Bioorganic & Medicinal Chemistry 21 (2013) 2217–2228

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery of disubstituted piperidines and homopiperidines as potent dual NK_1 receptor antagonists–serotonin reuptake transporter inhibitors for the treatment of depression

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ARTICLE INFO

Article history:
Received 7 January 2013
Revised 1 February 2013
Accepted 11 February 2013
Available online 19 February 2013

Keywords:
NK_1 receptor (NK_1R) antagonist
Serotonin reuptake transporter (SERT) inhibitor
Dual NK_1 receptor antagonists–serotonin reuptake transporter inhibitor

ABSTRACT

This report describes the synthesis, structure–activity relationships and activity of piperidine, homopiperidine, and azocane derivatives combining NK_1 receptor (NK_1R) antagonism and serotonin reuptake transporter (SERT) inhibition. Our studies culminated in the discovery of piperidine **2** and homopiperidine **8** as potent dual NK_1R antagonists-SERT inhibitors. Compound **2** demonstrated significant activity in the gerbil forced swimming test, suggesting that dual NK_1R antagonists-SERT inhibitors may be useful in treating depression disorders.

1. Introduction

Since their introduction in the 1980s, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine,[1] fluoxetine and citalopram (Chart 1) have enjoyed tremendous clinical and commercial success due to their improved safety profile over the first-generation tricyclic antidepressants like imipramine (Chart 1).[2] Nevertheless, they still display several side effects including gastrointestinal distress, anxiety, insomnia, weight gain and sexual dysfunction. Like other currently approved antidepressants, SSRIs also suffer from slow onset of action, and as a result, a significant number of depressed patients do not show signs of mood improvement until 4–3 weeks after the initial treatment.[3–5] The delay of therapeutic effects of SSRIs is believed to result from activation of the inhibitory role of serotonin 1A ($5\text{-}HT_{1A}$) autoreceptors. Upon administration of an SSRI, some of the increased synaptic serotonin (5-HT) acting at $5\text{-}HT_{1A}$ receptors reduces the firing of serotonergic neurons, resulting in a muted increase of synaptic 5-HT. After initial desensitization of the $5\text{-}HT_{1A}$ autoreceptors with repeated SSRI treatment, the serotonergic neurons resume normal firing, allowing an increase of synaptic 5-HT, and thus generating a therapeutic antidepressant effect. Indeed, a beneficial effect on the onset of action of SSRIs has been observed in the clinical studies with co-administration of 5-HT1A antagonists.[6,7] Moreover, this combination therapy has resulted in significant improvements among SSRI-resistant patients.[6,7]

Another potential combination strategy might involve neurokinin 1 receptor (NK_1R) antagonists[8–12] and SSRIs. NK_1R antagonists alone may not be sufficient in treating depression in humans. For example, aprepitant, an NK_1R antagonist currently used in combination with other antiemetics to help prevent the acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapies, showed some antidepressant effect in early clinical studies,[13] but its development for the treatment of depression was later discontinued after the compound's effects failed to separate from placebo effects in phase III trials.[14] Since NK_1R antagonists indirectly modulate 5-HT function[15,16] and attenuate presynaptic $5\text{-}HT_{1A}$ receptor function, NK_1 receptor antagonism may augment the antidepressant activity of SSRIs. Consistent with this hypothesis, Bourin et al. demonstrated that GR205171 (Chart 1), a selective and brain penetrant NK_1R antagonist, selectively potentiated the antidepressant activity of subactive doses of two SSRIs, citalopram and paroxetine, in the mouse forced swimming test (FST).[17] Thus, combination therapy of SSRIs with NK_1R antagonists has potential as a new treatment for depression

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http://dx.doi.org/10.1016/j.bmc.2013.02.010

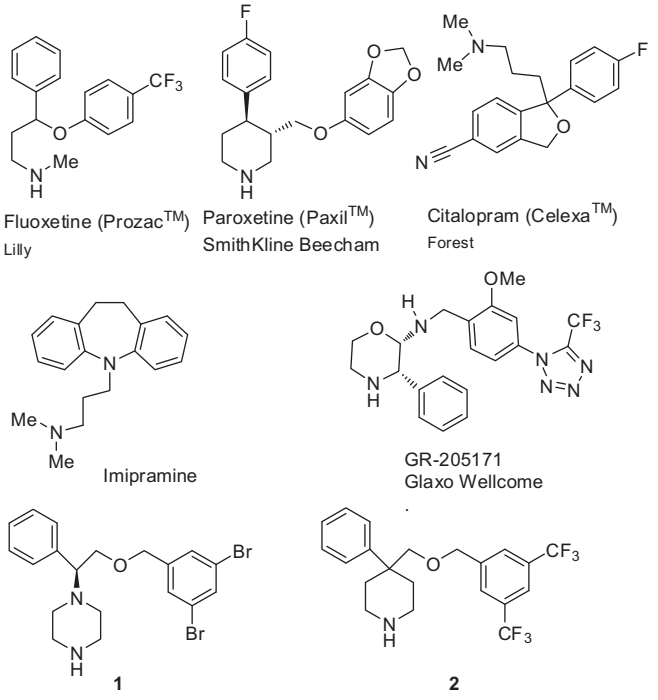
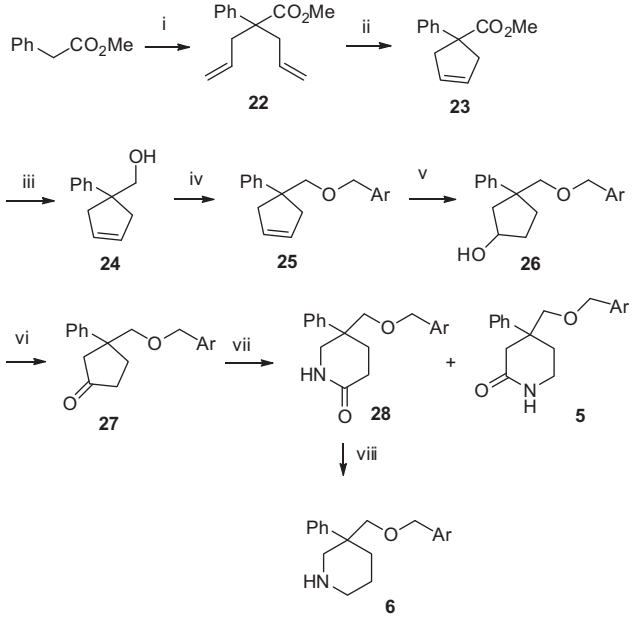


Chart 1.



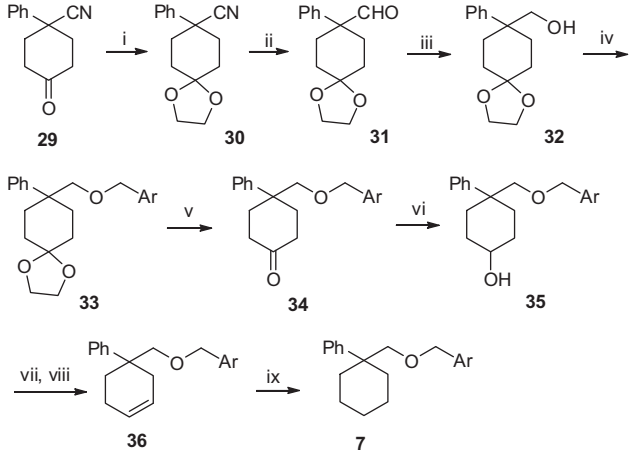
Scheme 1. Reagents and conditions: (i) allyl bromide, NaH, DMF, rt, 100%; (ii) Grubbs I catalyst, CH_2Cl_2, reflux, 91%; (iii) $LiAlH_4$, ether, 0 °C, 100%; (iv) NaH, $ArCH_2Br$, DMF, rt, 75%; (v) BH_3·THF, 0 °C; H_2O_2, NaOH, rt, 50%; (vi) PCC, CH_2Cl_2, rt, 100%; (vii) sodium azide, trifluoroacetic acid, benzene, 65 °C, 29% (28) and 26% (5); (viii) BH_3·THF, THF, 65 °C; 1 N HCl, 65 °C, 67%. Ar: 3,5-bis(trifluoromethyl)phenyl.

with more rapid onset of action and improved efficacy. However, combination therapy with two compounds can have potential disadvantages, including challenges with differing PK profiles of the individual components, enhanced risk of drug–drug interactions, increased number or intensity of side effects, potentiation of dose-related or idiosyncratic side effects and pharmacokinetic interactions. An attractive alternative to combination therapy of two different molecules would be a single compound that has both serotonin reuptake transporter (SERT) inhibition and NK_1R antagonism. In 2002, Ryckmans et al. described a series of benzyloxyphenethyl piperazine derivatives as dual NK_1R antagonists-SERT inhibitors.[18,19] One of the best compounds in the series, (*S*)-1-(2-(3,5-dibromobenzyloxy)-1-phenylethyl)piperazine (**1**, Chart 1), demonstrated oral activity in an animal model of depression sensitive to both mechanisms.

We also undertook a program to identify dual NK_1R antagonists-SERT inhibitors. We selected a known potent NK_1R antagonist, 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-4-phenylpiperidine (**2**, Chart 1),[14] as one of the lead compounds for our medicinal chemistry program because of its structural similarity to known SSRIs such as paroxetine. We sought to add SERT inhibitory activity by judiciously incorporating key features of SSRIs into the molecule, while maintaining NK_1R antagonism. It was in this context that we discovered that **2** was not only a potent NK_1R antagonist but also a potent SERT inhibitor. This finding led to a series of 4,4-disubstituted piperidines and homopiperidines designed as potent dual NK_1R antagonists-SERT inhibitors. This report details the synthesis, SAR and preliminary behavioral studies of these compounds.

