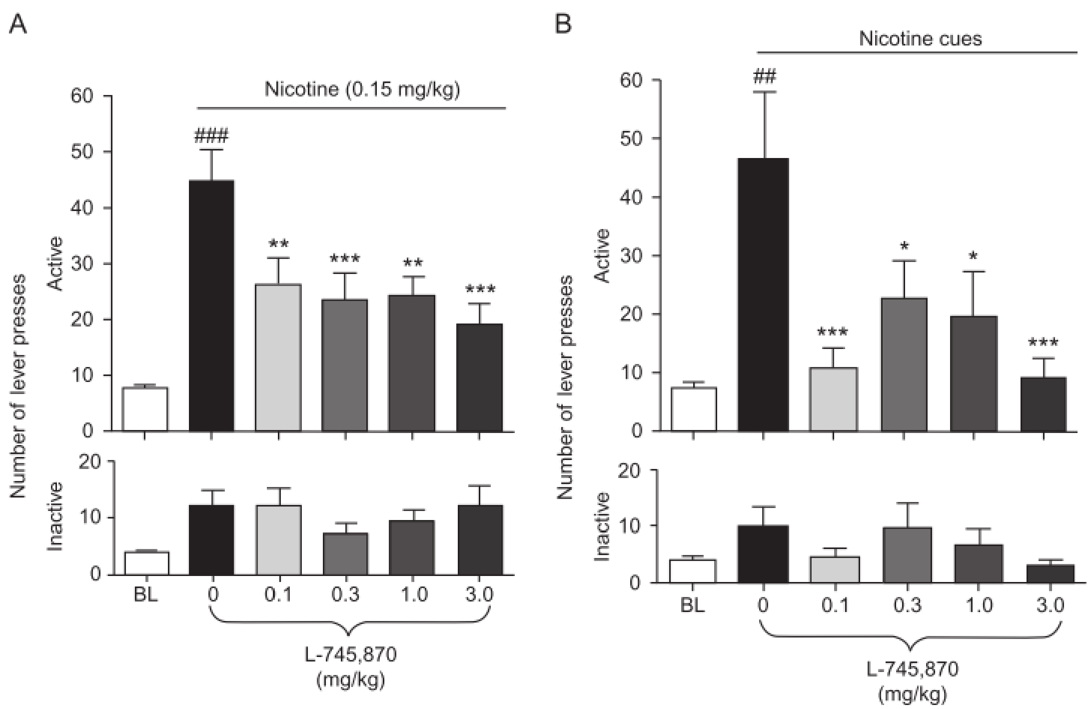


Figure 3. Effect of *DRD4* antagonist L-745,870 on the mean ± SEM reinstatement of nicotine-seeking behavior in rats. *p<0.05; **p<0.01, ***p<0.001 versus vehicle pre-treatment. Student's paired t-test ##p<0.01; ###p<0.001 versus the baseline (BL).[28]

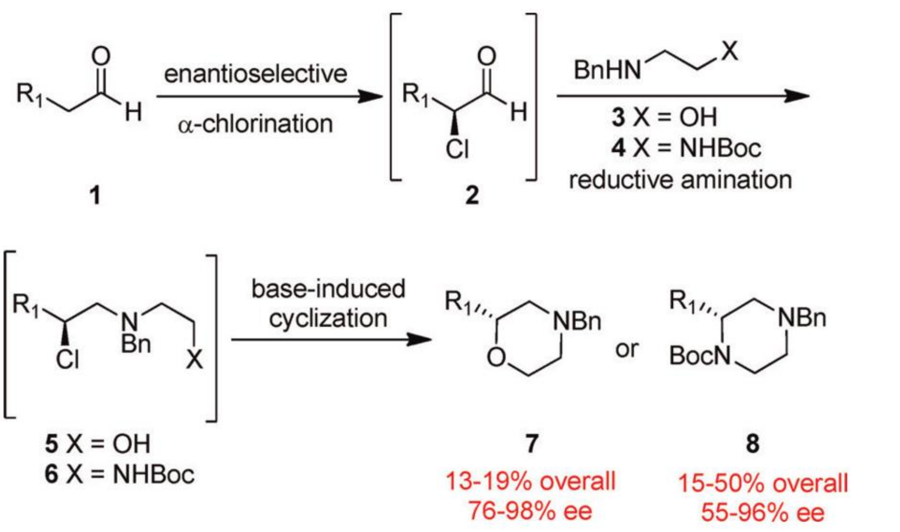
Once the response is completely extinguished, conditions are introduced which reinstates the response. A dopamine D_4 receptor antagonist, L-745, 870, is shown to interrupt the reinstatement of stimulant seeking when induced by introduction of the associated drug or cues.[28] Exposure to nicotine resulted in reinstatement of response to pre-extinguished levels; the dosing of L-745,870 significantly reduced the number of active lever presses induced by injection of nicotine (0.15 mg/kg s.c.; n=23). L-745,870 considerably diminished the number of active lever presses triggered by cues associated with nicotine (n=13) (**Figure 3**).[28] Findings from L-745,870 demonstrate that D_4 antagonist prolong abstinence and do not increase self-drug administration making D_4 antagonists viable for treatments of drug dependence. Stimulation of dopamine D_4 receptor is not rewarding on its own meaning it may not have an additive potential making another reason it is a viable target for drug dependence.[28]

CHAPTER 2

LEAD OPTIMIZATION AND CHARACTERIZATION OF DOPAMINE D_4 RECEPTOR ANTAGONISTS

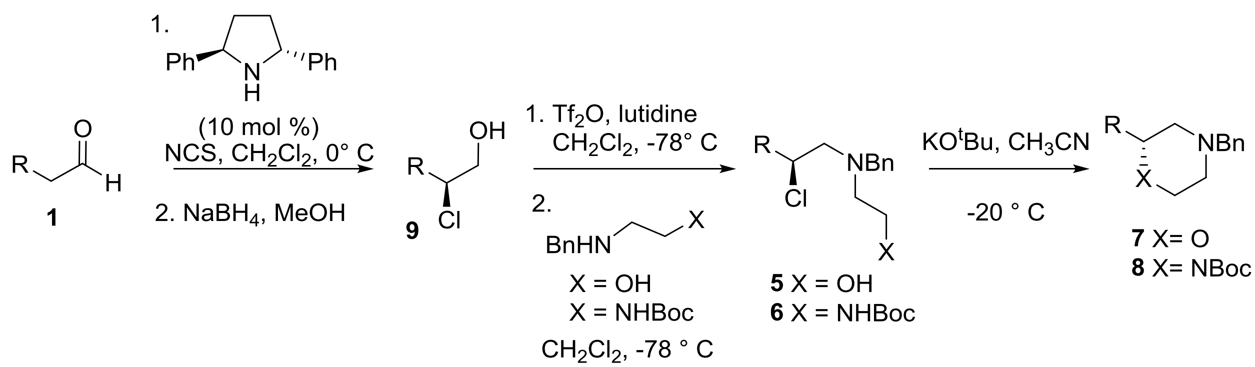
2.1 Methodology for Accessing D_4 active Chiral Morpholine Scaffold.

Methodology for enantioselective synthesis was developed as a means of accessing enantiopure C2- functionalized morpholines and piperazines using a chiral pyrrolidine catalyst. [29]



Scheme 1. Organocatalytic approach for enantioselective synthesis of benzyl protected morpholines and orthogonally protected piperazines.[29]

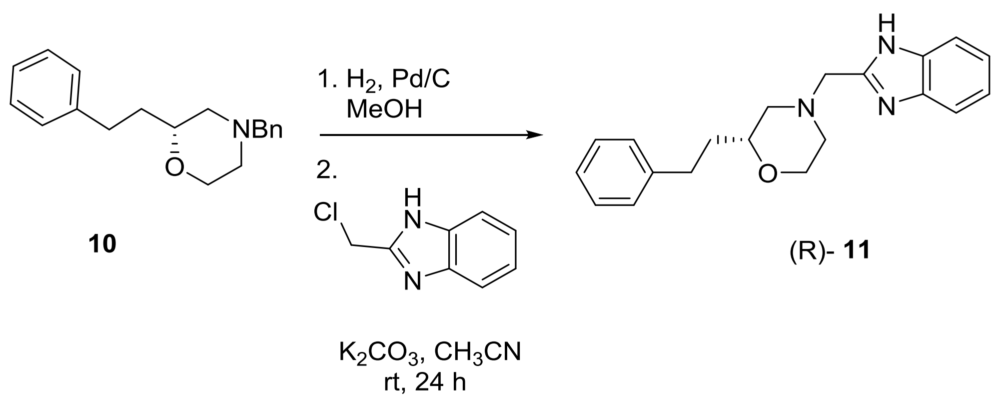
The enantioselective chlorination of aldehyde (**1**) was achieved to produce the alpha chlorinated aldehyde (**2**). No purification methods were necessary. Reductive amination gives the alcohol (**5**) or the protected amine (**6**) followed by base induced cyclization renders the final products chiral morpholine (**7**) or orthogonally protected piperazine (**8**). The three step synthetic pathway (Scheme **1**) has a few limitations. The yields were low, less than 50% in most cases. Epimerization was another drawback. The ee% is highly variable. Hemiaminal formation can further compromise product yields.[29] The restrictions with the methodology led to the use of Jørgensen methodology where the alpha chlorinated aldehyde is immediately reduced to an alcohol to prevent epimerization.[30,31]



Scheme 2. Five step synthetic pathway for achieving chiral morpholine in up to 98% ee and up to 60% overall yields.

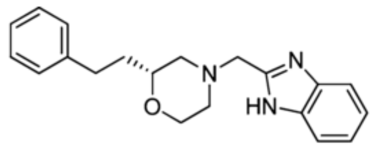
Starting with the aldehyde (**1**), enantioselective alpha chlorination was achieved by utilization of a chiral diphenylpyrrolidine. Reduction of the aldehyde with sodium borohydride produced the alcohol (**9**). The alcohol (**9**) was converted to a triflate and displaced by the benzyl protected amine to give the either the alcohol (**5**) or Boc protected amine (**6**). Deprotonation with Potassium *tert*-butoxide gives the enantiospecific chiral morpholine (**7**) or chiral piperazine (**8**) (**Scheme 2**). The overall yields for the enantiospecific cyclization ranging from 35 to 46% overall yield which is considerably better than the previous method (**Scheme 1**) with 13 to 19% overall yield.[29]

2.2 Discovery of ML398: Potent and Selective D_4 Receptor Antagonist



Scheme 3. Synthesis of chiral morpholine (**10**)**,** a reported (patented) dopamine D_4 receptor antagonist

The enantiopure morpholine synthesized previously was reported in a patent to be a specific Dopamine D_4 receptor antagonist although the potency and stereochemistry were not disclosed.[32] The morpholine analogue was subjected to evaluation against dopamine receptors (D_1 – D_4) to find that (*R*)- **11** is highly selective for subtype D_4 (Ki=0.07 μM, IC_{50}=0.18 μM).

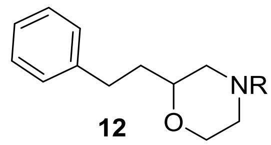


Receptor		(±)	(*S*)	(*R*)
D_1	K_i	>100	>100	>100
	IC_{50}	>100	>100	>100
D_2	K_i	>100	>100	>100
	IC_{50}	>100	>100	>100
D_3	K_i	10.8	25.9	15.7
	IC_{50}	31.8	76.4	46.2
D_4	K_i	0.14	>100	0.07
	IC_{50}	0.36	>100	0.18

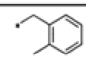
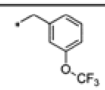
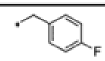
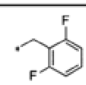
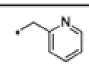
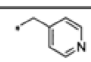
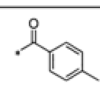
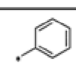
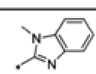
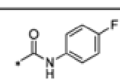
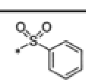
Figure 4. Initial hit of activity and structure. Values in μM.[33]

Racemic and enantiopure forms of **11** were completely inactive against D_1 and D_2 subtypes (IC_{50} = >100 μM and K_i = >100 μM). The selectivity for D_4 appears to lie completely with the (R)- enantiomer (IC_{50} = 180 nM and K_i = 70 nM). Activity against D_3 is also observed for this patented molecule. This hit lead to the use of the phenethyl morpholine scaffold to further explore the structure activity relationship and lead optimization for development of a dopamine D_4 receptor antagonist.[29] A number of analogues were made around the phenethyl morpholine scaffold and assayed against D_4 (**Table 1**).

