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2,5-Disubstituted tetrahydrofurans as selective serotonin re-uptake inhibitors

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ABSTRACT

Enhancement of 5-hydroxytryptamine (5-HT, serotonin) neurotransmission is a viable means of treating depression. On the basis of this observation, agents that inhibit re-uptake of 5-HT were prepared based on (−)-cocaine and aryltropanes as lead compounds because they are reasonably potent 5-HT re-uptake inhibitors. Molecular dissection of an aryltropane provided a series of 5- and 6-membered ring compounds. From among this library of compounds a series of disubstituted tetrahydrofurans bearing 2-alkyl aryl and 5-alkyl amino groups were identified as having highly potent and selective 5-HT re-uptake inhibition. The compounds were evaluated for their ability to compete with radiolabeled RTI-55 binding and to inhibit re-uptake of neurotransmitters at the human dopamine, serotonin and norepinephrine transporters. Based on potency (e.g., K_i = 800 pM) and significant functional selectivity (e.g., IC_{50} ratios for human dopamine:serotonin or norepinephrine:serotonin, ⩾1397) highly potent and selective serotonin re-uptake inhibitors were identified. Optimal features playing a dominant role in binding affinity and re-uptake inhibition included lipophilic substitution on the aromatic moiety, *trans* relative stereochemistry of the 2,5-disubstituted tetrahydrofuran ring, and a total of four or five methylene groups between the alkyl amine and the alkyl aryl moiety and the tetrahydrofuran group. A number of the most potent serotonin re-uptake inhibitors were tested in Balb/c mice in the forced-swim test (FST), a behavioral test used to measure the effects of antidepressant agents. Acute administration of **32c** (10 mg/kg), or **32d** (10 mg/kg) ip tended to decrease the duration of mouse immobility in the FST although the effect was not statistically significant.

1. Introduction

Serotonin and related biogenic amine transporters are important in modulating motor, endocrine and emotional functions.[1] Serotonin (5-HT) is altered in neurological and psychiatric disorders associated with depression and other conditions including drug abuse.[1] Histochemical studies have shown that brain 5-HT neuronal fibers are distinct from dopamine and norepinephrine neurons and 5-HT may play a role in altering depression and psychiatric disorders. New agents may provide insight into structure-activity relationships, and may lead to more selective ligands for improved understanding of differences in potency and selectivity of the human serotonin transporter (hSERT) and for understanding brain physiology and disease.[2] Synthesis of novel, highly potent and selective re-uptake inhibitors of hSERT could provide structure–activity information required for producing more effective antidepressants with fewer side effects. This may also lead to highly potent ligands needed for brain tomography studies that could help to elucidate the pathophysiological mechanisms of 5-HT neurotransmission and the relationship between hSERT occupancy and central nervous system drug action.[3]

Cocaine blocks the re-uptake of dopamine (DA), serotonin (5-HT) and norepinephrine (NE).[4] (−)-Cocaine and aryltropanes (Fig. 1) are relatively potent at inhibiting 5-HT and DA re-uptake, respectively, and influencing neurotransmission.[5,6] Because of their relatively high affinity for the hSERT, (−)-cocaine and aryltropanes were utilized as starting points to develop selective serotonin re-uptake inhibitors (SSRIs). Theoretically, molecular dissection of aryltropanes (i.e., compound **2**, Fig. 1) via cleavage of the 2,3-carbon bond leads to 5-membered ring systems (i.e., compound **3**, Fig. 1).[7,8] Based on the observation that aryltropanes[9] or 'β-CPT compounds' (i.e., (−)-2β-Carbomethoxy-3β-phenyltropane (Troparil))[10] that possess aryl functionality were more metabolically stable than cocaine ester analogs, we designed and synthesized metabolically stable compounds derived from molecular dissection of aryltropanes. The observation that oxa[11] or carbon[12,13] analogs of aryltropanes (structure **3**, Fig. 1) were potent ligands for neurotransmitter transporters[14] and that nortropanes[2] possessed greater binding selectivity for the SERT prompted the synthesis of 2,5-disubstituted heterocyclic analogues (structure **3**, Fig. 1). The pharmacophore points proposed to overlap in the two structures (i.e., **2** and **3**) include the aryl ring, the

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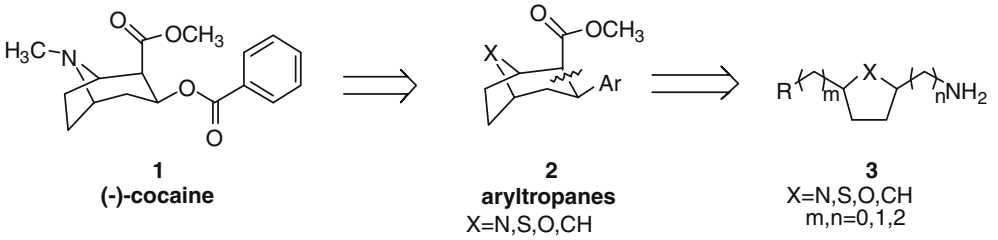


Figure 1. Modification of (−)-cocaine (**1**) affords the more metabolically stable aryltropane system (**2**). Cleavage of the 2,3-carbon bond yields the 5-membered heterocyclic ring systems (**3**).

five-membered ring and a polar functionality approximately two to three carbons from the heteroatom of the five-membered ring. Preliminary investigations of mono- or di-substituted pyrrolidines and tetrahydrothiophenes (i.e., X = N or S, respectively, structure **3**, Fig. 1) showed these compounds possessed very little affinity for the human dopamine transporter (hDAT) or human norepinephrine transporter (hNET) (i.e., K_i values >10 μM). However, 2,5-disubstituted tetrahydrofurans (i.e., X = O, structure **3**, Fig. 1) showed considerably greater potency and were subsequently optimized by a medicinal chemistry approach. After the process of identifying highly potent and selective 2,5-disubstituted tetrahydrofuran hSERT re-uptake inhibitors by binding and re-uptake studies, selected compounds were employed in the process of dynamic medicinal chemistry where metabolic stability considerations were built into the design and synthesis of increasingly more potent and selective compounds. It was also noted that certain alkyl- and halogen-substituents of the aromatic moiety of aryltropanes led to significant increases in affinity for the hSERT.[2] While our investigations of substituents of aromatic ring analogues of 2,5-disubstituted tetrahydrofurans was not exhaustive, it supported the hypothesis that appropriate substitution markedly enhanced the potency and selectivity of re-uptake inhibition for the hSERT. Herein is described the synthesis and characterization of a new class of 2,5-disubstituted tetrahydrofurans that show potent, selective re-uptake inhibition of hSERT and low affinity for hDAT and hNET.