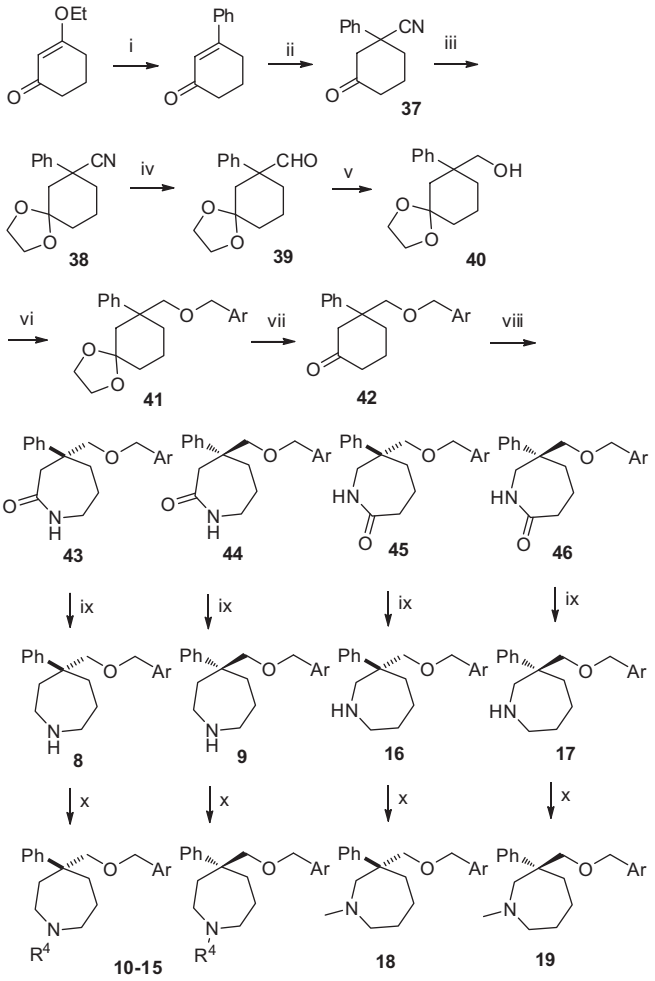
2. Chemistry

The compounds in Table 1 were prepared as follows. Piperidines **2** and **3** were synthesized following the procedures described by Stevenson et al.[20] Compound **4** was made from **2** via standard Boc protection. Analogues **5–7** were prepared as outlined in Schemes 1 and 2.

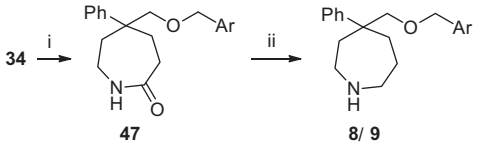


Scheme 2. Reagents and conditions: (i) ethylene glycol, benzene, Dean–Stark trap, reflux, 98%; (ii) DIBAL-H, toluene, −78 °C, 100%; (iii) $NaBH_4$, MeOH, rt, 94%; (iv) NaH, $ArCH_2Br$, DMF, rt, 38%; (v) HCl, acetone, reflux, 100%; (vi) $NaBH_4$, MeOH, rt, 100%; (vii) MsCl, Et_3N, rt; (viii) DBU, benzene, 80 °C, 25% for two steps; (ix) H_2, Pd/C, MeOH, 50 psi, rt, 80%. Ar: 3,5-bis(trifluoromethyl)phenyl.

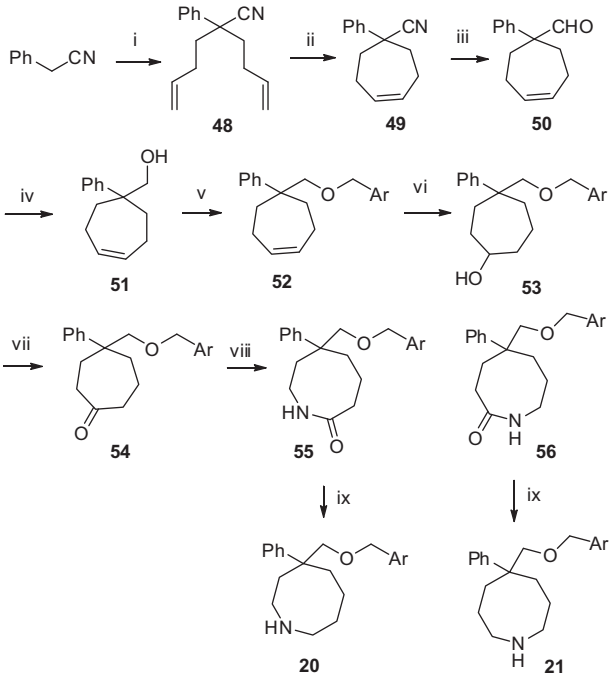
Scheme 1 describes the synthesis of lactam **5** and piperidine **6** (Table 1). Double α-allylation of methyl 2-phenylacetate gave methyl 2-allyl-2-phenylpent-4-enoate **22**. Ring closing metathesis of **22** proceeded smoothly with Grubbs I catalyst to furnish the cyclopentene derivative **23** in good yield. The ester of **23** was reduced with lithium aluminum hydride to give primary alcohol **24**. *O*-Benzylation of **24** under standard conditions led to benzyl ether **25**, hydroboration of the olefin gave alcohol **26**, and oxidation generated cyclopentanone **27**. Exposure of this ketone to sodium azide and trifluoroacetic acid resulted in smooth Schmidt reaction[21] to give an approximately 1:1 mixture of two lactams **5** and **28**. Reduction of lactam **28** with borane in THF generated piperidine **6**. Both lactam **5** and piperidine **6** shown in Table 1 are racemates.



Scheme 3. Reagents and conditions: (i) PhMgBr, THF; HCl, rt 100%; (ii) KCN, trimethylamine hydrochloride, DMF, 93 °C, 92%; (iii) ethylene glycol, benzene, Dean–Stark trap, reflux, 48%; (iv) DIBAL-H, toluene, −78 °C, 85%; (v) $NaBH_4$, MeOH, rt, 87%; (vi) NaH, $ArCH_2Br$, DMF, rt, 71%; (vii) HCl, acetone, reflux, 92%; (viii) sodium azide, trifluoroacetic acid, benzene, 65 °C, 71%; chiral HPLC separation; (ix) BH_3·THF, THF, 65 °C; 1 N HCl, 65 °C, 100%; (x) HCHO, HCO_2H, $CHCl_3$ or Ti(O*i*–Pr)$_4$, aldehyde, toluene; $NaBH_4$. Ar: 3,5-bis(trifluoromethyl)phenyl.



Scheme 4. Reagents and conditions: (i) sodium azide, trifluoroacetic acid, benzene, 65 °C, 48%; (ii) BH_3·THF, THF, 65 °C; 1 N HCl, 65 °C, 92%. Ar: 3,5-bis(trifluoromethyl)phenyl.



Scheme 5. Reagents and conditions: (i) 4-bromobut-1-ene, NaH, DMF; 4-bromobut-1-ene, rt, 38%; (ii) Grubbs I catalyst, CH_2Cl_2, reflux, 100%; (iii) DIBAL-H, toluene, −78 °C, 73%; (iv) $NaBH_4$, MeOH, rt, 100%; (v) NaH, $ArCH_2Br$, DMF, rt, 61%; (vi) BH_3·THF, 0 °C; H_2O_2, NaOH, rt, 47%; (vii) PCC, CH_2Cl_2, rt, 81% (viii) sodium azide, trifluoroacetic acid, benzene, 65 °C, 26% (71) and 31% (72); (ix) BH_3·THF, THF, 65 °C; 1 N HCl, 65 °C, 89%. Ar: 3,5-bis(trifluoromethyl)phenyl.

Scheme 2 describes the synthesis of the cyclohexane derivative **7** (Table 1). The commercially available 4-cyano-4-phenylcyclohexanone (**29**) was converted to the ketal **30**, which was reduced to the primary alcohol **32** via aldehyde **31**. Alcohol **32** underwent *O*-benzylation to give benzyl ether ketal **33**. The ketal was deprotected to give ketone **34**, which was reduced to afford alcohol **35**. Cyclohexene derivative **36** was obtained from **35** via mesylation followed by elimination. Finally, hydrogenation of **36** generated cyclohexane analog **7**.

Scheme 3 describes a divergent synthetic route leading to both 4,4-disubstituted-homopiperidine analogs **8–15** (Table 2) and 3,3-disubstituted-homopiperidine analogs **16–19** (Table 3). Reaction of 3-ethoxycyclohex-2-enone with phenylmagnesium bromide gave 3-phenylcyclohex-2-enone, which underwent Michael reaction with potassium cyanide to provide 3-cyano-3-phenylcyclohexanone (**37**). Reaction of **37** with ethylene glycol was followed by conversion of the resulting ketal **38** to the benzyl ether ketone **42** via a four step sequence. This ketone underwent Schmidt reaction to give a mixture of four lactams (two pairs of enantiomers): **43–46**, which were separated by chiral HPLC. The isomeric identity of the lactams was easily assigned according to spectroscopic data, but we have not yet determined the absolute stereochemistry of each enantiomer. Therefore, we arbitrarily assigned the absolute stereochemistry to the four lactams in Tables 2 and 3 for the purpose of differentiating them in our discussion. The four lactams were reduced individually to amines **8**, **9**, **16** and **17**. Reductive alkylation led to tertiary amines **10–15** and **18–19**. The stereochemistry of homopiperidines **8–19** shown in Tables 3 and 4 follows their corresponding lactams.

For a more direct synthesis of 4,4-homopiperidines, an alternative approach was employed as shown in Scheme 4. This approach utilized the symmetrical cyclohexanone derivative **34** (Scheme 2) as the substrate for Schmidt reaction. Exposure of ketone **34** to typical Schmidt conditions resulted in the formation of a single lactam **47** in good yield. Reduction of **47** gave racemic **8**/**9**.

Scheme 5 details the synthesis of azocane analogs **20** and **21** (Table 4), which were prepared from 2-phenylacetonitrile following the same reaction sequence shown in Scheme 1. Azocane **20** was obtained as a racemate, and no attempts were made to separate the respective enantiomers due to its moderate SERT inhibitory activity (Table 4).

3. Binding assays

The hNK_1R binding affinity of the test compounds in this study was determined using U373 cells that express the human NK_1 receptor. Non-specific binding was measured in the presence of

certain concentrations of L-733,060, a non-peptide NK_1 antagonist.[12] The amount of radioligand bound in the presence and absence of L-733,060 was analyzed by plotting (−)log drug concentration versus the amount of radioligand specifically bound. The midpoint of the displacement curve (IC_{50}, nM) signifies the potency of the test compounds shown in Tables 1–4. In this assay, compound **2** exhibited an hNK_1R IC_{50} of 1 nM, which is the same as that reported in the literature.[14]

The affinity of the test compounds for the human serotonin transporter (hSERT) was evaluated by a [^{125}I]RTI-55 binding assay using recombinant HEK-293 cells that stably express human serotonin transporters. The binding affinities, expressed as IC_{50}s (nM), were obtained using the same method as described for hNK_1R. Under these assay conditions, paroxetine, a well known SSRI, displayed an IC_{50} of 0.15 nM, which is comparable to that described in the literature.[22]

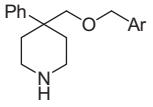
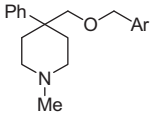
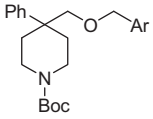
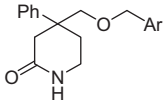
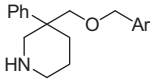
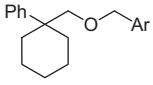
The detailed radioligand binding assay protocols are described in the Experimental section.