Table 1. SAR Evaluation of the N – Morpholine Analogues[33]



12

Entry	R	D_4 (% inh. @ 10 μM)
a		94
b		98
c		97
d		54
e		88
f		88
g		74
h		51
i		23
j		35
k		13
l		17
m		5
n		17
o		5
p		2

All assays performed on human receptor.[34]

Various substituted benzyl analogues were synthesized and assayed (**12a-12h**) exhibiting up to 98% inhibition against D_4. All pyridyl derivatives were inactive (**12i-12k**). Direct arylation of the morpholine (**12m-12n**) and modification of the linker to an amide (**12l**) were inactive. The urea (**12o**) and sulfonamide (**12p**) were also not tolerated. All of this suggests that the flexibility of the between the morpholine and substituent plays a crucial factor in SAR.[33]

Table 2. IC_{50} and K_i Evaluation of Active Benzyl Analogues[33]

compd	D_4 (% inh. @ 10 μM)^a	IC_{50} (μM)	K_i (μM)
(±)-**12 a**	94	0.16	0.043
(*R*)-**12 a**	96	0.23	0.065
(±)-**12 b**	98	0.17	0.046
(*R*)-**12 b**	86	0.10	0.028
Selectivity Profile^a: >20 μM against D_1, D_{2S}, and D_5			
D_{2L}, IC_{50} = 16.5 μM; K_i = 5.5 μM			
D_3, IC_{50} = 8.17 μM; K_i = 2.77 μM			
(±)-**12 c**	97	0.29	0.081
(*R*)-**12 c**	96	0.13	0.036
Selectivity Profile^a: >20 μM against D_1, D_{2S}, D_{2L}, D_3, and D_5			
(±)-**12 d**	54	3.68	1.02
(±)-**12 e**	88	0.39	0.11
(±)-**12 f**	88	1.14	0.32
(±)-**12 g**	74	1.48	0.41
(±)-**12 h**	51	3.88	1.07

All assays performed on human receptor.[34]

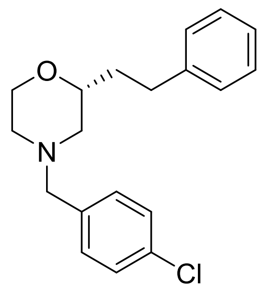
The active substituted benzyl compounds were evaluated for IC_{50} and K_i. A trend emerged. The most potent compounds contained a *meta*- or *para*-trifluoromethoxybenzyl group (**12a and 12e**), a *para*- methoxybenzyl (**12b**) or a *para*-

chlorobenzyl (**12c**). The racemic compounds (**12a – 12c**) were resolved to give the pure enantiomers of each. The enantiomerically pure analogues were evaluated and it was found that (*R*)-**12b** and (*R*)-**12c** were the most potent antagonists with the highest binding affinities. These analogues were evaluated against the full array of dopamine receptors. (*R*)-**12c** displayed the best selectivity; it was inactive (>20 μM) against other dopamine receptors. Based on the selectivity, binding affinity and potency, (*R*)-**12c** was stated to be a MLPCN probe (ML398). The DMPK properties of ML398 were determined; the compound is unstable towards oxidative metabolism and is predicted to have a higher than ideal clearance. It was also active against five other targets adrenergic, α_1A (77%); histamine, H_1 (93%); sigma, σ_1 (99%); dopamine transporter, DAT (72%); norepinephrine transporter, NET (68%). The cocaine induced hyperlocomotion assay was used to evaluate PK/PD relationship of ML398. Cocaine is known to induce hyperlocomotion meaning the cocaine is increasing the rate at which dopamine is transported; ML398 was shown to significantly reduce this locomotion. Further optimization of ML398 is necessary to address the pharmacokinetic issues with stability and clearance.[33]

CHAPTER 3

Lead Optimization of D_4 Antagonist

3.1. Chiral Phenylether Morpholine Library Synthesis

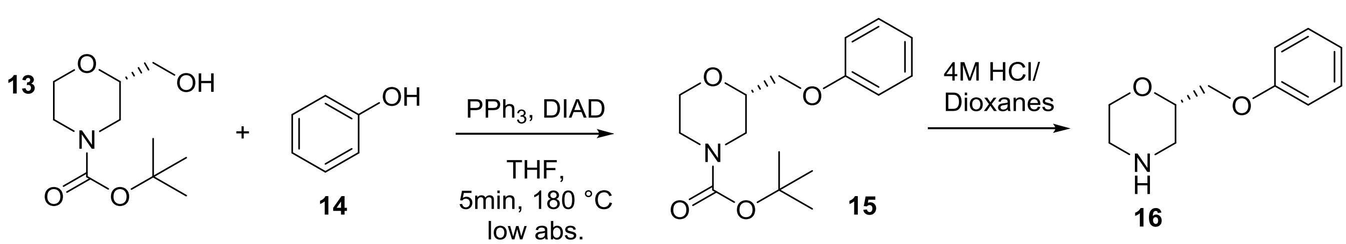


ML398: (*R*)- **12c**

Figure 5. ML398: Potent and Selective Dopamine D_4 receptor antagonist.

Starting from the lead compound, ML398, efforts have been made to further explore the SAR around the phenethyl linkage which has otherwise been uncharted. A library around a phenylether scaffold was synthesized.

Synthesis of phenyl ether scaffold



Scheme 4. General synthetic pathway phenyl ether morpholine scaffold.

The alcohol (**13)** and phenol (**14**) react under mitsunobu conditions to give Boc protected morpholine (**15**). Deprotection of the Boc- group and basic workup produced the free amine (**16**) which can be analogued as desired.

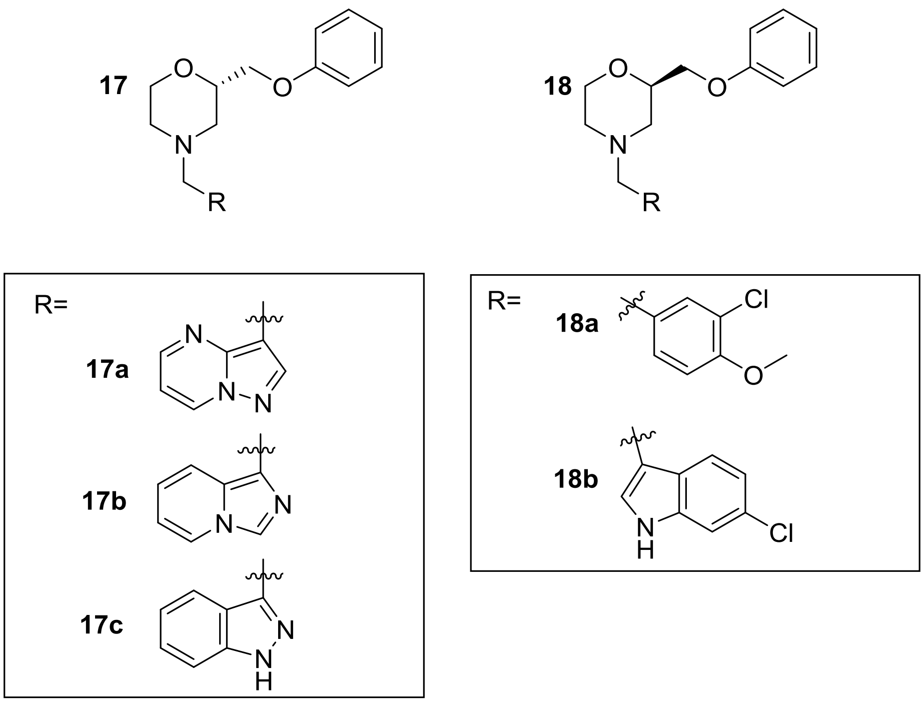
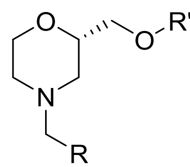


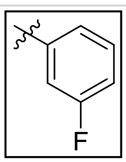
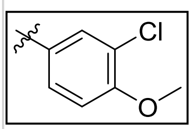
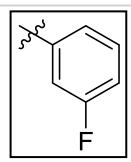
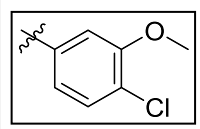
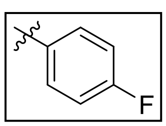
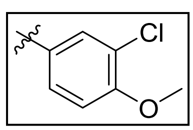
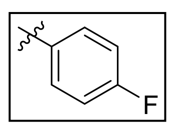
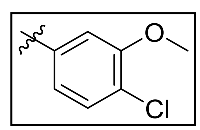
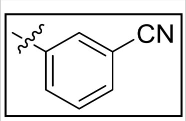
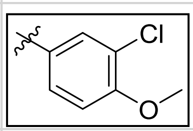
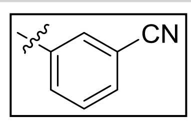
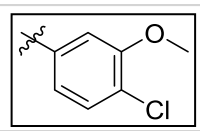
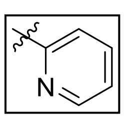
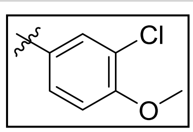
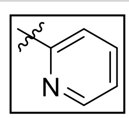
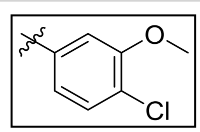
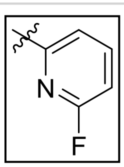
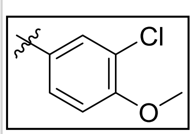
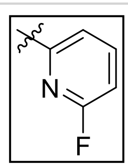
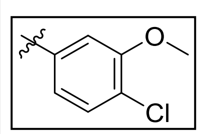
Figure 6. Analogues synthesized around chiral morpholine scaffolds with phenyl ether linkage.

Modification of the phenethyl linkage to a phenyl ether resulted to the first set of libraries to see if the ether linkage would be tolerated (**Figure 6**). The active enantiomer was previously determined to be *R* from the compounds analogued from the discovery of the ML398 probe.[33] Based on optical rotation, it was predicted that the (*S*)-enantiomer would be active in the phenyl ether series. Compound **17** was analogued giving the pyrazolopyrimidine (**17a**), imidazolopyridine (**17b**), and indazole (**17c**) derivatives. The (*R*)- enantiomer (**18**) was analogued giving the presumed inactive disubstituted benzene (**18a**) and indole (**18b**) derivatives.

Another set of libraries were synthesized with various substitutions around the phenyl ring (**Table 3**). Substitution at the *meta*- position of the phenyl with a fluorine afforded two analogues (**19** and **20**). Fluorine at the *para*- position resulted in a new scaffold that was further analogued to give two compounds (**21** and **22**). Two analogues were made with a *para* – cyano group (**23** and **24**).

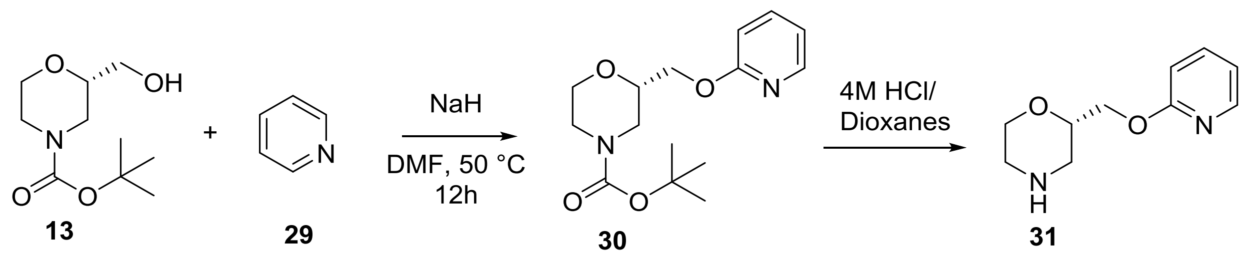
Table 3. List of synthesized N- Morpholine analogues with varying head and tail groups



Entry	R'	R	Entry	R'	R
19			**20**		
21			**22**		
23			**24**		
25			**26**		
27			**28**		

To further explore the structure activity relation, the phenyl ring was modified to a pyridine. The pyridine ether scaffold afforded two analogues (**25** and **26**); 2-fluoropyridinyl also gave two analogues (**27** and **28**). The substituted phenol scaffolds were all synthesized under the general mitsunobu conditions (**Scheme 4**); however the pyridine scaffolds were afforded under alternative conditions.

Synthesis of Pyridinylether Scaffold

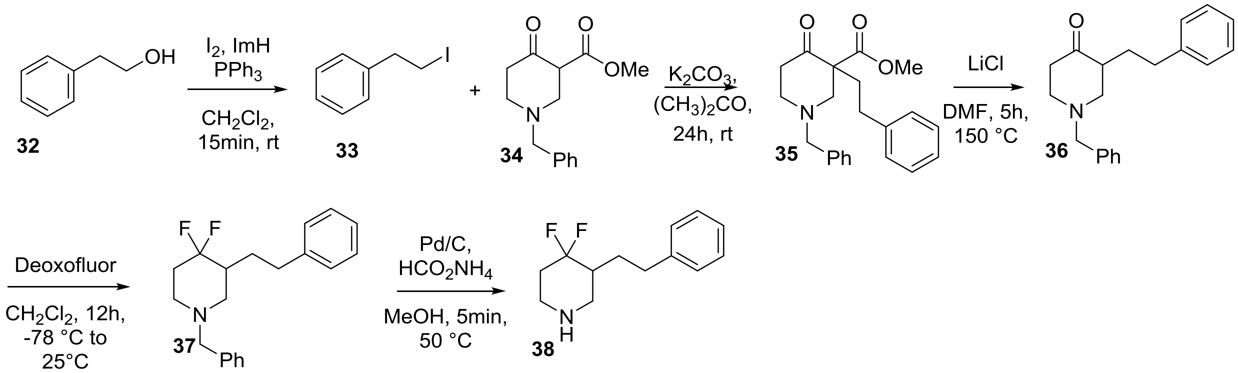


Scheme 5. General synthetic pathway for pyridinyl ether morpholine scaffold

The alcohol (**13)** and pyridine (**29**) react under nucleophilic aromatic substitution conditions to give boc protected morpholine (**30**). Deprotection of the Boc- group and basic workup produced the free amine (**31**) which can be analogued as desired.

3.2 Chiral Pyridinyether Morpholine Library Synthesis

Issues with the morpholine analogues lie with the stability and pharmacokinetic properties. In an effort to eliminate susceptibility to reductive processes and improve metabolic stability, a difluoropiperidine scaffold was explored.

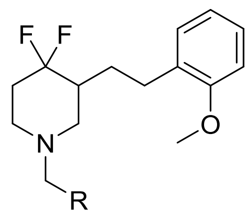
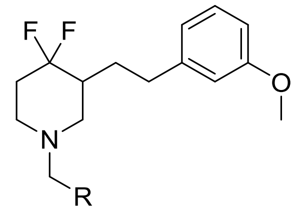


Scheme 6. General synthetic pathway for difluoropiperidine scaffolds

The synthesis is a five step pathway to get to the scaffold of interest (**Scheme 6**). Appel Iodination of the alcohol gives the iodide (**33**) used for alkylation to arrive at the carboxylate ester (**35)**. A Krapcho Decarboxylation gives the ketone (**35**) which can be fluorinated to provide benzyl protected amine (**37**). Hydrogenation to cleave the benzyl group produces the free amine (**38**) that can undergo reductive aminations to make various racemic analogues (**Table 4-6**).