2. Results

2.1. Chemistry

Retrosynthetic analysis of the target compounds is outlined in Figure 2. Briefly, the overall strategy involved obtaining the 2,5-disubstituted tetrahydrofuran scaffold **4** from *N*-bromosuccinimide-mediated cyclization of alcohol **5**. The alcohols depicted as **5**, in turn, were synthesized from the corresponding aldehydes **6** via a Grignard reaction with butenylmagnesium bromide.

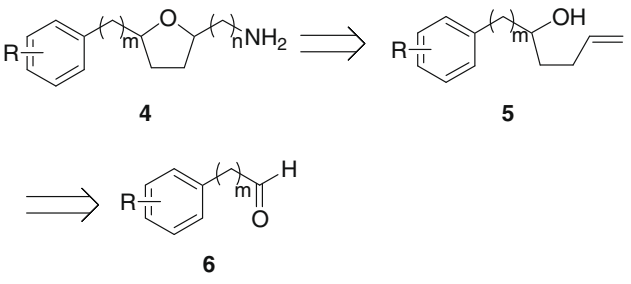


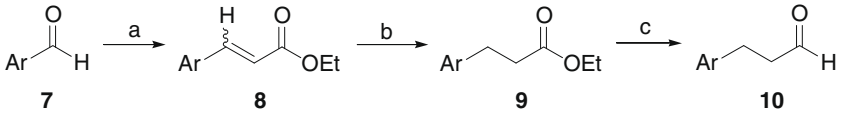
Figure 2. Retrosynthetic analysis of 2,5-disubstituted tetrahydrofuran compounds. R represents various aryl and heteroatom substituents.

The aldehydes shown as **6** (Fig. 2) were either commercially available or they were prepared using standard chemistry as shown in Scheme 1. Thus, (ethoxycarbonylmethylene)triphenylphosphorane was treated with NaH in THF at reflux for 1 h followed by addition of the requisite aryl aldehyde **7** to form after treatment of the crude product with H_2SO_4 in acetone at reflux for 6 h, the chain elongated esters **8**. Hydrogenation of the double bond was accomplished by treating the olefin **8** in the presence of an ethanolic solution of Pd/C under an atmosphere of hydrogen gas for 15 h at room temperature. Reduction of the ethyl ester **9** in the presence of a slight excess of DIBAL in toluene at −78 °C for 2 h followed by warming to 0 °C afforded the aldehydes **10** (Scheme 1).

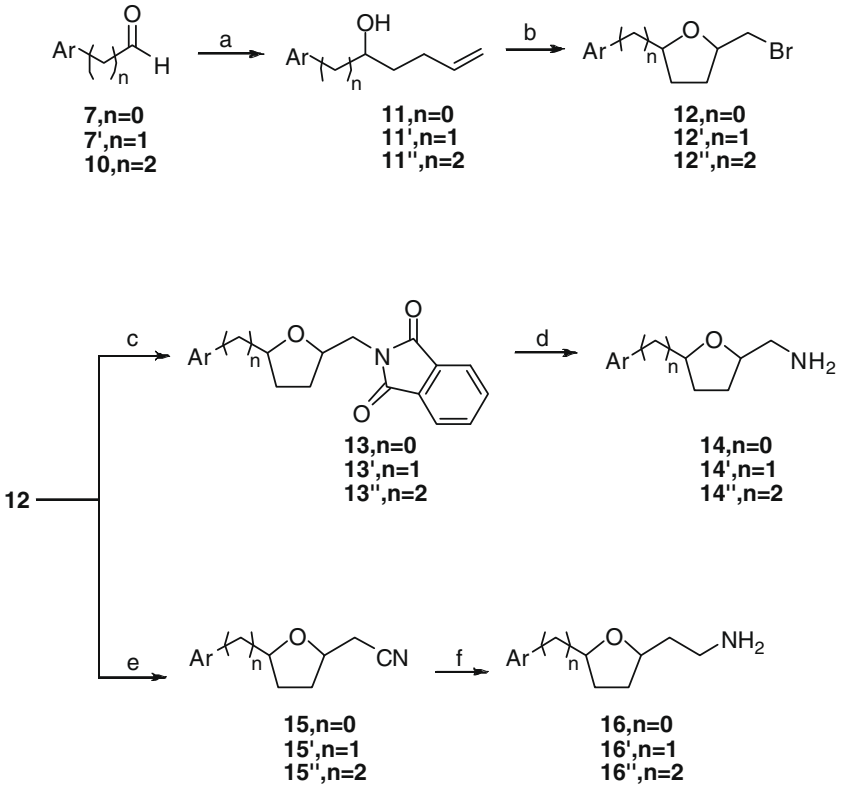
The syntheses of target compounds **14** and **16** are shown in Scheme 2. Treatment of aldehydes **7** or **10** with 1.1 equiv of 1-butenylmagnesium bromide in THF at 0 °C for 15 min resulted in the vinyl alcohols **11**. Cyclization of the vinyl alcohol was accomplished by treating **11** with a dichloromethane solution containing 1.1 equiv of *N*-bromosuccinimide at 0 °C followed by warming to room temperature for 12 h to form the disubstituted tetrahydrofurans **12**. The aryl-substituted bromomethyl tetrahydrofurans **12** were the precursor to both series of target compounds **14** and **16**. Accordingly, one portion of **12** was treated with 2.5 equiv of potassium phthalimide and a catalytic amount of NaI in the presence of DMSO at 70 °C for 12 h to afford **13**. Compound **13** was reduced in the presence of a methanolic solution containing excess hydrazine at room temperature for 12 h to form the target series **14**. Another portion of **12** was converted to the nitrile **15** by treating **12** with excess potassium cyanide and a catalytic amount of NaI at 70 °C for 12 h. The nitrile was then reduced by hydrogenation in the presence of Raney nickel and an atmosphere of hydrogen gas at room temperature for 48 h to form the target series **16**.