4. Results and discussion

Optimization of dual-acting molecules presents unique challenges in following SAR trends for two different targets. Based on our preliminary studies (data not shown), the 3,5-bis(trifluoromethyl)benzyl ether side chain appeared to be optimal for NK_1 activity. Therefore, this side chain was fixed throughout this study. As summarized in Table 1, N-methylation of the piperidine nitrogen in compound **2** (cf. **3**) had little impact on the NK_1R activity, but the SERT activity was significantly diminished. The basicity of the piperidine nitrogen appears to be beneficial to NK_1 receptor binding and essential to SERT activity as the *N*-Boc analog **4** and lactam **5** showed much reduced dual NK_1R/SERT activities. The 3,3-disubstituted piperidine analog **6** was less potent than the 4,4-disubstituted counterpart **2** by ~20-fold for both targets. The cyclohexane analog **7** showed virtually no dual activity, again indicating the essentiality of the piperidine basic nitrogen.

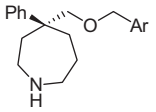
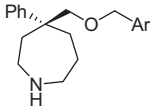
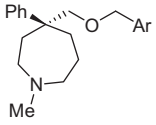
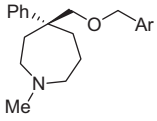
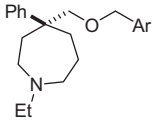
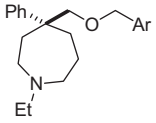
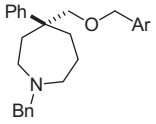
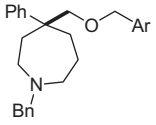
Table 2 shows the activity of the 4,4-substituted homopiperidine series. Enantiomers **8** and **9** showed the same NK_1R binding

Table 1
IC_{50} values of 4,4-disubstituted piperidines[a]

Compd	Structure	hNK_1R (nM)	hSERT (nM)
2		1.0	1.0
3		0.7	14
4		170	>1000
5[b]		57	970
6[b]		19	25
7		1700	>1000
paroxetine		900	0.2

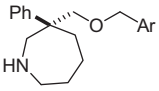
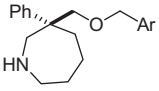
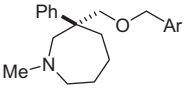
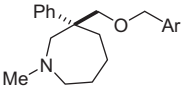
[a] All values are the mean of at least two separate assay determinations.
[b] Racemate. Ar: 3,5-bis(trifluoromethyl)phenyl.

Table 2
Activity of 4,4-disubstituted homopiperidines[a]

Compd	Structure	hNK_1R (NM)	hSERT (nM)
8		2.5	2.9
9		2.6	26
10		2.6	26
11		7.2	150
12		32	170
13		11	>1000
14		26	91
15		74	570

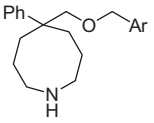
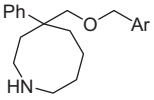
[a] See footnote of Table 1.

Table 3
Activity of 3,3-disubstituted homopiperidines[a]

Compd	Structure	hNK_1R (NM)	hSERT (nM)
16		16	140
17		410	490
18		110	860
19		660	660

[a] See footnote of Table 1.

Table 4
Activity of azocane analogs[a]

Compd	Structure	hNK$_1$R (NM)	hSERT (nM)
20		2.0	51
21[b]		6.7	53

[a] See footnote of Table 1.
[b] Racemate.

affinity, but they were nearly ten-fold different in SERT inhibition. As stated previously, we have not yet determined the preferred absolute stereochemistry. A stereochemical bias was previously observed in the benzyloxyphenethyl piperazine derivatives reported by Ryckmans et al.[19] As found in the piperidine series, N-methylation of **8** (cf. **10**) did not impact the NK$_1$R inhibitory potency but reduced the SERT activity by nearly ten-fold. In contrast, N-methylation of the enantiomer **9** (cf. **11**) resulted in moderate decrease in both NK$_1$R antagonism (3×) and SERT inhibition (6×). Among the *N*-alkyl homopiperidine compounds, the *N*-methyl analogs **10** and **11** exhibited excellent NK$_1$R inhibitory activity (IC$_{50}$ 3–7 nM), albeit with diminished SERT activity. There was little to no enantiomeric preference for NK1 receptor antagonism. The rank order of effect of the alkyl group was not identical for the NK$_1$R and SERT targets: however, a consistent finding was that introduction of any alkyl group onto the ring nitrogen significantly decreased SERT inhibitory potency. Similar to the piperidine series, the basic nitrogen is required for homopiperidines as seen by the reduced activity of the two lactams **43** and **44** (data not shown).

The data for the 3,3-disubstituted homopiperidines are summarized in Table 3. As compared with their 4,4-disubstituted counterparts, the 3,3-disubstituted homopiperidines exhibited much reduced potency towards both targets. The best compound from this series (**16**) was sixfold less potent for NK$_1$ receptor binding and 48-fold less potent for SERT inhibition relative to that of its 4,4-disubstituted analog (i.e., **8**). As expected, the two intermediate lactams **45** and **46** maintained moderate NK$_1$R binding activity but lost SERT activity (data not shown).

To further probe the pharmacophore of the dual NK$_1$/SERT binding interactions, we evaluated the 4,4- and 5,5-disubstituted azocane analogs shown in Table 4. Note that compound **20** is achiral, and **21** was a racemate. The two azocanes **20** and **21** retained potent NK$_1$ receptor binding affinities, but in terms of SERT binding, they were less potent than the lead compound **2**. Thus the optimal spatial arrangement between the quaternary carbon and the basic nitrogen appears to be a two-atom link for dual target binding interactions. As in the piperidine and homopiperidine series, the two intermediate azocanone lactams **55** and **56** possessed much reduced activity (data not shown).

5. Further in vitro profile of compound 2

In parallel with our efforts to expand the SAR around compound **2**, we elected to further profile this analog. Compound **2** was tested in a commercial screening package (PanLabs) and did not exhibit significant (<50% inhibition at 10 μM concentration) interactions with any of the over 70 other receptors except the following: NET, DAT, H$_1$, H$_2$, 5-HT$_{2B}$, Na^+ and Ca^{+2} channels). Follow-up in-house assays showed the IC$_{50}$'s for the dopamine and norepinephrine transporters to be > 1 μM. Likewise, the IC$_{50}$'s for serotonin receptors 5-HT$_{1A}$, 5-HT$_{1B,}$ 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$ were all >1 μM. In addition, compound **2** showed excellent selectivity versus all other NK receptors (IC$_{50}$'s for NK2 and NK3 receptors >1 μM).

6. Behavioral studies on 2

Species differences between the human NK$_1$ receptor and NK$_1$ receptors in rats and mice have resulted in many classes of NK$_1$R antagonists having reduced affinity for rat and mouse NK$_1$ receptors compared to human NK$_1$ receptors. These species differences make it difficult to test for efficacy in traditional rat and mouse behavioral models. However, NK$_1$R antagonists generally have similar affinity at gerbil and human NK$_1$ receptors. In the case of compound **2**, we found comparable potency for binding to both human and gerbil NK$_1$ receptors (IC$_{50}$:2 nM for gerbil NK$_1$R versus 1 nM for human NK$_1$R). Thus, we were able to perform behavioral studies in gerbils. To investigate the antidepressant effect of piperidine **2**, we utilized the gerbil forced swimming test (FST). This behavioral test is one of the most widely used preclinical paradigms for predicting antidepressant activity of drug candidates. The gerbil FST was carried out using the procedures described by Wallace et al.[23] In this test, immobility (i.e., no swimming or struggling) of the animals was a measure of despair. The compound was administered intraperitoneally (IP) 30 min prior to test. The results were expressed as the immobility time during the 6-min test period (mean ± S.E.M.) for the 10 gerbils tested in each group. Figure 1 shows the effect of various IP doses of compound **2** and fluoxetine at 10 mg/kg (PO). The lowest IP dose of **2** (0.1 mg/kg) did not modify the immobility times in gerbils when compared to the vehicle-treated control group. However, **2** decreased immobility time at 0.3, 1.0, and 3.0 mg/kg (IP). When administered at higher doses (10–30 mg/kg, IP), this compound did not alter immobility presumably due to untoward sedative effects. As expected, the positive control fluoxetine significantly decreased immobility in the gerbil FST.

We also evaluated **2** in a locomotor activity assay to determine whether the results obtained in the gerbil FST were influenced by a possible increase in spontaneous locomotor activity. The test compound was administered IP at doses shown to be efficacious in the FST 30 min prior to test, and the spontaneous activity of naïve animals was measured by determining the total distance travelled. As shown in Figure 2, compound **2** at the doses of 0.1, 0.3 and 1.0 mg/kg (IP) produced no significant changes in locomotor activity as compared with the vehicle-treated control group. Amphetamine (Amph), a psychostimulant drug, was used as our positive control, and it significantly increased the locomotor activity at 5 mg/kg (IP). Thus, we concluded that the reduction of the immobility time in the gerbil FST observed with piperidine **2** is consistent with an

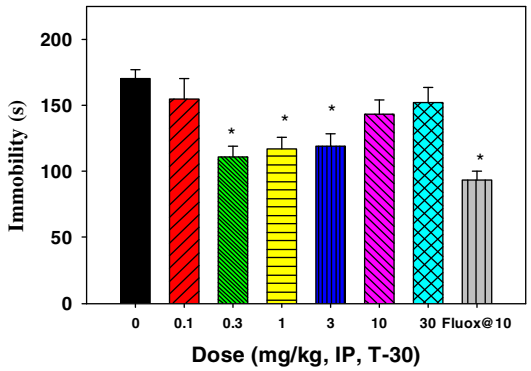


Figure 1. Effects of various intraperitoneal doses of **2** (0.1, 0.3, 1, 3 and 10 mg/kg) and fluoxetine (10 mg/kg, PO) in gerbil FST. Results are expressed as mean immobility time ± S.E.M. *P <0.01. T-30: 30 min pretreatment time.

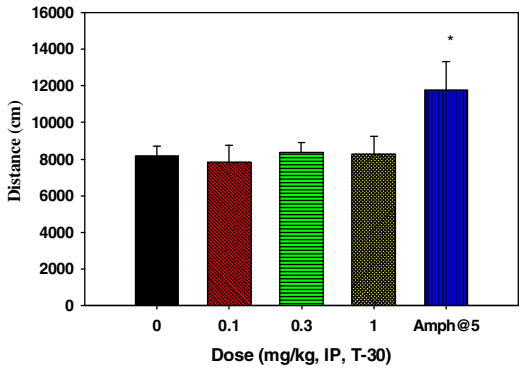


Figure 2. Effect of various intraperitoneal doses of 2 on the spontaneous locomotor activity in gerbil. Results are expressed as the total distance travelled ± S.E.M. $^{*}P$ <0.01. T-30: 30 min pretreatment time.