From the data available, it appears the fluoro- substitution on the phenyl ring is well tolerated. The 6-fluoro indole tail has the highest inhibition of all the derivatives. Chiral resolution and pharmacokinetic data is needs to be acquired of the analogues with >85% D_4 inhibition (**Table 4-6**).

Table 4. SAR Evaluation of 2-methoxy and 3-methoxy difluoropiperidine analogues.

39  **40** 

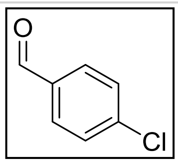
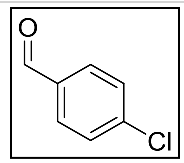
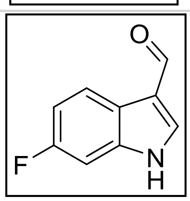
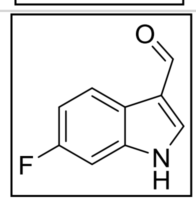
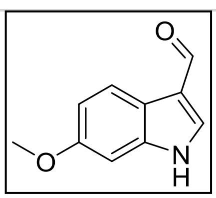
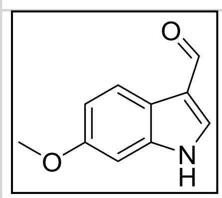
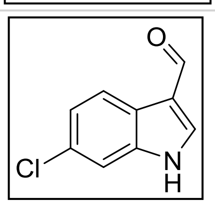
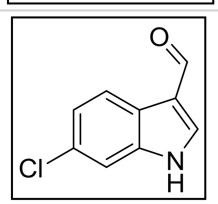
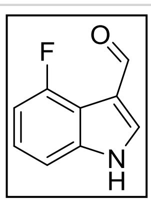
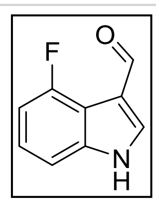
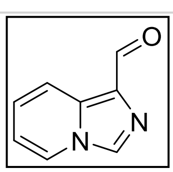
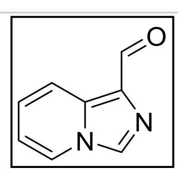
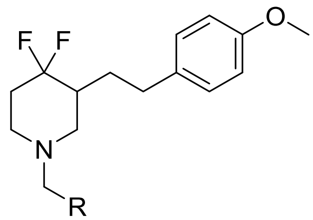
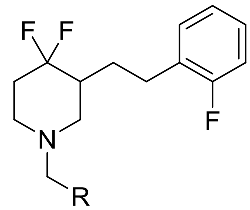
Entry	R	D_4 (% Inh. @ 10 µM)	Entry	R	D_4 (% Inh. @ 10 µM)
39a		NA	**40a**		67
39b		94	**40b**		88
39c		NA	**40c**		NA
39d		94	**40d**		85
39e		NA	**40e**		NA
39f		NA	**40f**		66

Table 5. SAR Evaluation of 4-methoxy and 2-fluoro difluoropiperidine analogues.

41 

42 

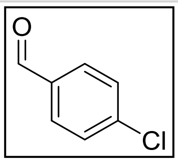
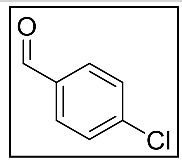
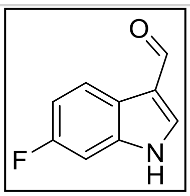
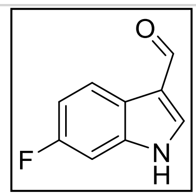
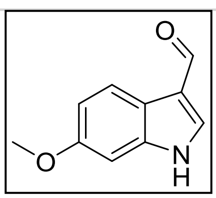
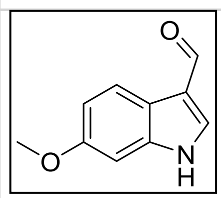
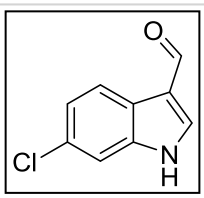
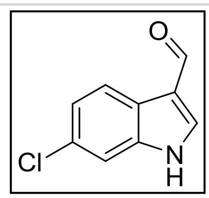
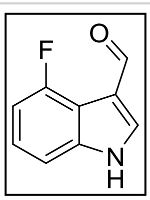
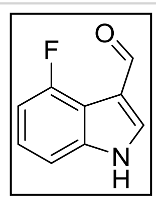
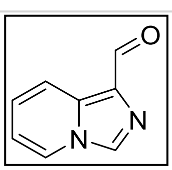
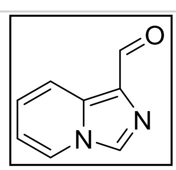
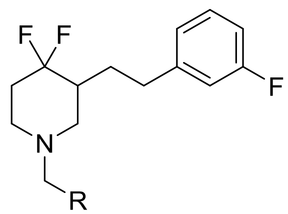
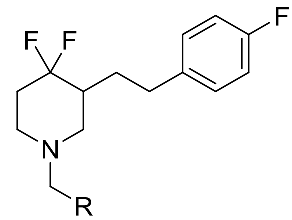
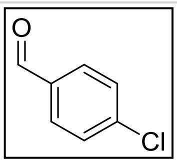
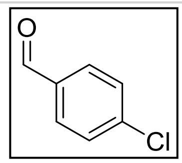
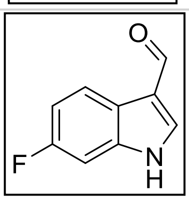
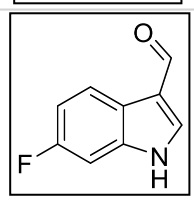
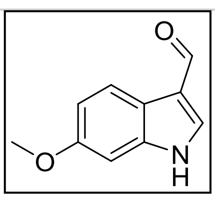
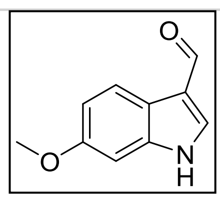
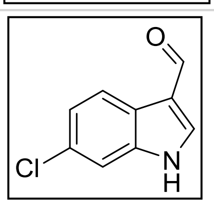
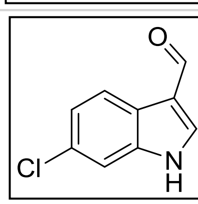
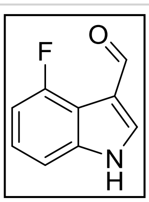
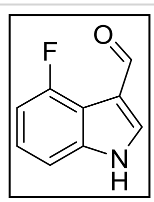
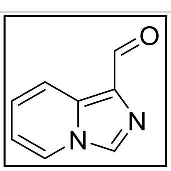
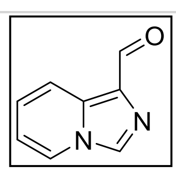
Entry	R	D_4 (% Inh. @ 10 μM)	Entry	R	D_4 (% Inh. @ 10 μM)
41a		83	**42a**		92
41b		91	**42b**		95
41c		93	**42c**		95
41d		88	**42d**		93
41e		NA	**42e**		62
41f		84	**42f**		92

Table 6. SAR Evaluation of 3-fluoro and 4-fluoro difluoropiperidine analogues.

43  **44** 

Entry	R	D_4 (% Inh. @ 10 μM)	Entry	R	D_4 (% Inh. @ 10 μM)
43a		85	**44a**		95
43b		92	**44b**		94
43c		93	**44c**		89
43d		94	**44d**		93
43e		59	**44e**		84
43f		78	**44f**		97

CHAPTER 4

EXPERIMENTAL

4.1 Materials and Methods

Contents:

1-(2-iodoethyl)-2-methoxybenzene

1-(2-iodoethyl)-3-methoxybenzene

1-(2-iodoethyl)-3-methoxybenzene

1-(2-iodoethyl)-4-methoxybenzene

1-fluoro-2-(2-iodoethyl) benzene

1-fluoro-3-(2-iodoethyl) benzene

1-fluoro-4-(2-iodoethyl) benzene

1-benzyl-3-(2-methoxyphenethyl) piperidin-4-one

1-benzyl-3-(3-methoxyphenethyl) piperidin-4-one

1-benzyl-3-(4-methoxyphenethyl) piperidin-4-one

1-benzyl-3-(2-fluorophenethyl) piperidin-4-one

1-benzyl-3-(3-fluorophenethyl) piperidin-4-one

1-benzyl-3-(4-fluorophenethyl) piperidin-4-one

1-benzyl-4,4-difluoro-3-(2-methoxyphenethyl) piperidine

1-benzyl-4,4-difluoro-3-(3-methoxyphenethyl) piperidine

1-benzyl-4,4-difluoro-3-(4-methoxyphenethyl) piperidine

1-benzyl-4,4-difluoro-3-(2-fluorophenethyl)piperidine

1-benzyl-4,4-difluoro-3-(3-fluorophenethyl)piperidine

1-benzyl-4,4-difluoro-3-(4-fluorophenethyl)piperidine

4,4-difluoro-3-(2-methoxyphenethyl)piperidine

4,4-difluoro-3-(3-methoxyphenethyl)piperidine

4,4-difluoro-3-(4-methoxyphenethyl)piperidine

4,4-difluoro-3-(2-fluorophenethyl)piperidine

4,4-difluoro-3-(3-fluorophenethyl)piperidine

4,4-difluoro-3-(4-fluorophenethyl)piperidine

tert-butyl (S)-2-(phenoxymethyl)morpholine-4-carboxylate

tert-butyl (S)-2-((3-fluorophenoxy)methyl)morpholine-4-carboxylate

tert-butyl (S)-2-((4-fluorophenoxy)methyl)morpholine-4-carboxylate

tert-butyl (S)-2-((3-cyanophenoxy)methyl)morpholine-4-carboxylate

1-(4-chlorobenzyl)-4,4-difluoro-3-(2-methoxyphenethyl)piperidine

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(2fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(4-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((6-methoxy-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((6-methoxy-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

3-((4,4-difluoro-3-(4-fluorophenethyl)piperidin-1-yl)methyl)-6-methoxy-1H-indole

6-chloro-3-((4,4-difluoro-3-(3-methoxyphenethyl)piperidin-1-yl)methyl)-1H-indole

6-chloro-3-((4,4-difluoro-3-(4-methoxyphenethyl)piperidin-1-yl)methyl)-1H-indole

6-chloro-3-((4,4-difluoro-3-(2-fluorophenethyl)piperidin-1-yl)methyl)-1H-indole

6-chloro-3-((4,4-difluoro-3-(4-fluorophenethyl)piperidin-1-yl)methyl)-1H-indole

3-((4,4-difluoro-3-(2-methoxyphenethyl)piperidin-1-yl)methyl)-4-fluoro-1H-indole

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(2-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(3-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate
4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(4-fluorophenethyl)piperidin-1-ium2,2,2-trifluoroacetate

4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylmethyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylmethyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-3-(2-fluorophenethyl)-1-(imidazo[1,5-a]pyridin-1-ylmethyl)piperidin-1-ium 2,2,2-trifluoroacetate

4,4-difluoro-3-(4-fluorophenethyl)-1-(imidazo[1,5-a]pyridin-1-ylmethyl)piperidin-1-ium 2,2,2-trifluoroacetate

(S)-2-(phenoxymethyl)-4-(pyrazolo[1,5-a]pyrimidin-3-ylmethyl)morpholine

(S)-4-(imidazo[1,5-a]pyridin-1-ylmethyl)-2-(phenoxymethyl)morpholine

(S)-4-((1H-indazol-3-yl)methyl)-2-(phenoxymethyl)morpholine

(S)-4-(3-chloro-4-methoxybenzyl)-2-((4-fluorophenoxy)methyl)morpholine

(S)-4-(4-chloro-3-methoxybenzyl)-2-((4-fluorophenoxy)methyl)morpholine

(S)-3-((4-(4-chloro-3-methoxybenzyl)morpholin-2-yl)methoxy)benzonitrile

General. NMR spectra were obtained on a Bruker 400 MHz instrument. Data reported as follows: chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, q=quartet, br=broad, m=multiplet), integration, coupling constant (Hz). Low resolution mass spectra were obtained on an Agilent 1200 series 6130 mass spectrometer with electrospray ionization. High resolution mass spectra were obtained from a Waters Q-TOF API-US. Sorbtech silica gel GF 250 micron plates were used for analytical thin layer chromatography.

Synthesis of aryl ethyl iodides:

1-(2-iodoethyl)-2-methoxybenzene. To a solution of 2-(2-methoxyphenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (4.92g, 72.3mmol), and triphenyl phosphine (18.95g, 72.3 mmol). The Iodine (21.68g, 85.4 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (11.6 g, 67.4% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.25 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H), 7.13 (dd, J = 7.4, 1.7 Hz, 1H), 6.98 – 6.84 (m, 2H), 3.84 (s, 3H), 3.41 – 3.32 (m, 2H), 3.16 (dd, J = 8.4, 7.2 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 158.70, 131.16, 130.03, 129.26, 121.44, 111.53, 55.72, 49.25, 36.62, 4.80.

1-(2-iodoethyl)-3-methoxybenzene. To a solution of 2-(3-methoxyphenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (4.92g, 72.3mmol), and triphenyl phosphine (18.95g, 72.3 mmol). The Iodine (21.68g, 85.4 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (13.15g, 76.4% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.22 (t, J = 8.1 Hz, 1H), 6.86 – 6.77 (m, 3H), 3.79 (s, 3H), 3.40 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 161.24, 143.54, 130.49, 121.66, 115.03, 113.14, 55.58, 49.14, 41.37, 5.77.