2.2. Lead discovery

The workflow proceeded as follows: binding values were obtained and compounds (i.e., $K_i \sim 10$ μM or less) were examined in re-uptake assays. Binding affinity of each compound (i.e., K_i value) was calculated from the IC_{50} value and measured for each compound by assessing the potency of inhibition of binding of radiolabeled RTI-55 to the hDAT, hSERT and hNET. In vitro functional potency was measured by determining the re-uptake inhibition (i.e., IC_{50}) value of [^{3}H]-DA, [^{3}H]-5-HT or [^{3}H]-NE at the



Scheme 1. [a]Reagents and conditions: (a) EtOC(O)CH=PPh$_3$, NaH, THF, reflux, 1 h; H_2SO_4, acetone, reflux, 6 h, 92–99% yield; (b) H_2, Pd/C; (c) DIBAL, toluene, −78 °C to 0 °C, 2 h, 30–94% yield.

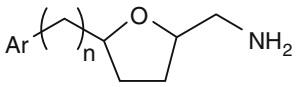


Scheme 2. [a]Reagents and conditions: (a) 1-butenylmagnesium bromide, THF, 0 °C, 15 min, 23–95% yield; (b) NBS, CH_2Cl_2, 0 °C to 25 °C, 23–97% yield; (c) potassium phthalimide, NaI, DMSO, 70 °C, 12 h, 26–99% yield; (d) NH_2NH_2, MeOH, room temperature, 12 h, 35–85% yield; (e) KCN, NaI, DMSO, 70 °C, 12 h, 43–78% yield; (f) Raney Ni, H_2, 1 M NH_3/MeOH, room temperature, 48 h, 32–56% yield.

recombinant hDAT, hSERT or hNET in HEK-293 cells transfected with the respective transporter cDNA. Molecular dissection of aryltropanes and replacement of the methyl ester with an amine functionality (Fig. 1) afforded pyrrolidines (i.e., **3**, X = N) that possessed little apparent affinity for the hDAT, hSERT and hNET (i.e., K_i values > 15 μM) and were not pursued further (data not shown). Next, an analogous 2,5-tetrahydrofuran series (i.e., **3**, X = O, *m* = 0, *n* = 1) was examined and modest potency for the transporters was observed (Table 1). Replacement of the methyl ester moiety (analogous to the methyl ester group of aryltropanes) with a methyl amino group and a two carbon aryl side chain afforded **3** (i.e., X = O, *m* = 2, *n = 1)* that showed in some cases, markedly increased potency against the hSERT (i.e., **14a** vs **14″h**; **14g** vs **14″i**) (Table 1). Based on this result the chemical synthesis of a mixture of *cis* and *trans* 2,5-disubstituted tetrahydrofurans was done by liquid phase parallel synthesis. To accelerate the lead compound discovery process, a mixture of *cis* and *trans* diastereomers was carried through to the final products and pharmacologically tested in vitro. As a practical matter, separation of the diastereomers was not readily achievable and the ratio of diastereomers was determined by high resolution ^{1}H NMR. In most cases, the diastereomer ratio was *cis*:*trans* = 1:2. However, for select compounds with great potency, *cis* and *trans* diastereomers were separated and tested individually. In the 2,5-disubstituted tetrahydrofuran analogs with one carbon atom between the tetrahydrofuran and amino group examined (compound **3**, Fig. 1), phenyl tetrahydrofurans (e.g., **14a** to **14e** K_i = 43.0 nM, IC_{50} = 1714 nM to K_i > 10,000 nM, IC_{50} = 637 nM), showed significant to poor potency at blocking radioligand binding to hSERT, and poor potency at blocking re-uptake of [^{3}H] 5-HT via the hSERT (Table 1) Aryl tetrahydrofurans with electron withdrawing groups (e.g., **14b** K_i = 1105 nM, IC_{50} = 31.9 nM and **14c**, K_i = 1114 nM, IC_{50} = 50.3 nM, all had poor potency at blocking binding to the hSERT, but were fairly potent at blocking re-uptake by the transporter (Table 1). Aryl compounds with electron donating groups (**14d**, K_i = 6877 nM, IC_{50} = 617 nM, and **14e,** K_i > 10,000 nM, IC_{50} = 636 nM) were also generally more potent at blocking re-uptake by the hSERT compared to their potencies at blocking binding. Naphthyl tetrahydrofurans (e.g., **14f**, K_i = 45 nM, IC_{50} = 4.1 nM and **14g**, K_i = 174 nM) showed good to modest potency at blocking hSERT binding and re-uptake (Table 1). Aryl alkyl tetrahydrofurans (e.g., **14″h**, K_i = 68 nM, IC_{50} = 129 nM **14″i**, K_i = 18.5 nM, IC_{50} = 23.3 nM, and **14″j**, K_i = 2126 nM, IC_{50} = 225 nM) were moderately potent in blocking hSERT re-uptake. In contrast, aromatic groups with heteroatoms present (e.g., **14″k**, K_i = 4546 nM, IC_{50} = 2721 nM) possessed poor potency as a binder and re-uptake inhibition at hSERT (Table 1) and were in large part not studied further. The conclusion from this work was that, compared with aryl tetrahydrofurans, a two-carbon spacer between the aryl and tetrahydrofuran moieties conferred higher potency for hSERT re-uptake inhibition (Table 1). In addition, introduction of lipophilicity into the aryl group also tended to improve hSERT re-uptake inhibition potency. To examine this in greater detail, one and two carbon spacers between the tetrahydrofuran group and the amine were examined with selected aryl substitutions (Table 2).