Table 5
Brain, serum concn and brain/serum ratio of **2**[a]

Dose (mg/kg)	Serum concn (nM)	Brain concn (nM)	Brain-to-serum ratio
0.1	3.6 (0.5)	8.8 (4.6)	2.3 (0.9)
0.3	12 (11)	44 (52)	3.2 (1.1)
1	35 (35)	150 (200)	3.2 (1.7)
3	210 (200)	880 (700)	4.2 (1.4)
10	730 (560)	4300 (3600)	5.2 (1.6)
30	2300 (3200)	7300 (9600)	2.3 (0.9)

[a] Compound dosed IP to gerbils as a solution in 100% PEG-400 with brain and serum samples taken at 36 min post injection. Data are mean values (n = 3) with SD in parentheses.

antidepressant-like effect and is not confounded by locomotor effects.

To understand the exposure-effect relationship, we obtained the brain and serum samples from gerbils following IP administration of **2**. These samples were taken 36 min post-dose, which accounts for the time elapsed between dosing and the end of evaluation in the behavioral model. Table 5 shows the exposure data from the doses tested in the gerbil FST. The minimal effective dose of **2** was 0.3 mg/kg, indicating that a brain concentration of 44 nM may be required to induce a significant decrease on the immobility test. Compound **2** also showed good brain penetration, and its brain and serum concentrations increased dose-dependently upon IP administration (Table 5).

7. Conclusion

Piperidine **2** and homopiperidine **8** were identified as potent dual NK_1R antagonists and SERT inhibitors. Behavioral studies of **2** in the gerbil forced swimming test (FST) suggest that dual NK_1R antagonists/SERT inhibitors may have potential for the treatment of depression disorders. Further SAR studies of this class of dual NK_1R antagonists/SERT inhibitors will be reported in due course.

8. Experimental section

8.1. Preparation of membranes

Crude membrane suspensions were prepared for the NK_1 and SERT radioligand binding assays from U373 cells or recombinant HEK-293 cells expressing hNK_1 and hSERT, respectively. Cells were harvested from T-175 flasks as follows. The medium is removed from the flasks and the cells rinsed with HBSS without Ca and without Mg. The cells are then incubated for 5–10 min in 10 mM Tris-Cl, pH 7.5, 5 mM EDTA before the cells are lifted with a combination of pipetting and scraping, as needed. To prepare membranes, the cell suspension is collected into centrifuge bottles and homogenized for 30 s with a Polytron homogenizer. The suspension is centrifuged for 30 min @ 32,000×g, 4 °C, then the supernatant is decanted and the pellet resuspended and homogenized in 50 mM Tris-Cl, pH 7.5, 1 mM EDTA for 10 s. The suspension is then centrifuged again for 30 min @ 32,000×g, 4 °C. The supernatant is decanted and the pellet resuspended in 50 mM Tris-Cl, pH 7.5, 1 mM EDTA and briefly homogenized. A Bradford assay (Bio-rad) is performed and the membrane preparation diluted to 2 mg/ml with 50 mM Tris-Cl, pH 7.5, 1 mM EDTA. Aliquots are prepared, and then frozen and stored at −80 °C.

8.2. NK_1 radioligand binding assay

Compounds are dissolved in 100% DMSO at a concentration 100× the desired highest assay concentration, serially diluted 1:3 in 100% DMSO, and 0.6 μL/well of each solution is dispensed to a Nunc polypropylene, round bottom, 384 well plate. 100% inhibition is defined with 0.6 μL/well of 1 mM L-733,060 (Sigma L-137) dissolved in DMSO. 30 μL/well of a 2× U373 membrane preparation (267 μg/ml in 100 mM Tris-Cl, pH 7.5, 6 mM $MgCl_2$, 0.2% (v/v) Sigma mammalian protease inhibitor cocktail (Sigma P-8340), and 4 μg/ml chymostatin, Sigma C-7268) and 30 μL/well of a 2× radioligand solution (400 pM [^{125}I]Substance P (Perkin Elmer NEX-190) in 1% (w/v) BSA (Sigma A-2153), 0.1 mg/ml bacitracin, Sigma B-0125) are added to the well and the reaction incubated for 1 h at room temperature. The contents of the assay plate are then transferred to a Millipore $Multiscreen_{HTS}$ GF/B filter plate which has been pretreated with 0.5% PEI for at least 1 h. The plate is vacuum filtered and washed with 7 washes of 100 ul/well 20 mM Tris-Cl, pH 7.5, 0.5% (w/v) BSA chilled to 4 °C. The filtration and washing is completed in less than 90 s. The plates are air-dried overnight, 12 μL/well of MicroScint scintillation fluid added, and the plates counted in a Trilux.

8.3. SERT radioligand binding assay

Compounds are dissolved in 100% DMSO at a concentration 100× the desired highest assay concentration, serially diluted 1:3 in 100% DMSO, and 0.4 μL/well of each solution is dispensed to a Nunc polypropylene, round bottom, 384 well plate. 100% inhibition is defined with 0.4 μL/well of 1 mM fluoxetine (Sigma F-132) dissolved in DMSO. 20 μL/well of a 2× HEK-hSERT membrane preparation (15 μg/ml in 50 mM Tris-Cl, pH 7.5, 120 mM NaCl, 5 mM KCl) and 20 μL/well of a 2× radioligand solution (520 pM [^{125}I]RTI-55 (Perkin–Elmer NEX-272) in 50 mM Tris-Cl, pH 7.5, 120 mM NaCl, 5 mM KCl) are added to each well and the reaction incubated for 1 h at room temperature. The contents of the assay plate are then transferred to a Millipore $Multiscreen_{HTS}$ GF/B filter plate which has been pretreated with 0.5% PEI for at least one hour. The plate is vacuum filtered and washed with 7 washes of 100 μL/well 50 mM Tris-Cl, pH 7.5, 120 mM NaCl, 5 mM KCl chilled to 4 °C. The filtration and washing is completed in less than 90 s. The plates are air-dried overnight, 12 μL/well of MicroScint scintillation fluid added, and the plates counted in a Trilux.

8.4. Data analysis

The raw data are normalized to percent inhibition using control wells defining 0% (DMSO only) and 100% (selective inhibitor) inhibition which are run on each plate. Each plate is run in triplicate, and the concentration response curve thus generated is fit

using the four-parameter dose response equation, Y = Bottom + (Top–Bottom)/(1+10^((LogIC_{50}-X)*HillSlope)) in order to determine the IC_{50} value for each compound. The radioligand concentration chosen for each assay corresponds to the K_d concentration determined through saturation binding analysis for each assay.

8.5. General chemistry

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM FT instrument operating at 400 or 500 MHz for proton (^{1}H) and 100 or 125 MHz for carbon (^{13}C). All spectra were recorded using tetramethylsilane (TMS) as an internal standard, and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brd s or d = broad singlet or doublet. The coupling constant (J) is in hertz. High-resolution mass spectrometry (HRMS) data was obtained using a standard flow injection technique on a Finnigan MAT 900 mass spectrometer in electrospray ionization (ESI) mode. All tested compounds possessed a purity of not less than 95% by LC/MS analysis using two methods. LC/MS was performed on a Shimadzu LC-10AS liquid chromatography using a SPD-10AV UV–Vis detector with mass spectrometry (MS) data determined using a Micromass LC platform in positive electrospray ionization mode (ESI+). LC/MS method A: column YMC ODS-A C18 S7 (3.0 × 50 mm), gradient system 10/90 to 90/10 methanol/water with a buffer consisting of 0.1% TFA over 2 min, flow rate 5 mL/min, wavelength 220 nm. Method B: the same as method A except column Phenomenex Luna C18 S10 (3.0 × 50 mm) was used.

8.6. Methyl 2-allyl-2-phenylpent-4-enoate (22)

To a solution of methyl 2-phenylacetate (**74**) (500 mg, 3,3 mmol) in DMF (1.0 mL) at 0 °C was added sodium hydride (95% oil dispersion, 210 mg, 8.3 mmol) and the resulting suspension was stirred at 0 °C for 10 min. Allyl bromide (0.72 mL, 8.3 mmol) was added, and the reaction mixture was stirred at rt for 30 min. Saturated sodium chloride was added and the reaction was extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo to give **22** as an oily material (770 mg, 100%). This crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (4H, m), 3.61 (3H, s), 5.01 (4H, m), 5.45 (2H, m), 7.18–7.30 (5H, m).

8.7. Methyl 1-phenylcyclopent-3-enecarboxylate (23)

To a solution of **22** (378 mg, 1.6 mmol) in dichloromethane (41 mL) was added benzylidene-bis(tricyclohexylphosphine)-dichloro-ruthenium (68 mg, 0.08 mmol) and the resulting suspension was heated under reflux for 1 h. The solvent was removed in vacuo, and the crude product was purified by preparative TLC eluting with 10% ethyl acetate/90% hexanes to give **23** as an oil (300 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (2H, d, J = 14.8 Hz), 3.40 (2H, d, J = 14.8 Hz), 3.63 (3H, s), 5.76 (2H, s), 7.22-7.31 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 52.5, 58.4, 126.6, 126.8, 128.7, 129.2, 143.7, and 176.6.

8.8. (1-Phenylcyclopent-3-enyl)methanol (24)

To a solution of **23** (298 mg, 1.5 mmol) in ether (10 mL) at 0 °C was added lithium aluminum hydride (1.0 M solution in ether, 1.48 mL, 1.5 mmol), and the resulting suspension was stirred at 0 °C for 30 min. The reaction was quenched with saturated sodium sulfate (0.5 mL) and then diluted with ether (100 mL). Anhydrous sodium sulfate was added, and the ether solution was filtered. The filtrate was evaporated in vacuo to give **24** as an oil (257 mg, 100%). The crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (4H, s), 3.54 (2H, d, J = 5.6 Hz), 5.75 (1H, s), 7.22–7.35 (5H, m).

8.9. 1-(((1-Phenylcyclopent-3-enyl)methoxy)-methyl)-3,5-bis(trifluoromethyl)benzene (25)

To a solution of **24** (257 mg, 1.3 mmol) and 3,5-(*bis*-trifluoromethyl)benzyl bromide (0.41 mL, 2.2 mmol) in DMF (2.5 mL) at 0 °C was added sodium hydride (95% oil dispersion, 75 mg, 3 mmol) and the resulting suspension was stirred at rt for 30 min. Water (2 mL) was added, and the reaction was extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo and the crude product was purified by preparative TLC eluting with 15% ethyl acetate/85% hexanes to give **25** as an oily material (382 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (4H, s), 3.51 (2H, s), 4.44 (2H, s), 5.74 (2H, s), 7.21–7.32 (5H, m), 7.57 (2H, s), and 7.72 (1H, s).