1-(2-iodoethyl)-3-methoxybenzene. To a solution of 2-(3-methoxyphenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (4.92g, 72.3mmol), and triphenyl phosphine (18.95g, 72.3 mmol). The Iodine (21.68g, 85.4 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (13.15g, 76.4% yield).

1-(2-iodoethyl)-4-methoxybenzene. To a solution of 2-(4-methoxyphenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (4.92g, 72.3mmol), and triphenyl phosphine (18.95g, 72.3 mmol). The Iodine (21.68g, 85.4 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution.

The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (11.33g, 65.8% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.18 – 7.11 (m, 2H), 6.90 – 6.81 (m, 2H), 3.79 (s, 3H), 3.42 – 3.30 (m, 2H), 3.09 (t, J = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 159.94, 134.24, 130.40, 114.91, 55.65, 40.58, 6.69.

1-fluoro-2-(2-iodoethyl) benzene. To a solution of 2-(2-fluorophenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (5.35g, 78.5mmol), and triphenyl phosphine (20.59g, 78.5 mmol). The Iodine (21.75g, 85.68 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (15.17g, 84.9% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 – 7.22 (m, 2H), 7.18 – 7.01 (m, 2H), 3.45 – 3.36 (m, 2H), 3.22 (t, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 163.53, 161.10, 131.95, 131.91, 129.85, 129.77, 128.82, 128.65, 125.33, 125.29, 116.36, 116.14, 34.55, 34.53, 3.84, 3.82.

1-fluoro-3-(2-iodoethyl) benzene. To a solution of 2-(3-fluorophenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (5.35g, 78.5mmol), and triphenyl phosphine (20.59g, 78.5 mmol). The Iodine (21.75g, 85.68 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (14.7g, 82.4% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 – 7.26 (m, 1H), 7.05 (ddd, J = 7.6, 1.8, 1.1 Hz, 1H), 6.98 (ddd, J = 9.0, 6.7, 1.1 Hz, 2H), 3.42 (m, 2H), 3.17 (t, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 165.48, 163.04, 144.74, 144.66, 131.19, 131.11, 125.33, 125.30, 116.23, 116.02, 114.48, 114.27, 40.69, 5.27.

1-fluoro-4-(2-iodoethyl) benzene. To a solution of 2-(4-fluorophenyl)ethan-1-ol (10g, 65.7mmol) in methylene chloride (100 mL) was added imidazole (5.35g, 78.5mmol), and triphenyl phosphine (20.59g, 78.5 mmol). The Iodine (21.75g, 85.68 mmol) was added gradually over 5 minutes. The solution stirred at room temperature until full conversion was observed via TLC at 30 minutes. The reaction mixture was diluted with methylene chloride was washed with saturated sodium thiosulfate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was diluted in 2:1 diethyl ether: hexanes and filtered and concentrated *in vacuo* to give a residue, which was purified via column chromatography (ISCO combiflash) using 5% ethyl acetate in hexanes to afford the iodide (14.47g, 81.1% yield). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.29 – 7.18 (m, 2H), 7.08 – 6.95 (m, 2H), 3.39 (m, 2H), 3.14 (t, J = 7.5

Hz, 2H); ^{13}C NMR (101 MHz, Methanol-d4) δ 164.29, 161.87, 138.01, 137.98, 131.18, 131.10, 116.18, 115.97, 48.83, 40.27, 6.13.

Synthesis of Substituted 1-benzyl-3-phenthylpiperidin-4-one derivatives:

1-benzyl-3-(2-methoxyphenethyl) piperidin-4-one. To a solution of 1-(2-iodoethyl)-2-methoxybenzene (11.6g, 44.3 mmol) in acetone (150mL) was added potassium carbonate (14.12g, 102.2 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (9.66g, 34.1 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(2-methoxyphenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (6.054 g, 15.88 mmol) was added to DMF (150 mL). Lithium Chloride (6.73 g, 158 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(2-methoxyphenethyl) piperidin-4-one (1.066g, 20.8% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 – 7.25 (m, 5H), 7.16 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H), 7.02 (dd, J = 7.4, 1.7 Hz, 1H), 6.98 – 6.76 (m, 2H), 3.78 (s, 3H), 3.71 – 3.56 (m, 2H), 3.15 – 2.98 (m, 2H), 2.67 – 2.42 (m, 5H), 2.42 – 2.32 (m, 1H), 2.24 (dd, J = 11.3, 10.0 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.52 – 1.39 (m, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.81, 158.88, 139.18, 131.10, 130.89, 130.31, 129.42, 128.47, 128.34, 121.48, 111.43, 62.64, 59.67, 55.68, 54.82, 49.91, 41.59, 28.72, 28.45, 23.70.

1-benzyl-3-(3-methoxyphenethyl) piperidin-4-one. To a solution of 1-(2-iodoethyl)-3-methoxybenzene (13.15g, 50.2 mmol) in acetone (150mL) was added potassium carbonate (16.01g, 115.8 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (10.96g, 38.6 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(3-methoxyphenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (7.49 g, 19.7 mmol) was added to DMF (150 mL). Lithium Chloride (8.33 g, 196.5 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(3-methoxyphenethyl) piperidin-4-one (2.17g, 34.17% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.25 (m, 5H), 7.22 – 7.11 (m, 1H), 6.77 – 6.66 (m, 3H), 3.77 (s, 3H), 3.64 (d, J = 4.6 Hz, 2H), 3.14 – 3.00 (m, 2H), 2.66 – 2.42 (m, 5H), 2.42 – 2.29 (m, 1H), 2.23 (dd, J = 11.3, 10.1 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.58 – 1.43 (m, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.53, 161.24, 144.62, 139.17, 130.36, 130.28, 129.44, 128.47, 121.75, 115.02, 112.34, 101.38, 62.58, 59.46, 55.53, 54.79, 49.50, 41.62, 34.07, 30.09.

1-benzyl-3-(4-methoxyphenethyl) piperidin-4-one. To a solution of 1-(2-iodoethyl)-4-methoxybenzene (11.33g, 43.3 mmol) in acetone (150mL) was added potassium carbonate (13.79 g, 99.8 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (9.44g, 33.27 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(4-methoxyphenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (6.245 g, 16.4 mmol) was added to DMF (150 mL). Lithium Chloride (6.95 g, 163.8 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(4-methoxyphenethyl) piperidin-4-one (1.97 g, 37.21% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.26 (m, 5H), 7.02 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 3.77 (s, 3H), 3.64 (d, J = 1.9 Hz, 2H), 3.06 (m, 2H), 2.64 – 2.42 (m, 5H), 2.41 – 2.29 (m, 1H), 2.22 (t, J = 10.7 Hz, 1H), 2.12 – 1.98 (m, 1H), 1.54 – 1.40 (m, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.59, 159.38, 139.21, 134.96, 130.28, 130.26, 129.42, 128.47, 114.82, 101.38, 62.58, 59.37, 55.62, 54.81, 49.60, 41.62, 33.08, 30.36.

1-benzyl-3-(2-fluorophenethyl) piperidin-4-one. To a solution of 1-fluoro-2-(2-iodoethyl)benzene (15.17g, 60.7 mmol) in acetone (150mL) was added potassium carbonate (19.36 g, 140.05 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (13.25 g, 46.68 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(2-fluorophenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (6.68g, 18.1 mmol) was added to DMF (150 mL). Lithium Chloride (7.67 g, 181 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(2-fluorophenethyl)piperidin-4-one (1.907 g, 33.9% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.47 – 7.12 (m, 7H), 7.12 – 6.92 (m, 2H), 3.65 (d, J = 7.7 Hz, 2H), 3.16 – 3.00 (m, 2H), 2.76 – 2.42 (m, 5H), 2.41 – 2.19 (m, 2H), 2.15 – 2.01 (m, 1H), 1.49 (ddt, J = 13.7, 8.5, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.30, 163.69, 161.27, 139.15, 131.83, 131.78, 130.27, 129.65, 129.43, 128.97, 128.89, 128.47, 125.28, 125.24, 116.18, 115.96, 62.57, 59.57, 54.73, 49.82, 49.08, 41.62, 28.93, 27.31, 27.29.

1-benzyl-3-(3-fluorophenethyl) piperidin-4-one. To a solution of 1-fluoro-3-(2-iodoethyl)benzene (14.7 g, 58.8 mmol) in acetone (150mL) was added potassium carbonate (18.76 g, 135.7 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (12.84 g, 45.2 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(3-fluorophenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (8.608g, 23.3 mmol) was added to DMF (150 mL). Lithium Chloride (9.89 g, 233 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(3-fluorophenethyl) piperidin-4-one (0.837g, 11.5% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 – 7.08 (m, 6H), 7.08 – 6.74 (m, 3H), 3.70 – 3.55 (m, 2H), 3.09 (dddd, J = 14.7, 9.2, 5.6, 3.4 Hz, 1H), 2.94 – 2.43 (m, 5H), 2.42 – 1.77 (m, 4H), 1.64 – 1.24 (m, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.34, 165.56, 163.14, 139.20, 131.08, 130.99, 130.27, 129.63, 129.49, 129.44, 128.49, 128.23, 125.23, 116.09, 115.88, 113.68, 113.47, 62.58, 59.43, 54.79, 53.56, 49.67, 41.65, 33.78, 29.99.

1-benzyl-3-(4-fluorophenethyl) piperidin-4-one. To a solution of 1-fluoro-4-(2-iodoethyl)benzene (14.47 g, 57.9 mmol) in acetone (150mL) was added potassium carbonate (18.46 g, 133.6 mmol), and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (12.63 g, 44.5 mmol). The solution was refluxed at 80° C for 12 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C, filtered and concentrated *in vacuo*. The crude product was diluted with methylene chloride and washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a golden colored residue which was purified via column chromatography (ISCO combiflash) using 10-15% ethyl acetate in hexanes to afford a mixture of methyl 1-benzyl-3-(4-fluorophenethyl)-4-oxopiperidine-3-carboxylate and unknown contaminant. The product (8.29g, 22.5 mmol) was added to DMF (150 mL). Lithium Chloride (9.523 g, 224.6 mmol) was added to the solution. The reaction refluxed at 155° C for 4 hours. LCMS confirmed conversion. The reaction mixture was cooled to 0° C. 4mL of 1N HCl was added. A gray precipitate was formed visibly in the deep red solution. The reaction mixture was poured onto a solution of saturated sodium bicarbonate solution on ice, washed with diethyl ether 3 times. The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was diluted in methylene chloride (20 mL); silica gel was added to the solution and concentrated *in vacuo.* Purification via column chromatography (ISCO combiflash) was done using a step gradient of 5-10-20% ethyl acetate in hexanes to afford 1-benzyl-3-(4-fluorophenethyl) piperidin-4-one (1.28 g, 18.4% yield from second step). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 – 7.33 (m, 3H), 7.33 – 7.21 (m, 2H), 7.12 (dd, J = 8.4, 5.6 Hz, 2H), 7.04 – 6.89 (m, 2H), 3.79 – 3.60 (m, 2H), 3.07 (dtd, J = 9.6, 5.2, 4.8, 2.9 Hz, 1H), 2.69 – 2.46 (m, 5H), 2.40 – 2.29 (m, 1H), 2.22 (dd, J = 11.4, 10.2 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.57 – 1.41 (m, 1H); ^{13}C NMR (101 MHz, Methanol-d_4) δ 212.42, 161.51, 139.22, 139.01, 130.98, 130.90, 130.28, 129.43, 128.48, 116.02, 115.81, 62.58, 61.53, 59.40, 54.81, 49.67, 49.28, 41.64, 33.22, 30.33, 20.85, 14.46.

Synthesis of difluoro piperidine derivatives:

1-benzyl-4,4-difluoro-3-(2-methoxyphenethyl) piperidine. To a solution of 1-benzyl-3-(2-methoxyphenethyl)piperidin-4-one (1.066g, 3.30 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (2.19g, 9.90 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reacton was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(2-methoxyphenethyl) piperidine (0.6356g, 55.8% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.24 (m, 5H), 7.16 (td, J = 7.8, 1.7 Hz, 1H), 7.01 (dd, J = 7.4, 1.7 Hz, 1H), 6.95 – 6.75 (m, 2H), 3.78 (s, 3H), 3.62 – 3.48 (m, 2H), 2.90 (d, J = 11.5 Hz, 1H), 2.79 (d, J = 11.9 Hz, 1H), 2.73 – 2.44 (m, 2H), 2.44 – 2.20 (m, 1H), 2.16 – 1.81 (m, 5H), 1.60 – 1.49 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.24, 138.23, 130.03, 129.54, 128.69, 128.13, 126.97, 126.94, 123.14, 120.22, 110.07, 77.05, 61.99, 55.04, 54.80, 49.74, 49.64, 42.64, 42.43, 42.22, 33.85, 33.62, 33.38, 27.53, 25.11.

1-benzyl-4,4-difluoro-3-(3-methoxyphenethyl) piperidine. To a solution of 1-benzyl-3-(3-methoxyphenethyl)piperidin-4-one (2.17g, 6.714 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (4.46 g, 20.14 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reaction was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(3-methoxyphenethyl) piperidine (0.8537g, 36.8% yield). ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 7.41 – 7.24 (m, 5H), 7.16 (t, *J* = 8.1 Hz, 1H), 6.80 – 6.61 (m, 3H), 3.77 (s, 3H), 3.62 – 3.48 (m, 2H), 2.81 (m, 2H), 2.63 (m, 1H), 2.56 – 2.43 (m, 1H), 2.35 (t, *J* = 10.2 Hz, 1H), 2.13 – 1.82 (m, 5H), 1.57 (tt, *J* = 14.6, 8.4 Hz, 1H); ^{13}C NMR (101 MHz, Methanol-*d*$_4$) δ 144.41, 138.96, 130.39, 130.35, 129.40, 128.45, 121.71, 115.01, 112.37, 62.99, 55.54, 51.17, 51.07, 49.64, 49.43, 49.21, 49.00, 48.79, 48.58, 48.36, 43.06, 34.61, 34.05, 27.85.