Compound **16′a′**, possessing an unsubstituted aryl group and a one carbon spacer was not very potent at blocking binding or re-uptake at the hSERT (Table 2). However, compounds with substituents on the aryl group that contained both electron-donating and electron-withdrawing groups (e.g., **16″b′**, K_i = 688 nM, IC_{50} = 30 nM and **16″c′** and **16″d′**) were potent at blocking binding and re-uptake at the hSERT (Table 2). Compounds with polar functionality in the aryl group (i.e., **16″e′,** K_i = 7483 nM, IC_{50} = 4041 nM and **16f′**, K_i = >10,000 nM, IC_{50} = >10,000 nM) possessed poor potency

Table 1
Inhibition of radioligand binding in HEK-hDAT, HEK-hSERT, and HEK-hNET cells by 2,5-disubstituted tetrahydrofuran analog series **14**[a]



14

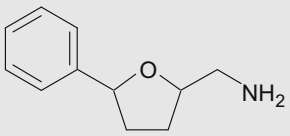
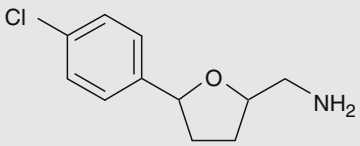
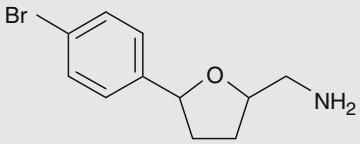
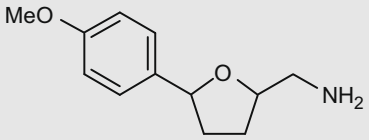
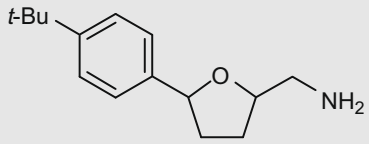
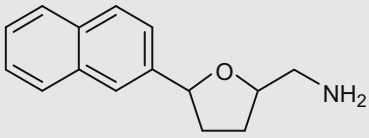
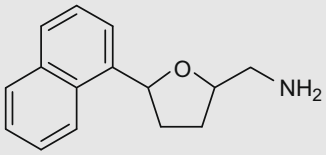
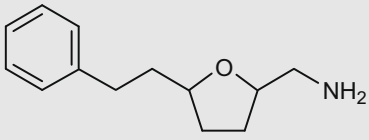
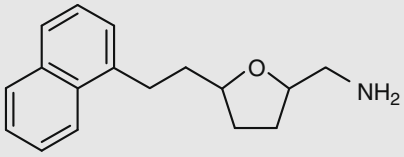
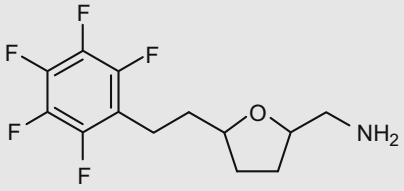
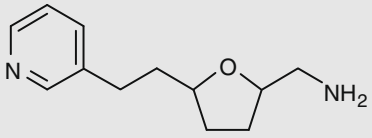
Compd #	Structure	*trans:cis*	Binding (K_i, nM)			Re-uptake (IC_{50}, nM)		
			hDAT	hSERT	hNET	hDAT	hSERT	hNET
	Cocaine		371 ± 81	276 ± 87	1116 ± 198	590 ± 170	642 ± 183	1281 ± 307
14a		2:1	916 ± 12	43 ± 11	2767 ± 111	147 ± 22	1714 ± 437	23 ± 5
14b		2:1	6830 ± 419	1105 ± 110	1106 ± 203	313 ± 76	32 ± 4	61 ± 19
14c		2:1	6117 ± 895	1114 ± 36	>10,000	167 ± 69	50 ± 3	59 ± 20
14d		2:1	>10,000	6877 ± 414	2013 ± 67	668 ± 215	617 ± 150	92 ± 29
14e		2:1	>10,000	>10,000	4543 ± 266	4301 ± 919	636 ± 191	2322 ± 801
14f		2:1	512 ± 33	45 ± 4	>10,000	28 ± 10	4 ± 1	58 ± 14
14g		1.5:1	8519 ± 229	174 ± 32	1494 ± 88	463 ± 119	24 ± 1	210 ± 19
14″h		2:1	1505 ± 278	68 ± 10	2736 ± 480	513 ± 68	129 ± 38	360 ± 15

Table 1 (*continued*)

Compd #	Structure	*trans:cis*	Binding (K_i, nM)			Re-uptake (IC_{50}, nM)		
			hDAT	hSERT	hNET	hDAT	hSERT	hNET
14″i		2:1	>10,000	18 ± 1	>10,000	>10,000	23 ± 3	3420 ± 655
14″j		1.5:1	>10,000	2126 ± 1180	634 ± 179	4589 ± 692	225 ± 88	1541 ± 99
14″k		2:1	>10,000	4546 ± 2130	8517 ± 977	>10,000	2721 ± 718	>10,000

[a] Inhibition of [^{125}I]-RTI-55 binding in HEK-hDAT, HEK-hSERT, or HEK-hNET cell membranes. Values represent the mean ± SEM for three to four experiments unless the mean of three experiments exceeded 10 μM.

at hSERT binding or re-uptake inhibition and were not pursued further. The conclusion from these studies supported the suggestion that two carbon linkers from the tetrahydrofuran moiety to the aryl and amino groups improved hSERT binding and re-uptake inhibition potency.