8.10. 3-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-3-phenylcyclopentanol (26)

To a solution of **25** (200 mg, 0.5 mmol) in THF (0.55 mL) at 0 °C was added borane–tetrahydrofuran complex (1.0 M solution, 0.55 mL, 0.6 mmol) dropwise, and the resulting solution was warmed to rt and stirred at rt for 12 h. The reaction mixture was cooled to 0 °C, and water (1.0 mL) was added slowly followed by 30% hydrogen peroxide (0.19 mL) and 1 N sodium hydroxide (0.55 mL). The resulting solution was stirred at rt for 5 min and then worked up with ethyl acetate. The residue was purified by preparative TLC eluting with 40% ethyl acetate/60% hexanes to give **26** as an oily material (100 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (m), 1.9–2.6 (m), 3.42 (s), 3.57 (q, J = 8.8 Hz), 4.45 (s), 4.3–4.6 (m), 7.1-7.5 (m), 7.47 (s), 7.64 (s), 7.74 (s), and 7.76 (s).

8.11. 3-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-3-phenylcyclopentanone (27)

To a solution of **26** (142 mg, 0.3 mmol) in dichloromethane (10 mL) at rt was added pyridinium chlorochromate (146 mg, 0.7 mmol and powered 4A° molecular sieves (146 mg), and the resulting mixture was stirred at rt for 1.5 h and then filtered through a small pad of silica gel. The filtrate was evaporated in vacuo, and the residue was purified by preparative TLC eluting with 30% ethyl acetate/70% hexanes to give **27** as an oily material (150 mg, 100%). This crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3–2.6 (4H, m), 2.68 (1H, d, J = 17.6 Hz), 2.76 (1H, d, J = 17.6 Hz), 3.52 (1H, q, J = 9.2 Hz), 3.58 (1H, d, J = 9.2 Hz), 4.52 (2H, s), 7.2-7.4 (5H, m), 7.59 (2H, s), 7.76 (1H, s).

8.12. 5-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-5-phenylpiperidin-2-one (28) and 4-((3,5-bis(trifluoromethyl)benzyloxy)methyl)-4-phenylpiperidin-2-one (5)

A mixture of **27** (34 mg, 0.08 mmol) and sodium azide solution (3.0 M in H_2O, 55 μL, 0.6 mmol) in trifluoroacetic acid (100 μL) was stirred at 65 °C for 1 h. After allowing to cool to rt, the mixture was concentrated under vacuum, and saturated sodium bicarbonate was added. The reaction mixture was extracted with dichloromethane, and the organic layer was separated and concentrated in vacuo, and the crude product was purified by preparative TLC eluting with 80% ethyl acetate/hexanes to give **28** (10 mg, 29% yield) and **5** (9 mg, 26% yield). Lactam **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, s), 7.62 (2H, s), 7.2–7.4 (5H, m), 5.55 (1H, br s), 4.53 (2H, apparent s), 3.62 (1H, d, J = 9.2 Hz), 3.53 (1H, d, J = 9.2 Hz), 3.25 (1H, m), 2.99 (1H, m), 2.91 (1 J, d, J = 17.2 Hz), 2.74 (1H, d,

J = 17.2 Hz). Lactam **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, s), 7.52 (2H, s), 7.2–7.4 (5H, m), 5.91 (1H, br s), 4.52 (1H, d, J = 12.8 Hz), 4.43 (1H, d, J = 12.8 Hz), 3.88 (1H, m), 3.65 (3H, m), 2.36 (1H, m), and 2.21 (3H, m).

8.13. 3-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-3-phenylpiperidine (6)

A solution of **28** (6 mg, 0.014 mmol) in BH_3·THF complex solution (1.5 M in diethyl ether, 46 μL, 0.069 mmol) was heated at 65 °C for 3 h. After the reaction mixture was allowed to cool to rt, methanol (0.1 mL) and 1 N HCl solution (0.1 mL) were added and the mixture was stirred at 65 °C for 1 h. The reaction mixture was concentrated under vacuum and neutralized with 1 N sodium hydroxide solution (0.1 mL) and extracted with dichloromethane, and the organic layer was separated and concentrated in vacuo to give **6** as a colorless oil (4 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (1H, s), 7.55 (2H, s), 7.2–7.4 (5H, s), 4.47 (1H, d, J = 13.2 Hz), 4.42 (1H, d, J = 13.2 Hz), 3.57 (1H, d, J = 9.2 Hz), 3.52 (1H, d, J = 9.2 Hz), 3.37 (1H, d, J = 12.8 Hz), 3.10 (1H, d, J = 12.8 Hz), 2.82 (2H, m), 1.96 (1H, m), 1.68 (1H, m). MS: 418.33 ($M+H^+$).

8.14. 8-Phenyl-1,4-dioxaspiro[4.5]decane-8-carbonitrile (30)

A mixture of **29** (5 g, 25 mmol), ethylene glycol (7 mL) and pyridinium *p*-toluene sulfonate (100 mg) in benzene (100 mL) was stirred at 111 °C in a Dean-Stark apparatus overnight. Saturated sodium bicarbonate was added, and the reaction was extracted with ether and the ether layer was concentrated in vacuo to give **30** (6 g, 98% yield). This crude product was used for the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3–7.6 (5H, s), 3.97 (4H, m), 2.16 (6H, m), and 1.84 (2H, m).

8.15. 8-Phenyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (31)

To a solution of **30** (1.8 g, 7.3 mmol) in toluene (40 mL) at −78 °C was added DIBAL-H (1.0 M solution in toluene, 10.9 mL, 10.9 mmol) slowly, and the reaction mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched with methanol, saturated ammonium chloride was added, and the reaction was extracted with ether and the organic layer was separated and concentrated in vacuo to give **31** as a colorless liquid (1.8 g, 100% yield). This crude material was used directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (1H, s), 7.2–7.4 (5H, m), 3.92 (4H, m), 1.3–2.4 (8H, m).

8.16. (8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (32)

To a solution of **31** (1.8 g, 7.3 mmol) in methanol (30 mL) and THF (10 mL) at 0 °C was added sodium borohydride (276 mg, 7.3 mmol), in portions, and the resulting suspension was stirred at room temperature for 1 h. The solvent was removed, and saturated sodium bicarbonate was added. The reaction mixture was extracted with ethyl acetate and the organic layer was separated and concentrated in vacuo to give **32** (1.7 g, 94% yield), which was used directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2–7.4 (5H, m), 3.90 (4H, m), 3.50 (2H, d, J = 6.0 Hz), 1.1–2.3 (7H, m).1.48–1.81 (7H, m).

8.17. 8-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-8-phenyl-1,4-dioxaspiro[4.5]decane (33)

To a solution of **32** (1.7 g, 6.9 mmol) and 3,5-(bis-trifluoromethyl)benzyl bromide (1.3 mL, 7.2 mmol) in DMF (15 mL) at 0 °C was added sodium hydride (95% oil dispersion, 260 mg, 10.3 mmol) and the resulting suspension was stirred at rt for 2 h. Water was added, and the reaction mixture was extracted with ether. The ether layer was separated and concentrated in vacuo. The crude material was purified by silica gel flash chromatography eluting with from 15–20% ethyl acetate/hexanes to give **33** as a colorless oil (1.2 g, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (1H, s), 7.54 (2H, s), 7.2–7.4 (5H, m), 4.41 (2H, s), 3.95 (4H, m), 3.40 (2H, s), 1.6–2.4 (8H, m).

8.18. 4-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-4-phenylcyclohexanone (34)

To a solution of **33** (1.2 g, 2.5 mmol) in acetone (40 mL) at rt was added 1 N HCl solution (10 mL) and the resulting mixture was heated at reflux for 1 h. Acetone was removed in vacuo, and the reaction mixture was extracted with ether. The ether layer was separated and concentrated in vacuo to give **34** as a colorless oil (1.1 g, 100%). This crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (1H, s), 7.55 (2H, s), 7.2–7.4 (5H, m), 4.45 (2H, s), 3.46 (2H, s), 2.65 (2H, m), 2.34 (4H, m), and 2.03 (2H, m).

8.19. 4-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-4-phenylcyclohexanol (35)

To a solution of **34** (400 mg, 0.9 mmol) in methanol (5 mL) was added sodium borohydride (53 mg, 1.4 mmol), and the reaction mixture was stirred at rt for 10 min. Methanol was removed in vacuo, water was added, and usual work-up with ethyl acetate provided **35** as a colorless oil (416 mg, 100%). This crude product was used directly for the next step without purification

8.20. 1-(((1-Phenylcyclohex-3-enyl)methoxy)methyl)-3,5-bis(trifluoromethyl)benzene (36)

To a solution of **35** (416 mg, 0.9 mmol) in pyridine (3 mL) at 0 °C was added methanesulfonyl chloride (0.11 mL, 1.5 mmol), and the reaction mixture was stirred at 0 °C for 1 h and then rt for 2 h. Water was added, and usual work-up with ethyl acetate gave the crude 4-((3,5-bis(trifluoromethyl)benzyloxy)methyl)-4-phenylcyclohexyl methanesulfonate. To this crude mesylate were added DBU (0.97 mL) and DMAP (20 mg), and the resulting mixture was heated at 80 °C for 12 h. Water and ethyl acetate were added, and the reaction was worked up as usual. The crude product was purified by preparative TLC eluting with 15% ethyl acetate/hexanes to give olefin **36** as a colorless oil (100 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, s), 7.58 (2H, s), 7.2–7.4 (5H, m), 5.76 (1H, m), 5.74 (1H, m), 4.47 (2H, apparent d), 3.61 (1H, d, J = 8.8 Hz), 3.52 (1H, d, J = 8.8 Hz), 2.9 (1H, br. d), 2.4 (1H, br. d), 1.7-2.1 (4H, m).

8.21. 1-(((1-Phenylcyclohexyl)methoxy)methyl)-3,5-bis(trifluoromethyl)benzene (7)

A mixture of **36** and 10% Pd/C (5 mg) in ethanol (0.4 mL) was hydrogenated under hydrogen balloon for 12 h. The reaction mixture was passed through a pad of Celite, and the filtrate was evaporated in vacuo to give 7 as a colorless oil (4 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.56 (2H, s), 7.2–7.4 (5H, m), 4.41 (2H, s), 3.40 (2H, s), 2.20 (2H, m), 1.75 (2H, m), 1.2–1.7 (6H, m).