1-benzyl-4,4-difluoro-3-(4-methoxyphenethyl) piperidine. To a solution of 1-benzyl-3-(4-methoxyphenethyl)piperidin-4-one (1.97 g, 6.095 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (4.046 g, 18.29 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reaction was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(4-methoxyphenethyl) piperidine (1.25g, 59.4% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.17 (m, 5H), 7.07 – 6.93 (m, 2H), 6.81 – 6.70 (m, 2H), 3.73 (s, 3H), 3.55 – 3.38 (m, 2H), 2.75 – 2.62 (m, 2H), 2.61 – 2.37 (m, 2H), 2.27 (m, 1H), 2.11 – 1.80 (m, 5H), 1.51 (dq, *J* = 10.3, 6.8, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.94, 138.48, 133.93, 129.35, 129.00, 128.46, 127.33, 125.87, 123.44, 113.94, 77.36, 62.24, 55.39, 54.84, 50.20, 50.10, 42.55, 42.34, 42.13, 34.15, 33.91, 33.68, 32.49, 27.34.

1-benzyl-4,4-difluoro-3-(2-fluorophenethyl)piperidine. To a solution of 1-benzyl-3-(2-fluorophenethyl)piperidin-4-one (1.907 g, 6.128 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (4.068 g, 18.39 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reaction was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(2-fluorophenethyl)piperidine (1.026g, 50.2% yield). ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.16 (m, 5H), 7.16 – 7.02 (m, 2H), 7.02 – 6.88 (m, 2H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 2.76 (d, *J* = 11.5 Hz, 1H), 2.60 (m, 3H), 2.28 (td, *J* = 10.6, 3.2 Hz, 1H), 2.10 (t, *J* = 10.3 Hz, 1H), 2.05 – 1.78 (m, 4H), 1.56 (dq, *J* = 10.9, 6.6, 6.1 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.14, 138.10, 130.34, 130.28, 128.83, 128.68, 128.48, 128.31, 128.16, 127.50, 127.42, 127.02, 123.81, 123.77, 123.02, 115.16, 114.94, 61.95, 54.64, 49.76, 49.67, 42.53, 42.32, 42.11, 33.80, 33.56, 33.33, 26.45, 26.43, 25.61.

1-benzyl-4,4-difluoro-3-(3-fluorophenethyl)piperidine. To a solution of 1-benzyl-3-(3-fluorophenethyl)piperidin-4-one (0.8369 g, 2.69 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (1.785 g, 8.07 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reaction was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(3-fluorophenethyl)piperidine (0.2995 g, 33.4% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.19 (m, 5H), 7.15 (td, *J* = 7.9, 6.1 Hz, 1H), 6.95 – 6.72 (m, 3H), 3.51 (d, *J* = 13.0 Hz, 1H), 3.43 (d, *J* = 13.1 Hz, 1H), 2.69 (q, *J* = 7.6, 6.1 Hz, 2H), 2.61 – 2.43 (m, 2H), 2.29 (td, *J* = 10.7, 6.6 Hz, 1H), 2.11 – 1.79 (m, 5H), 1.53 (dt, *J* = 11.4, 6.1 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.95, 144.17, 144.09, 138.09, 129.62, 129.54, 128.67, 128.18, 127.08, 123.80, 123.78, 123.05, 115.10, 114.90, 112.72, 112.51, 77.05, 61.93, 54.46, 49.91, 49.81, 42.25, 42.04, 41.83, 33.57, 32.87, 26.67.

1-benzyl-4,4-difluoro-3-(4-fluorophenethyl)piperidine. To a solution of 1-benzyl-3-(4-fluorophenethyl)piperidin-4-one (1.28 g, 4.13 mmol) in methylene chloride (30 mL) was added Bis(2-methoxyethyl)aminosulfur trifluoride (2.74 g, 12.38 mmol) dropwise at -78° C. The reaction was warmed to room temperature and stirred for 12 hours. LCMS confirmed conversion. The reaction was quench by adding saturated sodium bicarbonate solution dropwise. The reaction was diluted with methylene chloride and washed with brine. The combined organic layer was dried over anhydrous sodium sulfate, decanted, silica gel added and concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 10-20% ethyl acetate in hexanes to afford 1-benzyl-4,4-difluoro-3-(4-fluorophenethyl)piperidine (0.6519 g, 40.5% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.20 (m, 5H), 7.20 – 7.02 (m, 2H), 7.02 – 6.70 (m, 2H), 3.53 (m, 2H), 2.74 (s, 2H), 2.68 – 2.43 (m, 2H), 2.33 (q, *J* = 10.5, 9.9 Hz, 1H), 2.21 – 1.80 (m, 4H), 1.33 – 1.15 (m, 1H), 1.09 – 0.70 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.95, 160.53, 138.75, 137.76, 137.73, 130.14, 130.06, 129.32, 128.80, 127.69, 123.71, 115.66, 115.45, 77.68, 62.57, 55.09, 50.57, 50.47, 42.87, 42.66, 42.44, 34.47, 34.24, 34.01, 32.95, 27.60.

Hydrogenation of benzyl protected difluoropiperidine derivatives:

4,4-difluoro-3-(2-methoxyphenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(2-methoxyphenethyl)piperidine (0.8265g, 2.39 mmol) in methanol (40 mL) was added ammonium formate (0.7544 g, 11.96 mmol), and palladium on carbon (0.8265g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(2-methoxyphenethyl)piperidine (0.810 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 (q, *J* = 7.7, 6.4 Hz, 1H), 7.14 (d, *J* = 6.3 Hz, 1H), 6.95 – 6.81 (m, 2H), 3.81 (d, *J* = 4.4 Hz, 3H), 3.48 (d, *J* = 2.6 Hz, 2H), 3.16 (d, *J* = 13.4 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.83 (t, *J* = 11.9 Hz, 1H), 2.71 (s, 1H), 2.67 (s, 1H), 2.64 – 2.43 (m, 2H), 2.02 (s, 2H), 1.52 (ddd, *J* = 14.5, 9.6, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.51, 130.26, 129.77, 127.28, 125.81, 123.37, 120.94, 120.54, 110.38, 55.35, 48.46, 48.39, 44.37, 44.17, 43.96, 43.65, 43.56, 35.49, 35.27, 35.04, 29.81, 27.81, 25.14, 25.11, 25.07

4,4-difluoro-3-(3-methoxyphenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(3-methoxyphenethyl)piperidine (0.8537g, 2.47 mmol) in methanol (40 mL) was added ammonium formate (0.779 g, 12.35 mmol), and palladium on carbon (0..8537g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (0.532 g, 84.4% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.15 (m, 1H), 6.82 – 6.69 (m, 3H), 3.80 (s, 3H), 3.15 – 3.00 (m, 2H), 2.88 – 2.70 (m, 2H), 2.70 – 2.50 (m, 3H), 2.15 – 1.96 (m, 2H), 1.92 – 1.67 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 129.53, 120.90, 114.27, 111.40, 77.36, 55.31, 48.64, 33.56.

4,4-difluoro-3-(4-methoxyphenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(4-methoxyphenethyl)piperidine (1.25 g, 3.62 mmol) in methanol (40 mL) was added ammonium formate (1.141 g, 18.09 mmol), and palladium on carbon (1.25g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (0.5171 g, 51.7% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.07 (m, 2H), 6.86 – 6.79 (m, 2H), 3.79 (s, 3H), 3.14 – 2.99 (m, 2H), 2.88 – 2.76 (m, 1H), 2.73 – 2.61 (m, 1H), 2.58 (td, *J* = 7.8, 3.2 Hz, 1H), 2.54 (dd, *J* = 10.4, 1.8 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.90 – 1.59 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.01, 133.90, 129.36, 123.39, 113.99, 77.36, 55.41, 48.61, 48.54, 44.03, 43.83, 43.65, 43.56, 35.57, 35.35, 35.12, 32.57, 31.08, 27.03.

4,4-difluoro-3-(2-fluorophenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(2-fluorophenethyl)piperidine (1.026 g, 3.077 mmol) in methanol (40 mL) was added ammonium formate (0.9703 g, 15.39 mmol), and palladium on carbon (1.026 g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(2-fluorophenethyl)piperidine (0.643 g, 85.9 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.10 (m, 2H), 7.10 – 6.93 (m, 2H), 3.19 – 2.99 (m, 2H), 2.89 – 2.52 (m, 4H), 2.13 – 1.96 (m, 2H), 1.92 – 1.68 (m, 2H), 1.55 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.47, 160.04, 130.63, 130.58, 128.75, 128.60, 127.88, 127.80, 125.73, 124.19, 124.16, 123.30, 120.86, 115.51, 115.29, 77.36, 48.54, 48.47, 44.23, 44.03, 43.82, 43.64, 43.56, 35.53, 35.30, 35.07, 26.71, 25.64.

4,4-difluoro-3-(3-fluorophenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(3-fluorophenethyl)piperidine (0.2995 g, 0.898 mmol) in methanol (40 mL) was added ammonium formate (0.2832 g, 4.49 mmol), and palladium on carbon (0.2995 g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(3-fluorophenethyl)piperidine (0.126 g, 57.7 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.18 (m, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.88 (t, *J* = 8.7 Hz, 2H), 3.19 – 2.99 (m, 2H), 2.82 (td, *J* = 12.0, 3.1 Hz, 1H), 2.76 – 2.62 (m, 2H), 2.57 (m, 1H), 2.06 (m, 2H), 1.84 (dd, *J* = 10.2, 5.1 Hz, 1H), 1.78 (td, *J* = 12.7, 11.4, 4.9 Hz, 1H), 1.59 – 1.46 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.26, 161.82, 144.40, 144.33, 129.97, 129.89, 125.61, 124.10, 124.07, 123.17, 115.37, 115.16, 113.06, 112.85, 77.39, 48.48, 48.41, 43.85, 43.64, 43.49, 43.44, 43.39, 35.34, 35.12, 34.89, 33.22, 26.64, 26.61.

4,4-difluoro-3-(4-fluorophenethyl)piperidine. To a solution of 1-benzyl-4,4-difluoro-3-(4-fluorophenethyl)piperidine (0.6519 g, 1.96 mmol) in methanol (40 mL) was added ammonium formate (0.617 g, 9.78 mmol), and palladium on carbon (0.6519 g). The reaction was warmed to 70° C for 5 minutes. TLC confirmed conversion. The reaction was cooled to 0 ° C, filtered through a pad of celite with methanol (350 mL), concentrated *in vacuo* to give oil 4,4-difluoro-3-(3-fluorophenethyl)piperidine (0.1925 g, 40.5 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.05 (m, 2H), 7.04 – 6.91 (m, 2H), 3.33 (dt, *J* = 12.7, 3.8 Hz, 2H), 3.02 (tt, *J* = 12.7, 6.5 Hz, 1H), 2.84 – 2.55 (m, 3H), 2.43 – 2.16 (m, 3H), 2.11 (m, 2H), 1.61 – 1.46 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.66, 160.24, 137.44, 137.40, 129.82, 129.77, 129.74, 125.75, 123.31, 120.88, 115.39, 115.18, 77.36, 58.54, 53.16, 48.59, 48.53, 43.97, 43.76, 43.59, 43.56, 43.50, 35.51, 35.28, 35.06, 32.70, 32.55, 32.15, 31.07, 30.64, 27.06, 27.03, 26.99, 18.58.

Synthesis of Substituted Phenylether Morpholine Scaffolds

tert-butyl (S)-2-(phenoxymethyl)morpholine-4-carboxylate

To a solution of tert-butyl (S)-2-(hydroxymethyl)morpholine-4-carboxylate (0.3 g, 1.38 mmol), phenol (0.118g, 1.25 mmol), and triphenyl phosphine (0.329 g, 1.25 mmol) in THF (3 mL) was added diisopropyl azodicarboxylate (0.305 g, 1.2 mmol) at 0º C. The reaction was placed in a microwave reactor for 5 minutes at 180º C set to low absorbance. The solution was diluted with methylene chloride, silica gel added, concentrated *in vacuo*. . Purification via column chromatography (ISCO combiflash) was done using 0- 15% ethyl acetate in hexanes to afford the desired product (0.112 g, 28%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.23 (m, 2H), 6.99 – 6.88 (m, 3H), 4.03 (dd, *J* = 10.0, 5.3 Hz, 2H), 3.94 (dt, *J* = 10.8, 5.4 Hz, 3H), 3.82 – 3.72 (m, 1H), 3.58 (td, *J* = 11.6, 2.8 Hz, 1H), 2.99 (s, 1H), 2.84 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.58, 154.77, 129.50, 121.18, 114.63, 80.19, 73.87, 68.56, 66.63, 45.34, 43.91, 28.44.

tert-butyl (S)-2-((3-fluorophenoxy)methyl)morpholine-4-carboxylate

To a solution of tert-butyl (S)-2-(hydroxymethyl)morpholine-4-carboxylate (0.150 g, 0.69 mmol), 3-fluorophenol (0.232g, 2.07 mmol), and triphenyl phosphine (0.416 g, 1.58 mmol) in THF (3 mL) was added diisopropyl azodicarboxylate (0.265 g, 1.31 mmol) at 0º C. The reaction was placed in a microwave reactor for 5 minutes at 180º C set to low absorbance. The solution was diluted with methylene chloride, silica gel added, concentrated *in vacuo*. . Purification via column chromatography (ISCO combiflash) was done using 0- 15% ethyl acetate in hexanes to afford the desired product (84.5 mg, 39.3%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (td, *J* = 8.2, 6.8 Hz, 1H), 6.71 – 6.56 (m, 3H), 3.99 (dd, *J* = 9.9, 5.4 Hz, 2H), 3.91 (dd, *J* = 10.0, 4.7 Hz, 2H), 3.84 (s, 1H), 3.75 (dtd, *J* = 10.4, 5.0, 2.8 Hz, 1H), 3.56 (td, *J* = 11.7, 2.8 Hz, 1H), 2.97 (s, 1H), 2.82 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.80, 162.36, 159.97, 159.87, 154.73, 130.31, 130.21, 110.38, 110.35, 108.10, 107.88, 102.56, 102.31, 80.24, 73.68, 68.87, 66.62, 45.36, 43.20, 28.41.