Based on the observation that disubstituted aryl groups of 2,5-disubstituted tetrahydrofurans showed significant potency as hSERT re-uptake inhibitors (e.g., compound **16″b′**) and electron-withdrawing combined with electron-donating groups showed improved potency, a series of 2′-methoxy-5′-fluorophenyl 2,5-disubstituted tetrahydrofurans were synthesized. The synthesis of 2,5-disubstituted tetrahydrofurans incorporating the 2′-methoxy-5′-fluorophenyl group in compound **18** (Scheme 3), compound **21** (Scheme 4) and compound **24** and **26** (Schemes 5 and 6) was analogous to the synthetic procedure used in the synthesis of **10**. Compounds **18, 21, 24** and **26** were used in the synthesis of the lead discovery series described below. The 2′-methoxy-5′-fluorophenyl substituted tetrahydrofurans were synthesized and tested (Table 3) and in some cases, were very selective and potent at inhibiting re-uptake via the hSERT.

2.3. Selectivity for hSERT

Generally, the 2,5-disubstituted tetrahydrofurans that were examined possessed very poor potency for inhibition of binding of radiolabeled RTI-55 to the hDAT (i.e., range 512 to >10,000 nM) or to the hNET (i.e., 634 to >10,000 nM). However, in some cases (i.e., **14b, 14c** and **14f**, for the hNET and **14a** and **14f** for the hDAT, respectively), the compounds possessed considerable potency at blocking transporter re-uptake.

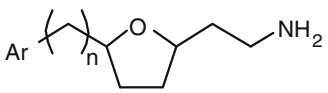
2.4. Structure–activity studies of the optimal lead compound

As described above, during the lead discovery phase, it was observed that halogen and methoxy substituents increased the affinity of the compounds for the hSERT (e.g., **16″b′, 16″c′**) and electron deficient substituents increased functional activity against the hSERT (i.e., **14b, 14c**, **16″b′**). From among a large number of other disubstituted compounds, the 2′-methoxy-5′-fluoro disubstituted aryl analogs **30** and **32** were synthesized to further investigate the structure–activity relationship for this series (Scheme 7). In addition, the 2′-methoxy-5′-fluoroaryl substitution pattern afforded compounds that were more amenable to separation of *cis* and *trans* diastereomers by chromatography. The side chain length was also varied because it was observed that hSERT binding and re-uptake inhibition was dependent on both the carbon chain length between the aryl moiety and amine group and the *cis*/*trans* orientation of the 2,5-disubsituted tetrahydrofuran ring in this series (Tables 1 and 2). Thus, by increasing the chain length between the aryl group and tetrahydrofuran ring, the potency was also increased (e.g., **30a**, K_i = 6307 nM, IC_{50} = 2071 nM to **30d**, K_i = 0.8 nM, IC_{50} = 2.1 nM). Based on the compounds tested thus far (i.e., **30a–e** vs **32a–e**), a three carbon atom span between the aryl group and the tetrahydrofuran was optimal. Functional activity was also dependent on the number of carbon atoms between the tetrahydrofuran moiety and the terminal amine, with two carbon atoms generally being superior to one carbon atom. The overall chain length between the substituted aryl group, tetrahydrofuran, and the terminal amine was optimal with a total of five carbon atoms (i.e., **32d**, K_i = 1.1 nM, IC_{50} = 2.3 nM) (Scheme 8).

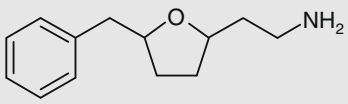
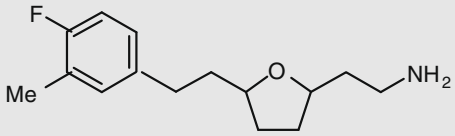
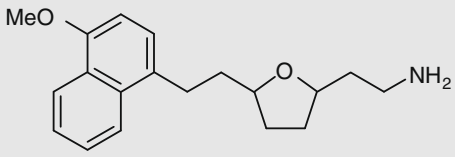
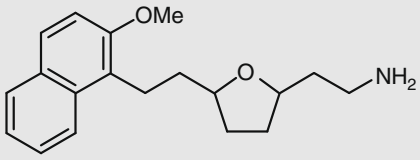
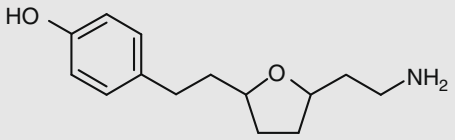
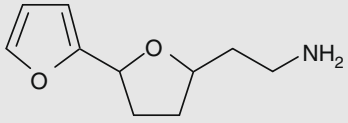
Overall, compounds possessing the *trans* orientation (e.g., *trans* **32c**, K_i = 2.1 nM, IC_{50} = 2.5) provided greater potency than the compound with the *cis* orientation (e.g., *cis* **32c**, K_i = 19.3 nM, IC_{50} = 17.5 nM). Generally, the *trans* orientation increased the potency in the hSERT binding and re-uptake activity approximately sevenfold compared to the corresponding *cis* 2,5-disubstituted tetrahydrofuran compound.

Compounds **30** and **32** were also tested for binding and re-uptake inhibition against hDAT and hNET, and these results are listed in Table 3. Generally, **30a–e** and **32a–e** possessed very low affinity for the hDAT (i.e., K_i values in the range 6288–41,257 nM) and very low affinity for the hNET (i.e., K_i values in the range 481–

Table 2
Inhibition of radioligand binding in HEK-hDAT, HEK-hSERT, and HEK-hNET cells by 2,5-disubstituted tetrahydrofuran analog series **16**[a]

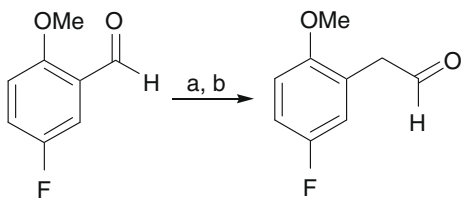


16

Compd #	Structure	*trans:cis*	Binding (K_i, nM)			Re-uptake (IC_{50}, nM)		
			hDAT	hSERT	hNET	hDAT	hSERT	hNET
	Cocaine		371 ± 81	277 ± 87	1116 ± 198	590 ± 170	642 ± 183	1281 ± 307
16′a′		2:1	>10,000	3822 ± 882	>10,000	565 ± 154	2260 ± 203	347 ± 70
16″b′		1.5:1	6376 ± 893	688 ± 119	882 ± 22	509 ± 136	30 ± 4	374 ± 110
16″c′		2:1	>10,000	92 ± 19	>10,000	ND[b]	ND	ND
16″d′		2:1	>10,000	86 ± 9	>10,000	ND	ND	ND
16″e′		1.5:1	5498 ± 381	7483 ± 977	5947 ± 550	2532 ± 298	4041 ± 845	2126 ± 345
16′f′		1:1	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000