8.22. 3-Phenylcyclohex-2-enone

To a solution of 3-ethoxycyclo-hex-2-enone (2.0 g, 14.3 mmol) in THF (2 mL) at 0 °C was added phenylmagnesium bromide (1.0 M solution in THF, 15 mL, 15 mmol) slowly. After the addition,

the reaction mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was quenched with 1 N HCl solution (15.16 mL) and then extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give 3-phenylcyclohex-2-enone as yellow solid (2.5 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (2H, dt, J = 4, 12 Hz), 2.48 (2H, t, J = 8 Hz), 2.77 (2H, dt, J = 2, 6 Hz), 6.41 (1H, t, J = 2 Hz), 7.39–7.41 (3H, m), 7.52–7.54 (2H, m).

8.23. 3-Oxo-1-phenylcyclohexanecarbonitrile (37)

A mixture of 3-phenylcyclohex-2-enone (2.5 g, 14.3 mmol), potassium cyanide (1.9 g, 29 mmol) and trimethylamine hydrochloride (2.1 g, 21.5 mmol) in H_2O (10 mL) and DMF (57 mL) was heated at 93 °C for 6 h. After the reaction mixture was allowed to cool to rt, saturated sodium bicarbonate was added, and the reaction mixture was extracted with ether. The ether layer was separated and concentrated in vacuo to give 2.6 g (92% yield) of the crude **37** which was directly taken to the next step without further purification.

8.24. 3,3-Ethylenedioxy-1-phenylcyclohexanecarbo-nitrile (38)

A mixture of **37** (2.6 g, 13.1 mmol), ethylene glycol (3.7 mL, 65.5 mmol) and pyridinium *p*-toluene sulfonate (100 mg) in benzene (40 mL) was stirred at 111 °C in Dean–Stark apparatus overnight. After the reaction mixture was allowed to cool to rt, saturated sodium bicarbonate was added, and the reaction mixture was extracted with ether. The organic layer was separated and concentrated in vacuo to give crude material that was purified by silica gel flash chromatography eluting with a gradient of 25% ethyl acetate/75% hexane to 30% ethyl acetate/70% hexane to give **38** as a white solid (1.7 g, 48% yield from 3-phenylcyclohex-2-enone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (1H, dt, J = 4, 16 Hz), 1.70–1.79 (1H, m), 1.89–1.96 (3H, m), 2.06–2.28 (3H, m), 3.89–3.97 (2H, m), 4.03–4.12 (2H, m), 7.28–7.32 (1H, m), 7.36–7.39 (2H, m), 7.48–7.51 (2H, m). MS: 266.37 ($M+Na^+$).

8.25. 3,3-Ethylenedioxy-1-phenylcyclohexanecarba-ldehyde (39)

To a solution of **38** (1.7 g, 6.8 mmol) in toluene (20 mL) at −78 °C was added DIBAL-H (1.0 M solution in toluene, 8.9 mL) slowly. The reaction mixture was stirred for 1 h. The reaction mixture was allowed to warm to rt, 1 N HCl solution (2.6 mL) was added, and the reaction mixture was stirred at rt for 1 h. Saturated sodium bicarbonate was added, and the reaction was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo and the crude material was purified by filtering through a short silica gel pad with dichloromethane to give **39** as a colorless sticky oil (1.4 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32–1.40 (1H, m), 1.46–1.54 (1H, m), 1.72–1.86 (3H, m), 2.08 (1H, d, J = 16 Hz), 2.59–2.67 (2H, m), 3.94–4.07 (4H, m), 7.15–7.36 (5H, m), 9.36 (1H, d, J = 4 Hz).

8.26. (3,3-Ethylenedioxy-1-phenylcyclohexyl)-methanol (40)

To a solution of **39** (1.4 g, 5.8 mmol) in methanol (25 mL) at 0 °C was added sodium borohydride (221 mg, 5.8 mmol) in portions, and the resulting suspension was stirred at rt overnight. Saturated sodium bicarbonate was added, methanol was removed under vacuum, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **40** as a clear colorless sticky oil (1.3 g, 87% yield). This crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.81 (7H, m), 1.88 (1H, d, J = 16 Hz), 2.06 (1H, d, J = 12 Hz), 2.22 (1H, d, J = 12 Hz), 3.73–4.06 (5H, m), 7.15–7.25 (2H, m), 7.31–7.38 (3H, m). MS: 271.40 ($M+Na^+$).

8.27. 1-(((3,3-Ethylenedioxy-1-phenylcyclohexyl)-methoxy)methyl)-3,5-bis(trifluoromethyl)-benzene (41)

To a solution of **40** (726 mg, 2.9 mmol) and 3,5-(bis-trifluoromethyl)benzyl bromide (1.1 mL, 5.8 mmol) in DMF (6 mL) at 0 °C was added sodium hydride (95% oil dispersion, 148 mg, 5.9 mmol), and the resulting suspension was stirred at rt for 2 h. Saturated sodium bicarbonate was added, and the reaction mixture was extracted with dichloromethane. The dichloromethane layer was separated and concentrated in vacuo The crude material was purified by silica gel flash chromatography eluting with a gradient from 10% acetone/90% hexanes to 15% acetone/85% hexanes to give **41** as clear pale yellow sticky oil (990 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (1H, m), 1.74 (4H, t, J = 8 Hz), 1.90 (1H, d, J = 12 Hz), 2.13 (1H, m), 2.24 (1H, d, J = 16 Hz), 3.70 (2H, dd, J = 8, 36 Hz), 3.91 (4H, m), 4.45 (2H, s), 7.21 (2H, t, J = 8 Hz), 7.29–7.38 (4H, m), 7.53 (2H, s), 7.71 (1H, s). MS: 475.14 ($M+H^+$).

8.28. 3-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-3-phenylcyclohexanone (42)

To a solution of **41** (990 mg, 2.1 mmol) in acetone (4 mL) at rt was added 1 N HCl solution (3.1 mL), and the resulting mixture was heated under reflux for 2 h. Saturated sodium bicarbonate was added, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **41** as clear pale yellow sticky oil (830 mg, 92% yield). The crude product was used directly for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (1H, m), 1.88 (1H, m), 2.19 – 2.24 (2H, m), 2.29–2.32 (2H, m), 2.85 (2H, dd, J = 12, 68 Hz), 3.51 (2H, dd, J = 12, 56 Hz), 4.52 (2H, dd, J = 16, 18 Hz), 7.22–7.25 (1H, m), 7.32 (4H, d, J = 4 Hz), 7.63 (2H, s), 7.77 (1H, s). MS: 453.37 ($M+Na^+$).

Isomer A (**43**) and isomer B (**44**) of 4-((3,5-bis(trifluoromethyl)benzyloxy)methyl)-4-phenyl-azepan-2-one and Isomer A (45) and isomer B (**46**) of 6-((3,5-bis(trifluoromethyl)-benzyloxy)methyl)-6-phenylazepan-2-one. A mixture of 42 (730 mg, 1.7 mmol) and sodium azide solution (3.0 M in water, 1.1 mL, 3.4 mmol) in trifluoroacetic acid (5.6 mL) was stirred at 65 °C for 1 h. After cooling down, the mixture was concentrated under vacuum, and saturated sodium bicarbonate. The reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo and the crude mixture was purified by silica gel flash chromatography eluting with from 30% acetone/70% hexanes to 40% acetone/60% hexanes to give a mixture of 43–46 as a colorless sticky oil (540 mg, 71% yield).

The above mixture of 4 isomers was separated by chiral HPLC (Chiralpak AS semi-prep column, 20 × 250 mm, 10 μm, solvents 5% EtOH/95% heptane for 83 min., 15% EtOH/ 85% heptane for 17 min., 5% EtOH/95% heptane for 10 min, flow rate 10 mL/min, UV 205 nm) to give **43** (110 mg), **44** (110 mg), **45** (80 mg) and **46** (90 mg) as colorless oils.

Compound **43**: Retention time is 44.02 min. with >99.9% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72–1.80 (2H, m), 2.04 (1H, m), 2.51 (1H, d, J = 16 Hz), 2.94 (1H, d, J = 16 Hz), 3.10 (1H, d, J = 16 Hz), 3.17 (1H, m), 3.24 – 3.32 (1H, m), 3.45 (2H, s), 4.46 (2H, s), 5.81 (1H, s), 7.24 (1H, t, J = 8 Hz), 7.34 (2H, t, J = 8 Hz), 7.47 (2H, d, J = 8 Hz), 7.61 (2H, s), 7.75 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 36.7, 42.9, 43.2, 44.1, 71.8, 81.0, 121.8 (quintet, J = 3 Hz), 123.7 (q, J = 271 Hz), 127.2, 127.5 (d, J = 4 Hz), 127.6, 128.8, 132.0 (q, J = 33 Hz), 141.4, 142.0, 175.9. Optical rotation, $[\alpha]_D^{24}$ −9.03 (*c* 1.77, CH_2Cl_2). HRMS calcd for $C_{22}H_{22}NO_2F_6$ 446.1555 ($M+H^+$), found 446.1571.

Compound **44**: Retention time is 53.38 min. with >99.8% *ee*. ^{1}H and ^{13}C NMR data are the same as **43**. Optical rotation, $[\alpha]_D^{24}$ +7.10 (*c* 1.69, CH_2Cl_2). HRMS calcd for $C_{22}H_{22}NO_2F_6$ 446.1555 (MH^+), found 446.1573.

Compound **45**: Retention time is 73.61 min. with >99.9% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (2H, m), 1.97 (1H, m), 2.28 (1H, m), 2.51 (2H, m), 3.50 (1H, d, J = 8 Hz), 3.59 (1H, d, J = 8 Hz), 3.61 (1H, dd, J = 8, 12 Hz), 3.77 (1H, dd, J = 8, 12 Hz), 4.43 (1H, d, J = 12 Hz), 4.53 (1H, d, J = 12 Hz), 5.72 (1H, br s), 7.23-7.38 (5H, m), 7.57 (2H, s), and 7.76 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 35.9, 37.0, 45.1, 47.7, 71.9, 76.9, 121.9 (quintet, J = 4 Hz), 123.6 (q, J = 271 Hz), 127.1, 127.3, 127.5 (d, J = 2 Hz), 129.1, 132.1 (q, J = 33 Hz), 141.1, 142.0, 177.9. HRMS calcd for $C_{22}H_{22}NO_2F_6$ 446.1555 (M+H$^+$), found 446.1556.

Compound **46**: Retention time is 95.79 min. with >99.9% *ee*. ^{1}H and ^{13}C NMR data are the same as **45**. HRMS calcd for $C_{22}H_{22}NO_2F_6$ 446.1555 (M+H$^+$), found 446.1549.