tert-butyl (S)-2-((4-fluorophenoxy)methyl)morpholine-4-carboxylate

To a solution of tert-butyl (S)-2-(hydroxymethyl)morpholine-4-carboxylate (0.150 g, 0.69 mmol), 4-fluorophenol (0.232g, 2.07 mmol), and triphenyl phosphine (0.416g, 1.58 mmol) in THF (3 mL) was added diisopropyl azodicarboxylate (0.265 g, 1.31 mmol) at 0º C. The reaction was placed in a microwave reactor for 5 minutes at 180º C set to low absorbance. The solution was diluted with methylene chloride, silica gel added, concentrated *in vacuo*. . Purification via column chromatography (ISCO combiflash) was done using 0- 15% ethyl acetate in hexanes to afford the desired product (161.8 mg, 75.3%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.88 (m, 2H), 6.88 – 6.78 (m, 2H), 4.07 – 3.81 (m, 5H), 3.75 (ddd, *J* = 10.7, 5.3, 2.9 Hz, 1H), 3.56 (td, *J* = 11.7, 2.8 Hz, 1H), 2.97 (t, *J* = 12.6 Hz, 1H), 2.82 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.70, 156.33, 154.76, 154.74, 115.98, 115.75, 115.67, 80.24, 73.85, 69.36, 66.64, 45.32, 43.89, 28.43.

tert-butyl (S)-2-((3-cyanophenoxy)methyl)morpholine-4-carboxylate

To a solution of tert-butyl (S)-2-(hydroxymethyl)morpholine-4-carboxylate (0.150 g, 0.69 mmol), 3-cyanophenol (0.247 g, 2.07 mmol), and triphenyl phosphine (0.416 g, 1.58 mmol) in THF (3 mL) was added diisopropyl azodicarboxylate (0.265 g, 1.31

mmol) at 0º C. The reaction was placed in a microwave reactor for 5 minutes at 180º C set to low absorbance. The solution was diluted with methylene chloride, silica gel added, concentrated *in vacuo*. Purification via column chromatography (ISCO combiflash) was done using 0- 15% ethyl acetate in hexanes to afford the desired product (159 mg, 72.3%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (t, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.01 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.90 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.00 (dd, *J* = 10.0, 5.4 Hz, 2H), 3.92 (dd, *J* = 9.9, 4.9 Hz, 3H), 3.76 (dtd, *J* = 10.4, 5.1, 2.9 Hz, 1H), 3.56 (td, *J* = 11.6, 2.8 Hz, 1H), 2.99 (d, *J* = 15.3 Hz, 1H), 2.82 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.31, 154.76, 129.50, 125.17, 123.20, 117.75, 116.05, 83.46, 80.26, 77.27, 73.74, 68.72, 66.62, 45.30, 43.23, 28.44.

General Procedure for synthesis of Difluoropiperidine and Morpholine Analogues

To a solution of amine (1 equiv) in methylene chloride (0.07 M) was added resin bound cyanoborohydride (2.5 equiv), aldehyde (1.5 equiv), and acetic acid (5eq). The reaction was placed in a microwave reactor for 7 minutes at 110º C set to low absorbance. The solution was filtered through a phase separator and the solvent evaporated under a current of nitrogen and purified via reverse phase HPLC.

1-(4-chlorobenzyl)-4,4-difluoro-3-(2-methoxyphenethyl)piperidine

According to the general procedure, 4,4-difluoro-3-[2-(2-methoxyphenyl)ethyl]piperidine (25mg, 0.098mmol) and 4-Chlorobenzaldehyde (20.6 mg, 0.147 mmol) afforded the desired product (7.7 mg, 20.7%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.5 Hz, 3H), 7.25 – 7.13 (m, 2H), 7.07 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.91 – 6.79 (m, 2H), 3.79

(s, 3H), 3.58 – 3.41 (m, 2H), 2.81 (m, 1H), 2.67 – 2.56 (m, 2H), 2.37 – 2.26 (m, 1H), 2.14 (m, 1H), 2.00 (dtt, *J* = 10.6, 6.8, 4.0 Hz, 4H), 1.57 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.55, 137.13, 132.98, 130.24, 129.82, 128.61, 127.30, 125.76, 123.34, 120.56, 110.41, 77.36, 61.52, 55.38, 55.01, 50.09, 50.00, 42.96, 42.75, 42.54, 33.89, 27.83, 25.34.

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-fluoro-1H-indole-3-carbaldehyde (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (15mg, 0.059 mmol) afforded the desired product (6.8 mg, 22.4%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (s, 1H), 7.63 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.19 – 7.01 (m, 3H), 6.95 – 6.83 (m, 1H), 6.77 – 6.62 (m, 3H), 3.82 – 3.63 (m, 5H), 2.81 (m, 2H), 2.64 – 2.47 (m, 2H), 2.36 (m, 1H), 2.10 – 1.93 (m, 4H), 1.65 – 1.57 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.76, 143.53, 136.47, 136.35, 129.45, 124.38, 123.74, 123.51, 120.88, 120.59, 120.49, 114.24, 113.19, 111.31, 108.66, 108.42, 97.65, 97.40, 77.36, 55.29, 54.85, 53.12, 50.11, 50.02, 42.66, 42.45, 42.24, 33.91, 33.52, 31.09, 27.09.

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-fluoro-1H-indole-3-carbaldehyde (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(4-methoxyphenethyl)piperidine (15 mg, 0.059 mmol) afforded the desired product (6.1 mg, 20.1%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.86 – 6.72 (m, 2H), 3.78 (s, 3H), 3.75 – 3.61 (m, 2H), 2.78 (s, 1H), 2.43 (m, 3H), 2.12 (s, 1H), 2.06 – 1.86 (m, 4H), 1.54 (dd, *J* = 9.4, 5.4 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.61, 129.02, 124.08, 123.31, 120.41, 120.31, 113.59, 108.33, 108.10, 97.31, 97.06, 77.05, 55.10, 52.86, 49.80, 42.09, 32.23, 27.08.

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(2-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-fluoro-1H-indole-3-carbaldehyde (15.1 mg, 0.092 mmol) and 4,4-difluoro-3-(2-fluorophenethyl)piperidine (15 mg, 0.061 mmol) afforded the desired product (6.3 mg, 21.3%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.65 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.20 – 6.98 (m, 5H), 6.98 – 6.95 (m, 1H), 6.95 – 6.85 (m, 1H), 3.82 – 3.63 (m, 2H), 2.87 (m, 1H), 2.78 (m, 1H), 2.59 (m, 2H), 2.36 (t, *J* = 10.7 Hz, 1H), 2.17 (s, 1H), 2.08 – 1.94 (m, 3H), 1.59 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.42, 161.41, 130.63, 130.58, 128.76, 128.60, 127.79, 127.71, 124.41, 124.11, 124.07, 123.63, 120.67, 120.57, 115.43, 115.21, 113.30, 108.64, 108.40, 97.62, 97.36, 77.36, 54.88, 53.16, 49.97, 42.87, 42.65, 42.45, 26.70, 25.97.

4,4-difluoro-1-((6-fluoro-1H-indol-3-yl)methyl)-3-(4-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-fluoro-1H-indole-3-carbaldehyde (15.1 mg, 0.092 mmol) and 4,4-difluoro-3-(4-fluorophenethyl)piperidine (15 mg, 0.061mmol) afforded the desired product (5.9 mg, 19.9%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.64 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.06 (td, *J* = 5.4, 4.9, 2.4 Hz, 2H), 7.00 – 6.84 (m, 5H), 3.78 – 3.62 (m, 2H), 2.78 (dd, *J* = 11.7, 5.3 Hz, 2H), 2.60 – 2.42 (m, 2H), 2.37 (t, *J* = 10.7 Hz, 1H), 2.15 – 1.83 (m, 5H), 1.61 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.58, 160.16, 159.05, 137.41, 136.51, 136.39, 129.78, 129.70, 124.37, 123.63, 123.59, 120.71, 120.61, 115.27, 115.06, 113.34, 108.66, 108.41, 97.66, 97.40, 77.36, 54.71, 53.19, 50.18, 42.66, 42.45, 42.24, 33.94, 32.74, 27.39

4,4-difluoro-1-((6-methoxy-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-methoxy-1H-indole-3-carbaldehyde (20.6 mg, 0.118 mmol) and 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (20 mg, 0.078 mmol) afforded the desired product (1.4 mg, 4.5%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.40 – 7.27 (m, 2H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.94 – 6.84 (m, 2H), 6.78 – 6.64 (m, 3H), 4.40 (d, *J* = 13.7 Hz, 1H), 4.30 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.59 (d, *J* = 9.0 Hz, 2H), 2.89 (t, *J* = 13.0 Hz, 1H), 2.63 (s, 2H), 2.22 (s, 1H), 2.10 (ddt, *J* = 14.6, 10.4, 5.4 Hz, 2H), 1.84 (s, 2H), 1.47 (s, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.92, 157.34, 129.72, 126.74, 121.57, 120.71, 118.33, 114.00, 111.93, 111.65, 102.86, 95.26, 77.36, 55.83, 55.31, 48.13, 33.18, 26.80.

4,4-difluoro-1-((6-methoxy-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 6-methoxy-1H-indole-3-carbaldehyde (20.6 mg, 0.118 mmol) and 4,4-difluoro-3-(4-methoxyphenethyl)piperidine (20 mg, 0.078 mmol) afforded the desired product (31.2 mg, 96.12%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.97 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.28 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.94 – 6.83 (m, 2H), 6.83 – 6.76 (m, 2H), 4.42 (m, 1H), 4.29 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.66 – 3.52 (m, 2H), 2.88 (s, 1H), 2.60 (m, 5H), 2.19 (s, 1H), 2.05 (m, 1H), 1.43 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.23, 157.22, 137.05, 132.83, 129.31, 126.89, 121.56, 118.27, 114.15, 111.55, 102.58, 95.30, 77.36, 55.79, 55.39, 53.02, 51.58, 48.19, 48.08, 40.32, 40.08, 32.05, 31.70, 31.44, 27.01.

3-((4,4-difluoro-3-(4-fluorophenethyl)piperidin-1-yl)methyl)-6-methoxy-1H-indole

According to the general procedure, 6-methoxy-1H-indole-3-carbaldehyde (21.6 mg, 0.123mmol) and 4,4-difluoro-3-(4-fluorophenethyl)piperidine (20 mg, 0.082 mmol) afforded the desired product (12.9 mg, 39.05%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.42 – 7.28 (m, 2H), 7.10 – 7.00 (m, 2H), 6.98 – 6.82 (m, 4H), 4.43 – 4.26 (m, 2H), 3.85 (s, 3H), 3.60 (d, *J* = 11.9 Hz, 2H), 3.36 (s, 1H), 2.90 (t, *J* = 12.5 Hz, 1H), 2.68 – 2.54 (m, 5H), 2.47 – 2.34 (m, 1H), 2.22 (s, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.32, 136.99, 136.34, 129.80, 129.72, 126.80, 121.51, 118.24, 115.58, 115.37, 111.67, 102.65, 95.29, 77.36, 55.82, 52.99, 51.61, 48.35, 40.72, 40.09, 32.25, 31.71, 26.91.

6-chloro-3-((4,4-difluoro-3-(3-methoxyphenethyl)piperidin-1-yl)methyl)-1H-indole

According to the general procedure, 6-chloro-1H-indole-3-carbaldehyde (15.8 mg, 0.088 mmol) and 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (15 mg, 0.059 mmol) afforded the desired product (4.8 mg, 19.5%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.21 – 7.05 (m, 3H), 6.72 (ddd, *J* = 8.2, 2.5, 1.1 Hz, 1H), 6.67 – 6.60 (m, 2H), 3.78 (s, 3H), 3.75 – 3.63 (m, 2H), 2.54 (pt, *J* = 13.9, 6.6 Hz, 2H), 2.36 (t, *J* = 10.6 Hz, 1H), 2.14 (s, 1H), 2.09 – 1.90 (m, 4H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.77, 143.52, 129.46, 128.31, 126.42, 124.05, 120.89, 120.72, 120.53, 114.24, 111.33, 111.16, 77.36, 55.30, 54.85, 53.05, 50.14, 50.04, 42.69, 42.48, 42.27, 33.92, 33.53, 27.09.

6-chloro-3-((4,4-difluoro-3-(4-methoxyphenethyl)piperidin-1-yl)methyl)-1H-indole

According to the general procedure, 6-chloro-1H-indole-3-carbaldehyde (15.8 mg, 0.088 mmol) and 4,4-difluoro-3-(4-methoxyphenethyl)piperidine (15 mg, 0.059 mmol) afforded the desired product (1.5 mg, 6.1%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.09 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.80 – 6.72 (m, 2H), 3.82 – 3.62 (m, 5H), 2.78 (s, 1H), 2.55 – 2.35 (m, 3H), 1.97 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.77, 143.52, 129.46, 128.31, 126.42, 124.05, 120.89, 120.72, 120.53, 114.24, 111.33, 111.16, 77.36, 55.30, 54.85, 53.05, 50.14, 50.04, 42.69, 42.48, 42.27, 33.92, 33.53, 27.09.