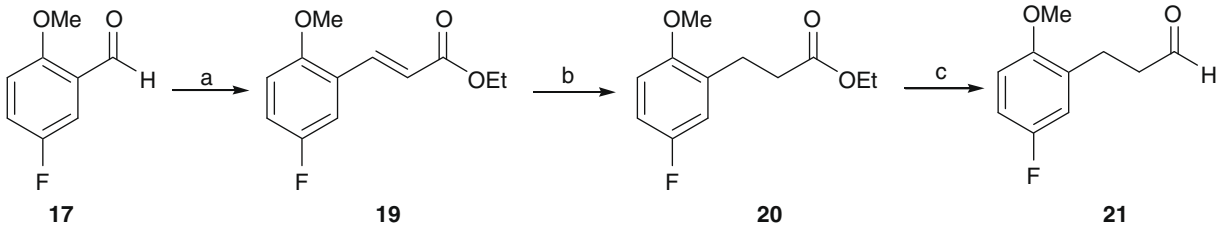
[a] Inhibition of [^{125}I]-RTI-55 binding in HEK-hDAT, HEK-hSERT, or HEK-hNET cell membranes. Values represent the mean ± SEM for three to four experiments unless the mean of three experiments exceeded 10 μM.
[b] ND, not determined.

10,000 nM). Thus, the compounds were selective for interaction with the hSERT. The selectivity ratios for inhibition of binding and re-uptake of biogenic amines by these compounds were considerable. Potency for binding inhibition and re-uptake inhibition at the hSERT correlated very well for the most active compounds such as **30a–d** and **32a–d** (i.e., average reuptake (IC_{50})/binding (K_i) correlation = 1.04). However, re-uptake (IC_{50})/binding (K_i) correlations calculated for **30e** (IC_{50}/K_i = 21.0) and **32e** (IC_{50}/K_i = 15.5) suggested that the properties controlling binding and re-uptake for these latter compounds were not exactly the same. The selectivity of **32c, 30d** and **32d** for hSERT versus other biogenic amine transporters expressed as ratios of binding (K_is) or re-uptake (IC_{50}) values showed that the most potent compounds possessed excellent transporter selectivity (K_i ratios ranging from 1162 to 10,676 or IC_{50} ratios ranging from 192 to 11,140) for hDAT/hSERT and hNET/hSERT, respectively.

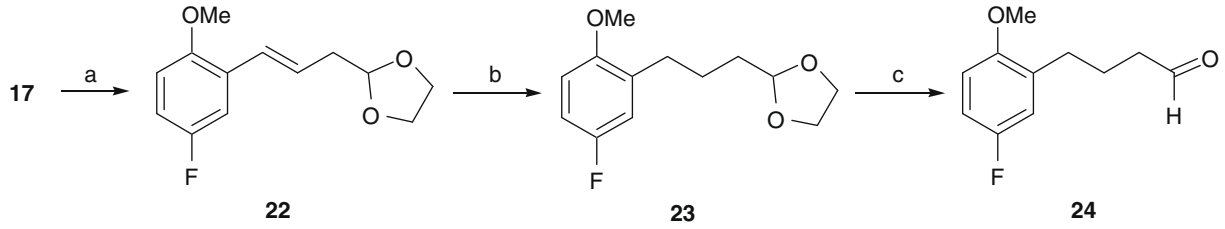


17 **18**

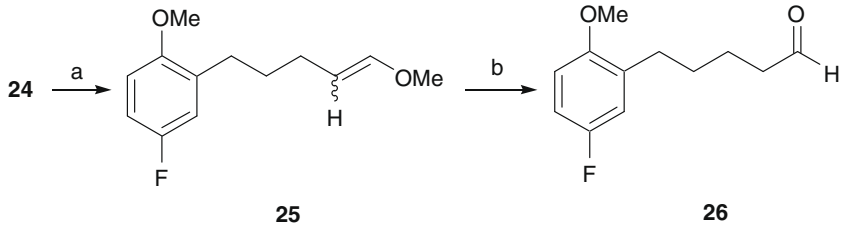
Scheme 3. Reagents and conditions: (a) MeOCH=PPh_3, THF, reflux, 1 h; (b) H_2SO_4, acetone, room temperature, 12 h, 66% yield.



Scheme 4. Reagents and conditions: (a) $EtOC(O)CH{=}PPh_3$, CH_2Cl_2, 0 °C to room temperature, 12 h, 95% yield; (b) H_2, Pd/C, room temperature, 15 h, 95% yield; (c) DIBAL, toluene, −78 °C, 2 h, 66% yield.



Scheme 5. Reagents and conditions: (a) [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide, THF, 0 °C to room temperature, 1 h, 66% yield; (b) H_2, Pd/C, room temperature, 72 h; (c) H_2SO_4, acetone, room temperature, 48 h, 53% yield.



Scheme 6. Reagents and conditions: (a) $MeOCH_2PPh_3$, NaH, THF, room temperature, 24 h, 43% yield; (b) H_2SO_4, acetone reflux, 1.6 h, 50% yield.

2.5. In vitro metabolic stability studies

After identifying the lead compounds on the basis of binding and re-uptake studies, selected compounds were taken forward for metabolic stability tests. Studies were done with **32c** in the presence of both mouse and rat liver microsomes supplemented with NADPH using a previously described general protocol.[15] Compound **32c** was more stable in the presence of rat liver microsomes (i.e., half life of 106 min) than in the presence of mouse liver microsomes (i.e., a half life of 56 min). The *N*-methyl amine, compound **34** (Scheme 7), was synthesized to potentially increase metabolic stability and act as a pro-drug. In vitro microsomal metabolism studies of compound **34** showed an increase in the metabolic stability in the presence of rat liver microsomes (i.e., a half-life of 129 min). However, compound **34** was not significantly more stable than **32c** and had a half-life of 58.5 min in the presence of mouse liver microsomes.