8.29. Isomer A of 4-((3,5-bis(trifluoromethyl)benzyloxy)-methyl)-4-phenylazepane (8)

A solution of **43** (90 mg, 0.2 mmol) in borane·THF complex solution (1.5 M in diethyl ether, 1.1 mL, 1.7 mmol) was stirred at rt overnight and then heated at 65 °C for 1 h. After being allowed to cool to rt, the reaction mixture was concentrated under vacuum, methanol (0.4 mL) was added followed by 1 N HCl solution (0.4 mL), and the reaction mixture was heated at 65 °C for 2 h. The mixture was concentrated under vacuum, neutralized with 1 N NaOH solution and extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **8** as a colorless sticky oil (90 mg, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65–1.73 (1H, m), 1.80–1.87 (1H, m), 1.94–2.01 (1H, m), 2.08 (1H, ddd, J = 4, 8, 16 Hz), 2.31–2.37 (1H, m), 2.48 (1H, dd, J = 4, 16 Hz), 2.86–3.01 (3H, m), 3.16 (1H, dd, J = 4, 16 Hz), 3.42 (2H, s), 4.43 (2H, s), 7.21–7.23 (1H, m), 7.30–7.36 (4H, m), 7.55 (2H, s), 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 34.0, 36.4, 43.5, 45.6, 48.2, 71.7, 81.5, 121.3 (quintet, J = 3 Hz), 123.3 (q, J = 271 Hz), 126.4, 126.9, 127.0 (d, J = 3 Hz), 128.5, 131.5 (q, J = 33 Hz), 141.2, 143.8. HRMS calcd for $C_{22}H_{24}NOF_6$ 432.1762 (M + H$^+$), found 432.1767.

8.30. Isomer B of 4-((3,5-bis(trifluoromethyl)-benzyl-oxy)methyl)-4-phenylazepane (9)

This compound was made from **44** in the same fashion as compound **8** to give the product as a clear colorless sticky oil (quantitative yield). ^{1}H and ^{13}C NMR data are the same as **8**. HRMS calcd for $C_{22}H_{24}NOF_6$ 432.1762 (M + H$^+$), found 432.1774.

8.31. (±)-4-((3,5-Bis(trifluoromethyl)-benzyl-oxy)methyl)-4-phenylazepane (47)

A mixture of **34** (100 mg, 0.07 mmol) and NaN_3 solution (3.0 M in H_2O, 0.15 mL) in trifluoroacetic acid (0.3 mL) was stirred at 65 °C for 1 h. Trifluoroacetic acid was removed in vacuo, saturated sodium bicarbonate was added, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give the crude product, which was purified by preparative TLC eluting with 80% ethyl acetate/hexanes to give (±)-**47** (48 mg, 48% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (1H, s), 7.53 (2H, s), 7.2–7.4 (5H, m), 5.96 (1H, br. s), 4.45 (2H, apparent s), 3.36 (2H, s), 3.3 (1H, m), 3.1 (1H, m), 2.4 (4H, m), 1.9 (2H, m). MS: 446.50 (M+H$^+$).

8.32. (±)-4-((3,5-Bis(trifluoro-methyl)-benzyl-oxy)methyl)-4-phenylazepane ((±)8/9)

A solution of **47** (38 mg, 0.09 mmol) in borane·THF complex solution (1.5 M in diethyl ether, 0.23 mL) was stirred at rt overnight and then heated at 65 °C for 1 h. After being allowed to cool down, the reaction mixture was concentrated under vacuum, methanol (0.2 mL) was added followed by 1 N HCl solution (0.2 mL), and the reaction mixture was heated at 65 °C for 2 h. The mixture was concentrated under vacuum, neutralized with 1 N NaOH solution and extracted with dichloromethane/The organic layer was separated and concentrated in vacuo to give (±)**8/9** as a colorless sticky oil (35 mg, 92% yield). The spectroscopic data are identical to those obtained following Scheme 3.

8.33. Isomer A 4-((3,5-bis(trifluoromethyl)benzyloxy)-methyl)-1-methyl-4-phenylazepane (10)

A solution of **8** (3 mg), paraformaldehyde (3 mg) and formic acid (2.2 mg) in chloroform (0.1 mL) was stirred at 65 °C for 12 h. The mixture was concentrated under vacuum and passed through an anion exchange cartridge to remove formic acid. The crude product was purified by preparative TLC eluting with 10% methanol/89% dichloromethane/1% NH_4OH to give **10** as a clear sticky oil (2 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67–1.74 (1H, m), 1.83–1.91 (1H, m), 2.05–2.23 (3H, m), 2.38 (3H, s), 2.42–2.61 (3H, m), 2.79 (2H, m), 3.45 (2H, s), 4.44 (2H, s), 7.22 (1H, t, J = 4 Hz), 7.32 (4H, d, J = 4 Hz), 7.55 (2H, s), 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.4, 29.8, 34.9, 45.5, 46.7, 53.3, 60.2, 71.8, 81.1, 121.3 (quintet, J = 3.75 Hz), 123.4 (q, J = 271 Hz), 126.3, 126.8, 127.1, 128.4, 131.6 (q, J = 32.5 Hz), 141.4, 145.7. HRMS calcd for $C_{23}H_{26}NOF_6$ 446.1919 (M+H$^+$), found 446.1916.

8.34. Isomer B of 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-1-methyl-4-phenylazepane (11)

This compound was made from **9** in the same fashion as **10** to give **11** as a clear sticky oil (2 mg, 67% yield). ^{1}H and ^{13}C NMR data are the same as **10**. MS: 446.04 (MH$^+$). HRMS calcd for $C_{23}H_{26}NOF_6$ 446.1919 (M+H$^+$), found 446.1929.

8.35. Isomer A of 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-1-ethyl-4-phenylazepane (12)

To a solution of **8** (3 mg) in glacial acetic acid (0.05 mL) was added sodium borohydride (2 mg) in two portions, and the reaction mixture was stirred at rt for 12 h. The mixture was concentrated under vacuum, saturated sodium bicarbonate was added, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **12** as a colorless sticky oil (1.8 mg, 56% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (3H, br. s), 1.68 (1H, m), 1.79 (1H, m), 2.02–2.10 (2H, m), 2.18 (1H, dd, J = 10, 15 Hz), 2.39 (1H, m), 2.49 (4H, m), 2.73 (2H, br s), 3.46 (2H, dd, J = 5, 15 Hz), 4.44 (2H, s), 7.21 (1H, t, J = 5 Hz), 7.30–7.35 (4H, m), 7.56 (2H, s), 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3, 23.7, 29.7, 34.9, 45.6, 50.1, 52.2, 57.3, 71.7, 81.2, 121.2 (quintet, J = 2.5 Hz), 123.4 (q, J = 271 Hz), 126.1, 126.9, 127.1 (d, J = 5 Hz), 128.3, 131.6 (q, J = 32.5 Hz), 141.5, 146.3. HRMS calcd for $C_{24}H_{28}NOF_6$ 460.2075 (M+H$^+$), found 460.2080.

8.36. Isomer B of 4-((3,5-bis(trifluoromethyl)-benzyloxy)ethyl)-1-ethyl-4-phenylazepane (13)

This compound was made from **9** in the same fashion as **12** from **8**. ^{1}H and ^{13}C NMR data are the same as **12.** HRMS calcd for $C_{24}H_{28}NOF_6$ 460.2075 (M+H$^+$), found 460.2075.

8.37. Isomer A of 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-1-benzyl-4-phenylazepane (14)

A mixture of **8** (3 mg) and benzaldehyde (3 mg) in methanol (0.15 mL) was stirred at room temperature for 0.5 hr, then sodium cyanoborohydride (1.0 M solution in THF, 0.02 mL) was added

followed by 1 drop of trifluoroacetic acid. The mixture was stirred at rt overnight and concentrated under vacuum. Saturated sodium bicarbonate was added, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **14** as a colorless oil (1.9 mg, 52% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62–1.72 (1H, m), 1.72–1.82 (1H, m), 2.00–2.08 (2H, m), 2.18–2.24 (1H, m), 2.30–2.36 (1H, m), 2.48–2.51 (2H, m), 2.65 (2H, m), 3.45 (2H, brd s), 3.54 (2H, brd s), 4.43 (2H, s), 7.21–7.33 (10H, m), 7.56 (2H, s), 7.73 (1H, s). HRMS *calcd* for $C_{29}H_{30}NOF_6$ 522.2232 ($M+H^+$), found 522.2241.

8.38. Isomer B of 4-((3,5-bis(trifluoromethyl)-benzyloxy)-methyl)-1-benzyl-4-phenylazepane (15)

This compound was made from **9** in the same fashion as **14** from **8**. ^{1}H NMR data are the same as **20.** HRMS *calcd* for $C_{29}H_{30}NOF_6$ 522.2232 ($M+H^+$), found 522.2219.

8.39. Isomer A of 3-((3,5-bis(trifluoromethyl)benzyloxy)methyl)-3-phenyl-azepane (16)

This compound was made from **45** in the same fashion as **8** from **43**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.4-2.0 (5H, m), 2.23 (1H, dd, J = 6, 13.6 Hz), 2.74 (1H, m), 2.98 (1H, m), 2.22 (1H, d, J = 14.4 Hz), 3.27 (1H, d, 14.4 Hz), 3.51 (1H, d, 8.8 Hz), 3.56 (1H, d, J = 8.8 Hz), 4.58 (2H, s), 7.1–7.4 (5H, m), 7.60 (2H, s), and 7.74 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 32.0, 35.5, 47.8, 51.2, 56.1, 71.9, 79.7, 121.3 (quintet, J = 4 Hz), 123.4 (q, J = 271 Hz), 126.3, 126.9, 127.1 (d, J = 3 Hz), 128.4, 131.7 (q, J = 25 Hz), 141.5, 145.0. HRMS calcd for $C_{22}H_{24}NOF_6$ 432.1762 ($M+H^+$), found 432.1763.

8.40. Isomer B of 3-((3,5-bis(trifluoromethyl)benzyloxy)methyl)-3-phenylazepane (17)

This compound was made from **46** in the same fashion as **8** from **43**. ^{1}H and ^{13}C NMR data are the same as **16**. HRMS calcd for $C_{22}H_{24}NOF_6$ 432.1762 ($M+H^+$), found 432.1762.