6-chloro-3-((4,4-difluoro-3-(2-fluorophenethyl)piperidin-1-yl)methyl)-1H-indole

According to the general procedure, 6-chloro-1H-indole-3-carbaldehyde (16.6 mg, 0.092 mmol) and 4,4-difluoro-3-(2-fluorophenethyl)piperidine (15 mg, 0.062 mmol) afforded the desired product (3.1 mg, 13.0%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 7.18 – 7.06 (m, 3H), 7.05 – 6.92 (m, 3H), 3.70 (q, *J* = 13.3 Hz, 2H), 2.85 (d, *J* = 11.4 Hz, 1H), 2.77 (d, *J* = 11.4 Hz, 1H), 2.68 – 2.51 (m, 3H), 2.41 – 2.31 (m, 1H), 2.17 (s, 2H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 130.63, 127.81, 124.12, 120.74, 120.54, 115.43, 115.21, 111.16, 77.36, 54.75, 53.03, 49.94, 42.60, 42.39, 33.85, 33.62, 31.09, 26.68, 25.93.

6-chloro-3-((4,4-difluoro-3-(4-fluorophenethyl)piperidin-1-yl)methyl)-1H-indole

According to the general procedure, 6-chloro-1H-indole-3-carbaldehyde (16.6 mg, 0.092 mmol) and 4,4-difluoro-3-(4-fluorophenethyl)piperidine (15 mg, 0.062 mmol) afforded the desired product (2.6 mg, 10.9%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.05 (m, 2H), 7.01 – 6.83 (m, 4H), 3.78 – 3.62 (m, 2H), 2.76 (s, 1H), 2.49 (tt, *J* = 9.2, 4.5 Hz, 2H), 2.39 (d, *J* = 10.7 Hz, 1H), 2.14 – 1.93 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.58, 136.90, 129.78, 129.70, 128.35, 123.99, 120.82, 120.55, 115.28, 115.07, 111.18, 77.36, 53.09, 50.18, 42.67, 42.46, 33.93, 32.75, 27.40.

3-((4,4-difluoro-3-(2-methoxyphenethyl)piperidin-1-yl)methyl)-4-fluoro-1H-indole

According to the general procedure, 4-fluoro-1H-indole-3-carbaldehyde (23.96 mg, 0.147 mmol) and 4,4-difluoro-3-(2-methoxyphenethyl)piperidine (25 mg, 0.098 mmol) afforded the desired product (5.9 mg, 14.97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.20 – 6.99 (m, 5H), 6.89 – 6.72 (m, 3H), 3.96 – 3.68 (m, 5H), 3.01 (d, *J* = 11.5 Hz, 1H), 2.88 (d, *J* = 11.5 Hz, 1H), 2.61 (td, *J* = 8.9, 6.5 Hz, 2H), 2.41 (t, *J* = 9.9 Hz, 1H), 2.28 – 2.15 (m, 1H), 2.00 (ddd, *J* = 11.9, 6.4, 2.7 Hz, 3H), 1.59 – 1.47 (m, 1H), 1.26 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.62, 157.56, 156.17, 139.11, 138.99, 130.47, 129.86, 127.20, 123.80, 123.51, 122.76, 122.69, 120.52, 116.83, 111.52, 110.39, 107.38, 107.34, 105.29, 105.09, 77.36, 55.36, 54.73, 53.14, 49.62, 49.53, 42.98, 42.78, 42.57, 34.05, 27.86, 25.47.

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 4,4-difluoro-3-(2-methoxyphenethyl)piperidine (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (15 mg, 0.059 mmol) afforded the desired product (2.8 mg, 11.8 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.6 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.14 (t, *J* = 7.7 Hz, 2H), 6.85 (dd, *J* =

11.6, 7.7 Hz, 1H), 6.79 – 6.63 (m, 3H), 4.59 – 4.42 (m, 2H), 3.78 (s, 3H), 3.61 (d, *J* = 12.3 Hz, 2H), 3.01 (t, *J* = 12.7 Hz, 1H), 2.74 (t, *J* = 12.4 Hz, 1H), 2.65 (s, 2H), 2.62 – 2.51 (m, 2H), 2.12 (ddt, *J* = 15.4, 10.8, 5.6 Hz, 3H), 1.48 (td, *J* = 14.2, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.89, 142.45, 138.57, 129.67, 128.92, 123.79, 123.71, 120.66, 113.97, 111.91, 108.59, 106.42, 106.23, 101.23, 77.36, 55.29, 52.92, 52.16, 33.17, 31.78, 26.82.

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 4-fluoro-1H-indole-3-carbaldehyde (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(4-methoxyphenethyl)piperidine (15 mg, 0.059 mmol) afforded the desired product (15.7 mg, 66.4%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.22 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.18 – 7.08 (m, 1H), 7.07 – 6.93 (m, 2H), 6.85 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.81 (dd, *J* = 13.1, 8.1 Hz, 3H), 4.55 (dd, *J* = 13.5, 2.4 Hz, 1H), 4.44 (d, *J* = 13.4 Hz, 1H), 3.77 (s, 3H), 3.69 – 3.53 (m, 2H), 3.05 – 2.93 (m, 1H), 2.75 (t, *J* = 12.4 Hz, 1H), 2.65 (s, 1H), 2.55 (d, *J* = 8.2 Hz, 2H), 2.48 (d, *J* = 15.2 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.22 (s, 1H), 2.15 – 2.01 (m, 1H), 1.45 (dq, *J* = 15.4, 7.8 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.49, 162.13, 157.89, 157.16, 154.74, 138.46, 132.44, 128.96, 128.72, 128.67, 123.33, 123.25, 116.01, 115.82, 113.82, 108.34, 105.96, 105.90, 105.76, 105.71, 100.63, 100.50, 77.04, 55.07, 52.78, 52.70, 51.96, 47.63, 47.51, 40.48, 39.95, 39.71, 39.48, 31.71, 31.41, 31.15, 26.69.

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(2-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 4-fluoro-1H-indole-3-carbaldehyde (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(2-fluorophenethyl)piperidine (14.3 mg, 0.059 mmol) afforded the desired product (12.4 mg, 54.0%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 2.8 Hz, 1H), 7.25 – 7.11 (m, 4H), 7.09 (dd, *J* = 7.6, 2.1 Hz, 1H), 7.06 – 6.90 (m, 2H), 6.84 (ddd, *J* = 12.1, 7.8, 1.8 Hz, 1H), 4.61 – 4.52 (m, 1H), 4.46 (m, 1H), 3.68 (d, *J* = 12.4 Hz, 1H), 3.60 (d, *J* = 12.5 Hz, 1H), 3.01 (td, *J* = 13.1, 3.0 Hz, 1H), 2.79 (t, *J* = 12.4 Hz, 1H), 2.69 – 2.60 (m, 3H), 2.51 – 2.34 (m, 1H), 2.26 – 2.22 (m, 1H), 2.22 – 2.04 (m, 2H), 1.48 (dt, *J* = 15.3, 7.7 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.74, 162.30, 159.87, 157.49, 155.08, 138.80, 138.69, 130.65, 130.60, 129.03, 128.35, 128.27, 127.62, 127.46, 124.32, 124.29, 123.66, 123.58, 120.07, 117.96, 116.33, 115.57, 115.35, 108.66, 108.62, 106.30, 106.11, 100.92, 77.36, 53.01, 52.93, 52.33, 48.01, 47.90, 40.75, 40.40, 40.17, 39.93, 31.98, 31.71, 31.45, 26.54, 25.51.

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(3-fluorophenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, 4-fluoro-1H-indole-3-carbaldehyde (14.4 mg, 0.088 mmol) and 4,4-difluoro-3-(3-fluorophenethyl)piperidine (14.3 mg, 0.059 mmol) afforded the desired product (6.1 mg, 26.6%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 2.6 Hz, 1H), 7.25 – 7.11 (m, 4H), 6.91 – 6.75 (m, 4H), 4.56 (d, *J* = 13.4 Hz, 1H), 4.47 (d, *J* = 13.4 Hz, 1H), 3.63 (t, *J* = 13.2 Hz, 3H), 3.08 – 2.97 (m, 1H), 2.82 – 2.53 (m, 6H), 2.10 (s, 1H), 1.48 (ddt, *J* = 14.0, 9.9, 6.6 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.40, 162.02, 143.26, 138.75, 138.65, 130.18, 130.10, 128.98, 124.02, 123.99, 123.78, 123.70, 117.71, 116.31, 115.24, 115.03, 114.82, 113.49, 113.28, 108.67, 108.64, 106.39, 106.20, 100.94, 77.36, 53.02, 52.94, 52.35, 48.11, 47.99, 40.55, 40.38, 40.15, 32.74, 32.00, 31.74, 31.48, 26.58.

4,4-difluoro-1-((4-fluoro-1H-indol-3-yl)methyl)-3-(4-fluorophenethyl)piperidin-1-ium2,2,2-trifluoroacetate

According to the general procedure, 4-fluoro-1H-indole-3-carbaldehyde (15.1 mg, 0.093 mmol) and 4,4-difluoro-3-(4-fluorophenethyl)piperidine (15 mg, 0.062 mmol) afforded the desired product (13.1 mg, 54.5%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.26 – 7.07 (m, 3H), 7.03 (ddd, *J* = 8.0, 5.4, 2.0 Hz, 2H), 6.94 – 6.77 (m, 3H), 4.53 (d, *J* = 13.4 Hz, 1H), 4.45 (d, *J* = 13.3 Hz, 1H), 3.59 (d, *J* = 12.2 Hz, 2H), 3.06 – 2.95 (m, 1H), 2.74 (t, *J* = 12.4 Hz, 1H), 2.69 – 2.51 (m, 4H), 2.46 – 2.32 (m, 1H), 2.24 (s, 1H), 2.09 (dq, *J* = 14.4, 5.9 Hz, 1H), 1.44 (ddt, *J* = 14.4, 9.2, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.78, 162.65, 162.28, 160.35, 155.05, 138.78, 138.67, 136.29, 136.26, 129.76, 129.68, 129.00, 123.65, 123.57, 120.10, 116.30, 116.12, 115.54, 115.33, 108.72, 108.69, 106.27, 106.08, 100.85, 77.36, 52.99, 52.91, 52.30, 48.09, 47.98, 40.69, 40.29, 40.05, 39.82, 32.24, 31.98, 31.72, 31.46, 26.87.

4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylmethyl)-3-(3-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, imidazo[1,5-a]pyridine-1-carbaldehyde (17.2 mg, 0.118 mmol) and 4,4-difluoro-3-(3-methoxyphenethyl)piperidine (20 mg, 0.078 mmol) afforded the desired product (26.7 mg, 88.5%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (s, 1H), 8.05 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.68 (dq, *J* = 9.4, 1.0 Hz, 1H), 7.18 (dt, *J* = 13.5, 7.9 Hz, 2H), 7.06 (ddd, *J* = 9.4, 6.6, 1.0 Hz, 1H), 6.86 (ddd, *J* = 7.4, 6.6, 1.1 Hz, 1H), 6.79 – 6.64 (m, 4H), 4.63 (s, 2H), 3.77 (d, *J* = 9.1 Hz, 6H), 3.16 (td, *J* = 12.6, 4.4 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.69 – 2.53 (m, 3H), 2.14 (dddd, *J* = 14.2, 9.5, 6.6, 4.6 Hz, 1H), 1.64 – 1.46 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.95, 161.57, 159.89, 142.38, 131.64, 129.80, 129.71, 127.73, 123.71, 123.01, 120.71, 117.24, 117.18, 116.49, 115.57, 114.19, 113.79, 112.06, 111.81, 77.36, 55.29, 55.25, 53.15, 51.04, 48.82, 40.41, 40.08, 33.15, 32.96, 31.62, 26.57.

4,4-difluoro-1-(imidazo[1,5-a]pyridin-1-ylmethyl)-3-(4-methoxyphenethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, imidazo[1,5-a]pyridine-1-carbaldehyde (17.2 mg, 0.118 mmol) and 4,4-difluoro-3-(4-methoxyphenethyl)piperidine (20 mg, 0.078 mmol) afforded the desired product (15.5 mg, 51.3%). H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.48 (m, 1H), 8.07 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.74 – 7.64 (m, 1H), 7.15 – 6.98 (m, 4H), 6.94 – 6.86 (m, 1H), 6.86 – 6.74 (m, 3H), 4.68 (s, 2H), 3.78 (d, *J* = 3.3 Hz, 5H), 3.63 (d, *J* = 12.5 Hz, 1H), 3.19 (s, 1H), 2.91 (t, *J* = 12.3 Hz, 2H), 2.59 (t, *J* = 7.9 Hz, 2H), 2.19 – 2.05 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.13, 161.74, 161.35, 158.19, 132.73, 132.50, 131.66, 129.32, 127.58, 124.22, 123.16, 117.18, 117.11, 116.04, 115.75, 114.25, 114.20, 114.15, 77.36, 55.44, 55.37, 53.31, 53.23, 50.64, 49.00, 48.90, 40.50, 40.26, 40.02, 39.86, 32.09, 31.96, 31.61, 31.35, 26.72.

4,4-difluoro-3-(2-fluorophenethyl)-1-(imidazo[1,5-a]pyridin-1-ylmethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, imidazo[1,5-a]pyridine-1-carbaldehyde (18 mg, 0.123 mmol) and 4,4-difluoro-3-(2-fluorophenethyl)piperidine (20 mg, 0.082 mmol) afforded the desired product (12.5, 40.7%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 7.1 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.25 – 6.79 (m, 9H), 4.89 (s, 2H), 3.72 (d, *J* = 9.7 Hz, 2H), 3.61 (d, *J* = 12.8 Hz, 1H), 3.35 (td, *J* = 12.5, 4.1 Hz, 1H), 3.24 – 3.06 (m, 2H), 2.39 – 2.23 (m, 4H), 1.57 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.96, 160.55, 131.77, 130.57, 130.52, 128.46, 128.37, 127.17, 126.27, 124.41, 123.76, 118.00, 117.10, 116.68, 115.59, 115.37, 113.84, 113.03, 77.37, 76.92, 53.63, 49.38, 49.20, 40.22, 39.33, 26.11, 25.17.