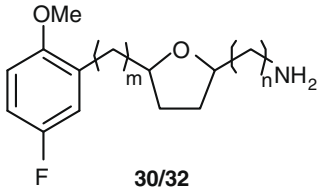
2.6. In vivo efficacy studies

Balb/c mice exhibit a relatively high immobility baseline and are sensitive to fluoxetine challenge in the forced-swim test (FST).[16] We examined fluoxetine and a 1:2 *cis:trans* ratio of compounds **32c** and **32d** in the FST. Acute administration of fluoxetine (20 mg/kg), **32c** (10 mg/kg), or **32d** (10 mg/kg, the latter two compounds as a mixture of 1:2 *cis:trans* diastereomers), did not statistically significantly alter the duration of immobility in the FST in Balb/c mice although there was a tendency for **32d** to show an effect (Fig. 3). In contrast, subchronic administration of a lower dose of fluoxetine (10 mg/kg) significantly decreased immobility ($P < 0.05$) (data not shown) but subchronic treatment with **32c** (10 mg/kg) did not statistically significantly change immobility compared to the vehicle control (data not shown).

3. Discussion

Based on molecular dissection of (−)-cocaine[17] and related aryltropane compounds,[18] we prepared structurally related pyrrolidines, tetrahydrothiophenes and tetrahydrofurans (Fig. 1). Various substituted or unsubstituted aryl, naphthyl or heteroaryl groups as well as compounds with carbon chains of 0, 1 or 2 carbon atoms between a tetrahydrofuran ring and an amino group were tested for binding and re-uptake inhibition at recombinant hDAT, hSERT, and hNET. In general, low binding inhibition potency and re-uptake inhibition potency for the 2,5-disubstituted tetrahydrofurans were observed for the hDAT and hNET. However, for certain 2-aryl or 2-arylalkyl-5-amino alkyl-disubstituted tetrahydrofurans, significant re-uptake inhibition of the hSERT was observed and this was explored in detail. Unsubstituted phenyl 2,5-disubstituted tetrahydrofuran compounds possessed modest potency. Affinity of the compound in the radioligand binding assay was generally decreased with bulky substituents on the aryl ring but potency was maintained when large aromatic groups such as 1- or 2-naphthyl groups were present. Affinity for the hSERT was decreased when a heteroaryl group (i.e., furan or pyridine) was introduced as a replacement for the aryl group. Disubstitution of the aryl moiety of the 2-arylalkyl tetrahydrofurans with electron-donating and electron-withdrawing groups such as methoxy and

Table 3
Inhibition of [^{125}I]-RTI-55 binding in HEK-hDAT, HEK-hSERT, and HEK-hNET cells by 2,5-disubstituted tetrahydrofuran analog series **30** and **32**[a]



30/32

Cmpd #	Isomers	Chain length			Binding (K_i, nM)			Re-uptake (IC_{50}, nM)		
		m	*n*	Total	hDAT	hSERT	hNET	hDAT	hSERT	hNET
30a	*trans*	0	1	1	>10,000	6307 ± 790	71,990 ± 4400	>10,000	2071 ± 903	>10,000
30a	*trans:cis* 1.5:1	0	1	1	42,760 ± 56,000	6885 ± 1650	57,020 ± 13,820	>10,000	9029 ± 12150	>10,000
32a	*trans*	0	2	2	32,940 ± 21,880	1808 ± 616	27,500 ± 5018	>10,000	1117 ± 813	>10,000
32a	*cis*	0	2	2	>10,000	4772 ± 297	48,870 ± 10870	>10,000	2576 ± 424	>10,000
30b	*trans*	1	1	2	27,240 ± 10,600	192 ± 25	24,120 ± 3005	28,940 ± 1866	122 ± 40	7983 ± 1966
30b	*cis*	1	1	2	97,180 ± 11,970	151 ± 20	9085 ± 1600	18,680 ± 3384	111 ± 37	3392 ± 1278
32b	*trans*	1	2	3	51,020 ± 847	20 ± 1	1782 ± 313	38,440 ± 14,470	27 ± 8	1774 ± 566
32b	*cis*	1	2	3	34,790 ± 125	21 ± 2	455 ± 44	36,340 ± 9680	23 ± 6	1864 ± 536
30c	*trans*	2	1	3	14,500 ± 3185	3.2 ± 0.2	5993 ± 283	8555 ± 741	2.5 ± 0.7	628 ± 66
30c	*cis*	2	1	3	30,320 ± 3020	21.9 ± 3.6	8520 ± 108	34,300 ± 7696	11.7 ± 3.0	4746 ± 1608
32c	*trans*	2	2	4	6500 ± 828	2.1 ± 0.2	2440 ± 215	27,850 ± 5129	2.5 ± 0.6	481 ± 158
32c	*cis*	2	2	4	16,370 ± 2006	19.3 ± 0.9	12,100 ± 810	36,710 ± 1174	17.5 ± 2.7	3101 ± 1243
30d	*trans*	3	1	4	7328 ± 315	0.8 ± 0.3	8541 ± 1289	7618 ± 723	2.1 ± 0.6	2934 ± 611
30d	*cis*	3	1	4	4576 ± 1112	2.8 ± 0.1	20,180 ± 2470	6288 ± 1470	2.6 ± 0.7	2857 ± 539
32d	*trans:cis* 2.5:1	3	2	5	7307 ± 1331	1.1 ± 0.1	10,600 ± 1880	16,990 ± 1352	2.3 ± 0.6	1930 ± 463
32d	*trans:cis* 1:3	3	2	5	21,190 ± 2687	7.0 ± 0.8	30,430 ± 1630	41,260 ± 11506	7.4 ± 0.3	5133 ± 1742
30e	*trans*	4	1	5	3868 ± 423	4.0 ± 1.1	2222 ± 350	16,540 ± 4025	84 ± 31	7124 ± 2043
32e	*trans:cis* 1:1	4	2	6	3387 ± 266	2.0 ± 0.7	4064 ± 1204	37,460 ± 1854	31 ± 9	8530 ± 1511

[a] Inhibition of [^{125}I]-RTI-55 binding in HEK-hDAT, HEK-hSERT, or HEK-hNET cell membranes. Values represent the mean ± SEM for three to four experiments unless the mean of three experiments exceeded 10 μM.

halogen groups led to compounds with potent hSERT re-uptake inhibition. When 2′-methoxy-5′-fluorophenyl substituents were present in the aryl portion of arylalkyl tetrahydrofuran molecules, highly potent and selective hSERT re-uptake inhibitors were observed.