8.41. Isomer A of 3-((3,5-bis(trifluoromethyl)benzyloxy)-methyl)-1-methyl-3-phenylazepane (18)

This compound was made from **16** in the same fashion as **10** from **8**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.6 (4H, m), 1.8 (1H, m), 2.1 (1H, m), 2.39 (3H, s), 2.45 (1H, m), 2.65 (1H, m), 2.79 (1H, AB quartet, J = 16 Hz), 2.94 (1H, AB quartet, J = 16 Hz), 3.57 (1H, AB quartet, J = 12 Hz), 3.71 (1H, d, J = 12 Hz0, 4.48 (1H, d, J = 12 Hz), 4.51 (1H, AB quartet, J = 12 Hz), 7.2–7.4 (5H, m), 7.60 (2H, s), and 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.4, 29.7, 36.6, 46.5, 49.1, 60.5, 64.8, 71.8, 78.6, 121.3 (quintet, J = 3 Hz), 123.4 (q, J = 271 Hz), 126.1, 126.7, 127.1, 128.2, 131.6 (q, J = 32.5 Hz), 141.6, 146.2. HRMS calcd for $C_{23}H_{26}NOF_6$ 446.1919 (MH^+), found 446.1924.

8.42. Isomer B of 3-((3,5-bis(trifluoromethyl)benzyloxy)-methyl)-1-methyl-3-phenylazepane (19)

This compound was made from **17** in the same fashion as **10** from **8**. ^{1}H and ^{13}C NMR data are the same as **24**. HRMS calcd for $C_{23}H_{26}NOF_6$ 446.1919 ($M+H^+$), found 446.1914.

8.43. 2-Butyl-2-phenylhex-5-enenitrile (48)

To a solution of 2-phenylacetonitrile (1 mL, 8.7 mmol) in DMF (1.0 mL) at 0 °C was added sodium hydride (95% oil dispersion, 547 mg, 21.7 mmol) and the resulting suspension was stirred at 0 °C for 10 min. 4-Bromobut-1-ene (2.2 mL, 21.7 mmol) was added, and the reaction mixture was stirred at rt for 2 h. Saturated sodium chloride was added, and the reaction mixture was worked up with ethyl acetate. The residue was purified by silica gel flash chromatography eluting with 10% ethyl acetate/90% hexanes to give **48** as an oil (773 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.8–2.3 (8H, m), 4.95 (4H, m), 5.73 (2H, m), and 7.31 (5H, m).

8.44. (Z)-1-Phenylcyclohept-4-enecarbonitrile (49)

To a solution of **48** (1.5 g, 6.7 mmol) in dichloromethane (140 mL) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (270 mg, 0.3 mmol) and the resulting suspension was heated under reflux for 1 h. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography eluting with 10% ethyl acetate/hexanes to give **49** as an oil (1.3 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (2H, t, J = 12.4 Hz), 2.11 (2H, m), 2.30 (2H, m), 2.57 (2H, t, J = 12.0 Hz), 5.91 (2H, m), 7.38 (5H, m).

8.45. (Z)-1-Phenylcyclohept-4-enecarbaldehyde (50)

To a solution of **49** (1.1 g, 5.6 mmol) in toluene (40 mL) at −78 °C was added DIBAL-H (1.0 M solution in toluene, 11.2 mL, 11.2 mmol), and the resulting solution was stirred at −78 °C for 1 h. The reaction was quenched with saturated ammonium and then extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo and the residue was purified by silica gel chromatography eluting with 10% ethyl acetate/hexanes to give **50** (800 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (6H, m), 2.37 (2H, m), 5.69 (2H, s), 7.30 (5H, m), and 9.38 (1H, s).

8.46. (*Z*)-(1-Phenylcyclohept-4-enyl)methanol (51)

To a solution of **50** (800 mg, 4 mmol) in methanol (30 mL) was added sodium borohydride (304 mg, 8 mmol), and the resulting mixture was stirred at room temperature for 1 h. Methanol was removed in vacuo, water was added, and the reaction mixture was extracted with ethyl acetate The organic layer was separated and concentrated in vacuo to give **51** as an oil (830 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (2H, m), 2.20 (6H, m), 3.55 (2H, s), 5.68 (2H, m), 7.35 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 32.9, 47.3, 71.7, 126.3, 127.4, 128.6, 131.2, 144.3.

8.47. (Z)-5-((3,5-Bis(trifluoromethyl)benzyloxy)-methyl)-5-phenylcyclohept-1-ene (52)

To a solution of **51** (830 mg, 4.11 mmol) and 3,5-(bis-trifluoromethyl)benzyl bromide (0.79 mL, 4.31 mmol) in DMF (8 mL) at 0 °C was added sodium hydride (95% oil dispersion, 156 mg, 6.17 mmol) and the resulting suspension was stirred at rt for 1 h. The reaction was quenched with water and then extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo and the residue was purified by silica gel chromatography eluting with 10% ethyl acetate/90% hexanes to give **52** as an oily material (1.1 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (2H, m), 2.15 (4H, m), 2.28 (2H, m), 3.47 (2H, s), 4.42 (2H, s), 5.67 (2H, m), 7.22 (1H, m), 7.34 (2H, m), 7.39 (2H, m), 7.54 (2H, s), and 7.72 (1H, s). HRMS m/z calcd for $C_{23}H_{21}F_6O$ $(M-H)^-$ 427.1497, found 427.1481.

8.48. 4-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-4-phenylcycloheptanol (53)

To a solution of **52** (56 mg, 0.13 mmol) in THF (0.55 mL) at 0 °C was added borane-tetrahydrofuran complex (1.5 M solution, 0.17 mL, 0.26 mmol) dropwise, and the resulting solution was

allowed to warm to rt and stirred at rt for 12 h. The reaction mixture was cooled to 0 °C, and water (10.50 mL) was added slowly followed by 30% hydrogen peroxide (0.19 mL) and 1 N sodium hydroxide (0.30 mL). The resulting solution was stirred at rt for 5 min and then extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo and the residue was purified by preparative TLC eluting with 40% ethyl acetate/60% hexanes to give **52** as an oily material (27 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3-2.4 (m), 3.40 (s), 3.44 (s), 4.43 (s), 7.32 (m), 7.56 (s), and 7.73 (s). HRMS *m*/*z* calcd for $C_{23}H_{23}F_6O_2$ $(M-H)^-$ 445.1602, found 445.1607.

8.49. 4-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-4-phenylcycloheptanone (54)

To a solution of **53** (26 mg, 0.058 mmol) in dichloromethane (0.5 mL) at rt were added pyridinium chlorochromate (25 mg) and powered 4A° molecular sieves (26 mg), and the resulting mixture was stirred at rt for 1.5 h and then filtered through a small pad of silica gel eluting with dichloromethane. The filtrate was evaporated in vacuo, and the residue was purified by preparative TLC eluting with 30% ethyl acetate/70% hexanes to give **54** as an oily material (21 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (3H, m), 1.98 (1H, dd, J = 11.6, 1.2 Hz), 2.48 (6H, m), 3.37 (1H, d, J = 8.8 Hz), 3.39 (1H, d, J = 8.8 Hz), 4.42 (2H, s), 7.28 (1H, m), 7.35 (4H, m), 7.56 (2H, m), and 7.74 (1H, s). HRMS *m*/*z* calcd for $C_{23}H_{21}F_6O_2$ $(M-H)^-$ 443.1446, found 443.1457.

6-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-6-phenylazocan-2-one (**55**) and 5-((3,5-bis(trifluoro-methyl)benzyloxy)methyl)-5-phenylazocan-2-one (**56**). To a solution of 54 (135 mg, 0.3 mmol) in trifluoroacetic acid (0.6 mL) was added sodium azide (3.0 M solution in water, 0.2 mL, 0.6 mmol) and the resulting solution was heated at 65 °C for 1 h. Trifluoroacetic acid was removed in vacuo, saturated sodium bicarbonate solution was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo and the residue was purified by preparative TLC eluting with 60% ethyl acetate/40% hexanes to give 55 (37 mg, 26%) and 56 (44 mg, 31%).

Compound **55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.5-2.2 (7H, m), 2.63 (1H, dd, J = 5.5, 115.0 Hz), 3.31 (1H, d, J = 8.5 Hz), 3.37 (1H, d, J = 8.5 Hz), 3.44 (1H, m), 3.77 (1H, m), 4.43 (1H, d, J = 8.0 Hz), 4.46 (1H, d, J = 8.0 Hz), 5.97 (1H, s), 7.26 (3H, m), 7.36 (2H, m), 7.49 (2H, s), and 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9, 30.2, 31.8, 38.8, 40.4, 45.5, 71.8, 84.1, 121.5, 123.4 (q, J = 262.5 Hz), 126.7, 127.1, 127.5, 128.5, 131.6 (q, J = 37.5 Hz), 141.1 (d, J = 25.0 Hz), 176.8.

Compound **56**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (1H, m), 1.85 (2H, m), 2.06 (2H, m), 2.49 (1H, m), 2.77 (4H, m), 3.33 (1H, d, J = 8.5 Hz), 3.37 (1H, d, J = 8.5 Hz), 4.34 (1H, d, J = 4.34 (1H, d, J = 13.0 Hz), 4.44 (1H, d, J = 13.0 Hz), 5.61 (1H, s), 7.28 (3H, m), 7.38 (t, J = 8.0 Hz), 7.50 (2H, s), and 7.73 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6, 29.9, 30.1, 40.9, 45.4, 71.8, 83.7, 121.4, 123.4 (q, J = 262.5 Hz), 126.6, 127.1, 127.5, 127.6, 128.4, 131.7 (q, J = 37.5 Hz), 141.1 (d, J = 25.0 Hz), 178.0.

8.50. 4-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-4-phenylazocane (20)

To a solution of **55** (18 mg, 0.04 mmol) in THF (0.10 mL) at rt was added borane-THF complex (1.50 M solution in THF, 0.10 mL, 0.16 mmol) and the resulting solution was heated at 65 °C in a sealed vial for 3 h. The solution was allowed to cool to room temperature, and methanol (0.10 mL) was added slowly followed by 1 N hydrochloric acid (0.10 mL), and the reaction mixture was heated at 65 °C for 2 h. The solvents were removed in vacuo, 1 N sodium hydroxide was added, and the reaction mixture was extracted with dichloromethane. The organic layer was separated and concentrated in vacuo to give **20** as an oil (16 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (5H, m), 2.09 (3H, m), 2.30 (1H, m), 2.94 (4H, m), 3.44 (1H, d, J = 8.8 Hz), 3.47 (1H, d, J = 8.8 Hz), 4.42 (2H, s), 7.21 (1H, m), 7.37 (4H, m), 7.55 (2H, s), and 7.73 (1H, s). MS: 446.03 ($M+H^+$).

8.51. 5-((3,5-Bis(trifluoromethyl)benzyloxy)methyl)-5-phenylazocane (21)

This compound was obtained from lactam **56** in the same fashion as **20** from **55**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (4H, m), 1.87 (1H, br s), 2.09 (4H, m), 2.72 (2H, m), 2.88 (2H, m), 3.43 (2H, s), 4.41 (2H, s), 7.21 (1H, m), 7.39 (4H, m), 7.54 (2H, s), and 7.21 (1H, s). MS: 446.03 ($M+H^+$).

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