4,4-difluoro-3-(4-fluorophenethyl)-1-(imidazo[1,5-a]pyridin-1-ylmethyl)piperidin-1-ium 2,2,2-trifluoroacetate

According to the general procedure, imidazo[1,5-a]pyridine-1-carbaldehyde (18 mg, 0.123 mmol) and 4,4-difluoro-3-(4-fluorophenethyl)piperidine (20 mg, 0.082 mmol) afforded the desired product (10 mg, 32.6%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.14 (m, 1H), 7.76 (dq, *J* = 9.4, 1.1 Hz, 1H), 7.23 (m, 2H), 7.17 – 6.84 (m, 7H), 4.81 (d, *J* = 1.4 Hz, 2H), 3.71 (d, *J* = 12.4 Hz, 1H), 3.56 (s, 1H), 3.29 (td, *J* = 12.2, 4.7 Hz, 1H), 3.01 (t, *J* = 12.3 Hz, 1H), 2.75 – 2.51 (m, 3H), 2.26 – 2.08 (m, 2H), 1.58 – 1.43 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.69, 161.29, 160.90, 160.50, 131.71, 129.84, 129.76, 129.73, 127.19, 125.66, 123.56, 117.43, 117.13, 116.81, 115.68, 115.52, 115.47, 115.31, 113.95, 113.82, 77.36, 53.54, 53.46, 49.61, 49.43, 49.33, 40.31, 40.07, 39.82, 39.45, 32.22, 31.99, 31.62, 26.53.

(S)-2-(phenoxymethyl)-4-(pyrazolo[1,5-a]pyrimidin-3-ylmethyl)morpholine

According to the general procedure, 3,3a-dihydropyrazolo[1,5-a]pyrimidine-3-carbaldehyde (21.2 mg, 0.142 mmol) and (S)-2-(phenoxymethyl)morpholine (18.3 mg, 0.095 mmol) afforded the desired product (14.8 mg, 47.9%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.56 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.27 (s, 1H), 7.32 – 7.23 (m, 2H), 7.02 – 6.93 (m, 2H), 6.93 – 6.81 (m, 2H), 4.54 (s, 2H), 4.26 (d, *J* = 10.8 Hz, 1H), 4.07 (m, 4H), 3.65 (d, *J* = 12.1 Hz, 1H), 3.55 (d, *J* = 12.2 Hz, 1H), 3.13 – 2.95 (m, 2H), 2.68 (s, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.21, 150.97, 148.21, 147.17, 135.93, 129.70, 121.75, 114.68, 109.23, 100.13, 97.34, 77.36, 72.11, 67.91, 64.05, 52.04, 50.30, 49.81.

(S)-4-(imidazo[1,5-a]pyridin-1-ylmethyl)-2-(phenoxymethyl)morpholine

According to the general procedure imidazo[1,5-a]pyridine-1-carbaldehyde (20.8 mg, 0.142 mmol) and (S)-2-(phenoxymethyl)morpholine (18.3 mg, 0.095 mmol) afforded the desired product (6.9 mg, 22.3%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 6.97 – 6.85 (m, 3H), 6.68 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.54 (t, *J* = 6.7 Hz, 1H), 4.04 – 3.83 (m, 6H), 3.76 (td, *J* = 11.3, 2.4 Hz, 1H), 2.97 (d, *J* = 11.2 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.33 (td, *J* = 11.3, 3.4 Hz, 1H), 2.18 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 129.52, 122.34, 121.07, 118.13, 114.78, 112.87, 77.36, 74.20, 69.39, 52.93.

(S)-4-((1H-indazol-3-yl)methyl)-2-(phenoxymethyl)morpholine

According to the general procedure, 1H-indazole-3-carbaldehyde (20.8 mg, 0.142 mmol) and (S)-2-(phenoxymethyl)morpholine (18.3 mg, 0.095 mmol) afforded the desired product (12.5 mg, 40.8%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.41 – 7.28 (m, 2H), 7.23 – 7.14 (m, 3H), 7.13 – 7.04 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.60 (dd, *J* = 10.5, 2.8 Hz, 1H), 4.40 (d, *J* = 13.3 Hz, 1H), 4.23 (ddd, J = 10.7, 6.9, 2.2 Hz, 2H), 4.18 – 4.05 (m, 2H), 4.05 – 4.00 (m, 1H), 3.48 (d, J = 13.3 Hz, 1H), 3.37 (d, J = 12.0 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.70 (s, 1H), 2.26 (td, J = 11.2, 5.3 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.48, 140.79, 132.50, 130.11, 126.83, 122.13, 122.02, 121.75, 118.81, 114.86, 111.08, 77.39, 72.99, 67.78, 64.25, 52.65, 51.65, 51.12.

(S)-4-(3-chloro-4-methoxybenzyl)-2-((4-fluorophenoxy)methyl)morpholine

According to the general procedure, 3-chloro-4-methoxybenzaldehyde (18 mg, 0.071 mmol) and (S)-2-((4-fluorophenoxy)methyl)morpholine (15 mg, 0.071 mmol) afforded the desired product (3.4 mg, 13.1%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.33 (m, 1H), 7.17 (dd, J = 8.4, 2.1 Hz, 1H), 7.03 – 6.76 (m, 5H), 4.17 – 3.95 (m, 2H), 3.95 – 3.89 (m, 5H), 3.89 – 3.81 (m, 1H), 3.81 – 3.58 (m, 1H), 3.45 (s, 1H), 2.87 – 2.72 (m, 1H), 2.71 – 2.52 (m, 1H), 2.31 – 2.16 (m, 1H), 2.11 – 2.01 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.98, 154.34, 130.97, 129.90, 128.49, 127.51, 127.48, 122.45, 116.14, 116.02, 115.85, 115.78, 112.08, 112.04, 111.96, 77.36, 74.22, 70.10, 69.83, 69.57, 67.01, 66.59, 62.32, 61.53, 61.49, 56.43, 56.34, 55.34, 54.69, 52.99, 52.06, 49.18, 46.89.

(S)-4-(4-chloro-3-methoxybenzyl)-2-((4-fluorophenoxy)methyl)morpholine

According to the general procedure, 4-chloro-3-methoxybenzaldehyde (18 mg, 0.071 mmol) and (S)-2-((4-fluorophenoxy)methyl)morpholine (15 mg, 0.071 mmol) afforded the desired product (2.7 mg, 10.4%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 7.05 – 6.75 (m, 5H), 4.17 – 3.84 (m, 7H), 3.84 – 3.58 (m, 2H), 3.50 (s, 1H), 2.89 – 2.74 (m, 1H), 2.73 – 2.52 (m, 1H), 2.33 – 2.18 (m, 1H), 2.16 – 2.02

(m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.57, 155.12, 154.95, 138.12, 130.69, 130.65, 130.02, 123.72, 121.93, 120.76, 116.16, 116.03, 115.93, 115.82, 115.75, 115.68, 112.73, 111.52, 77.36, 74.21, 74.01, 70.04, 69.75, 69.52, 67.00, 66.59, 63.02, 62.20, 62.15, 56.43, 56.28, 55.46, 54.74, 53.11, 52.13, 49.35, 47.06.

(S)-3-((4-(4-chloro-3-methoxybenzyl)morpholin-2-yl)methoxy)benzonitrile

According to the general procedure, 4-chloro-3-methoxybenzaldehyde (23.4 mg, 0.138 mmol) and (S)-3-(morpholin-2-ylmethoxy)benzonitrile (20 mg, 0.092 mmol) afforded the desired product (13.6 mg, 39.8%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.17 (m, 3H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.05 – 6.95 (m, 1H), 6.95 – 6.80 (m, 2H), 4.34 – 4.24 (m, 1H), 4.24 – 4.14 (m, 2H), 4.10 (td, *J* = 7.1, 6.4, 2.8 Hz, 3H), 4.03 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.90 (d, *J* = 4.1 Hz, 3H), 3.54 (d, *J* = 12.0 Hz, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.07 (s, 1H), 3.00 – 2.87 (m, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.56, 162.19, 157.87, 156.19, 130.83, 130.25, 129.75, 127.55, 125.80, 125.25, 123.64, 123.51, 119.62, 117.98, 115.85, 114.84, 114.21, 110.75, 83.24, 77.60, 77.36, 71.82, 67.99, 64.90, 63.88, 61.49, 56.30, 56.24, 52.70, 51.15, 40.51, 25.45.

References

(1) Di Ciano, P.; Grandy, D.; Le Foll, B. *Advances in pharmacology (San Diego, Calif.)* **2014**, *69*, 301.

(2) Scherzer CR, O. K., GearingM, et al. *Archives of neurology* **2004**, *61*, 1200.

(3) Papassotiropoulos, A.; Streffer, J. R.; Tsolaki, M.; et al. *Archives of neurology* **2003**, *60*, 29.

(4) Kölsch, L., Ludwig, Schulte, Ptok, Jessen, von Bergmann, Rao, Maier and Heun *Molecular Psychiatry* **2002**, *7*, 899.

(5) Wollmer, M. A.; Streffer, J. R.; Tsolaki, M.; Grimaldi, L. M.; Lutjohann, D.; Thal, D.; von Bergmann, K.; Nitsch, R. M.; Hock, C.; Papassotiropoulos, A. *Mol Psychiatry* **2003**, *8*, 635.

(6) Girault, J. A.; Greengard, P. *Archives of neurology* **2004**, *61*, 641.

(7) Kebabian, J. W. *Journal of Neurochemistry* **1978**, *30*, 1143.

(8) Beaulieu, J.-M.; Espinoza, S.; Gainetdinov, R. R. *British Journal of Pharmacology* **2015**, *172*, 1.

(9) Girault, J. A. *Progress in molecular biology and translational science* **2012**, *106*, 33.

(10) Svenningsson, P.; Nishi, A.; Fisone, G.; Girault, J. A.; Nairn, A. C.; Greengard, P. *Annual review of pharmacology and toxicology* **2004**, *44*, 269.

(11) Lichter, J. B.; Barr, C. L.; Kennedy, J. L.; Van Tol, H. H.; Kidd, K. K.; Livak, K. J. *Human molecular genetics* **1993**, *2*, 767.

(12) Van Tol, H. H.; Wu, C. M.; Guan, H. C.; Ohara, K.; Bunzow, J. R.; Civelli, O.; Kennedy, J.; Seeman, P.; Niznik, H. B.; Jovanovic, V. *Nature* **1992**, *358*, 149.

(13) Schoots, O.; Van Tol, H. H. M. *Pharmacogenomics J* **2003**, *3*, 343.

(14) Rondou, P.; Haegeman, G.; Van Craenenbroeck, K. *Cell. Mol. Life Sci.* **2010**, *67*, 1971.

(15) Seeman, P.; Van Tol, H. H. M. *Trends in Pharmacological Sciences* **1994**, *15*, 264.

(16) Ito, R.; Robbins, T. W.; McNaughton, B. L.; Everitt, B. J. *European Journal of Neuroscience* **2006**, *23*, 3071.

(17) Schultz, W. *Annual review of psychology* **2006**, *57*, 87.

(18) Bernaerts, P.; Tirelli, E. *Behavioural Brain Research* **2003**, *142*, 41.

(19) Rubinstein, M.; Phillips, T. J.; Bunzow, J. R.; Falzone, T. L.; Dziewczapolski, G.; Zhang, G.; Fang, Y.; Larson, J. L.; McDougall, J. A.; Chester, J. A.; Saez, C.; Pugsley, T. A.; Gershanik, O.; Low, M. J.; Grandy, D. K. *Cell* **1997**, *90*, 991.

(20) Wise, R. A.; Bozarth, M. A. *Psychological Review* **1987**, *94*, 469.

(21) Thanos, P. K.; Habibi, R.; Michaelides, M.; Patel, U. B.; Suchland, K.; Anderson, B. J.; Robinson, J. K.; Wang, G.-J.; Grandy, D. K.; Volkow, N. D. *Behavioural Brain Research* **2010**, *207*, 508.

(22) Yan, Y.; Pushparaj, A.; Gamaleddin, I.; Steiner, R. C.; Picciotto, M. R.; Roder, J.; Le Foll, B. *Behavioural Brain Research* **2012**, *230*, 34.

(23) Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *Journal of Medicinal Chemistry* **1996**, *39*, 1941.

(24) Pickens, R.; Thompson, T. *The Journal of pharmacology and experimental therapeutics* **1968**, *161*, 122.

(25) Woolverton, W. L. *Pharmacology Biochemistry and Behavior* **1986**, *24*, 531.

(26) Andreoli, M.; Tessari, M.; Pilla, M.; Valerio, E.; Hagan, J. J.; Heidbreder, C. A. *Neuropsychopharmacology* **2003**, *28*, 1272.

(27) Epstein, D.; Preston, K. *Psychopharmacology* **2003**, *168*, 31.

(28) Yan, Y.; Pushparaj, A.; Le Strat, Y.; Gamaleddin, I.; Barnes, C.; Justinova, Z.; Goldberg, S. R.; Le Foll, B. *Neuropsychopharmacology* **2012**, *37*, 685.

(29) O’Reilly, M. C.; Lindsley, C. W. *Organic letters* **2012**, *14*, 2910.

(30) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angewandte Chemie International Edition* **2004**, *43*, 5507.

(31) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *Journal of the American Chemical Society* **2004**, *126*, 4790.

(32) Merck, S. D. 1995.

(33) Berry, C. B.; Bubser, M.; Jones, C. K.; Hayes, J. P.; Wepy, J. A.; Locuson, C. W.; Daniels, J. S.; Lindsley, C. W.; Hopkins, C. R. *ACS Medicinal Chemistry Letters* **2014**, *5*, 1060.

(34) http://www.eurofins.com/en.aspx, E. S.