The hSERT is a tightly regulated Na^+ and Cl^--dependent transporter and calcium-dependent hSERT regulatory proteins are implicated in functional activity, regulation and internalization of SERT.[20] Because cytoplasmic calcium can alter pH by modulating Na^+/H^+ and ion channels it is possible that Ca^{2+} could contribute to the subcellular distribution and regulation of the SERT. For compound such as **32**, it is possible that the methoxy and furan oxygen atoms work together to coordinate cations (e.g., Ca^{2+}) and facilitate the SSRI mechanism of action. However, this was not examined in detail in this study. Nevertheless, synthesis of additional arylalkyl tetrahydrofurans with various carbon atom side chains with a 2′-methoxy-5′-fluorophenyl moiety afforded highly potent compounds. The most potent hSERT re-uptake inhibitors contained side chains possessing a total of 5 carbon atoms in length. In the 2′-methoxy-5′-fluorophenyl 2,5-disubstituted tetrahydrofuran series, compounds with the *trans* configuration at the 2,5- tetrahydrofuran ring junction afforded on average, about a seven-fold higher potency than the corresponding *cis* diastereomers. However, the absolute stereochemistry at the 2,5-position of the tetrahydrofuran was not investigated.

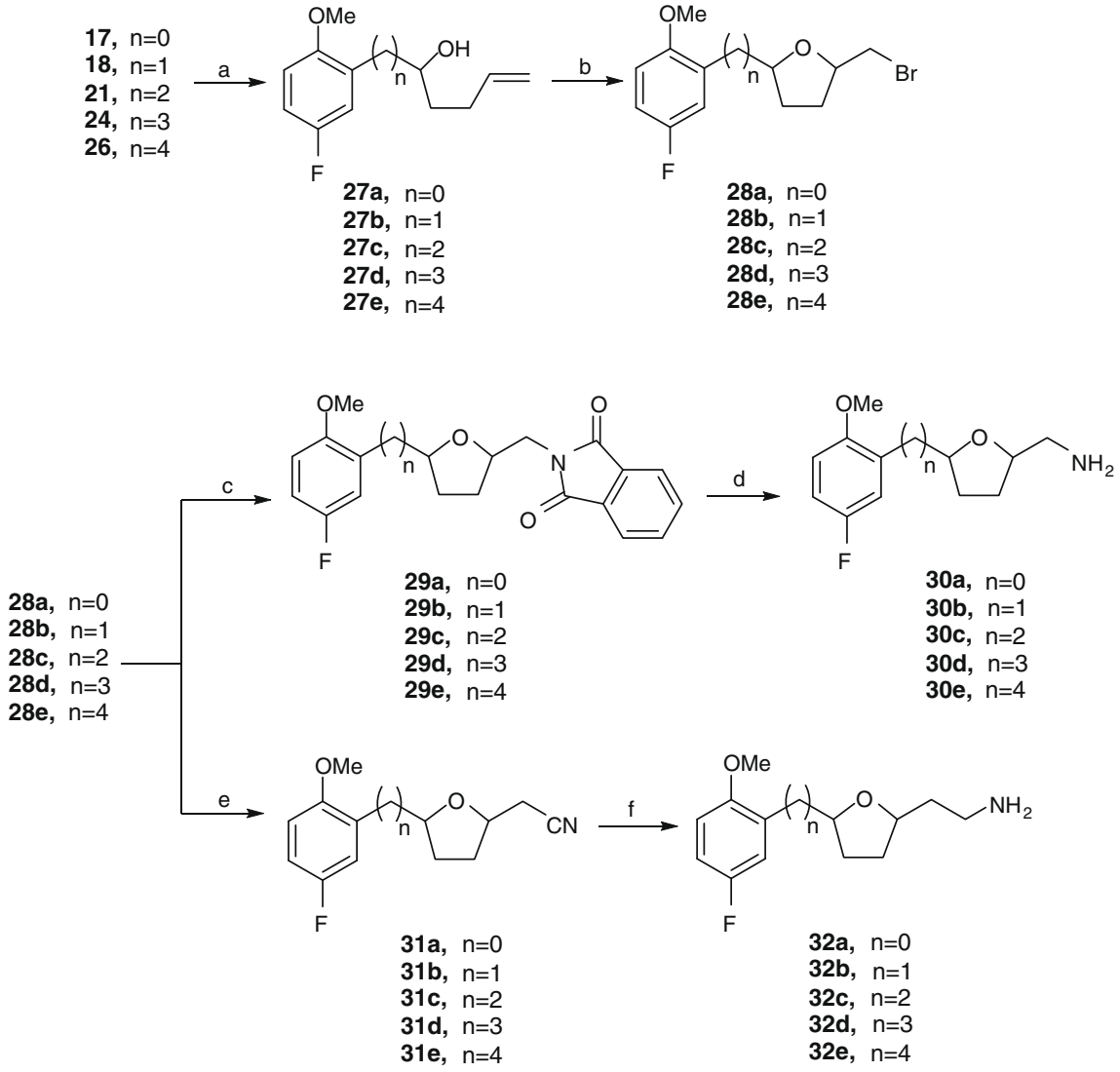
Acute treatment of mice with **32c** at doses of 10 and 30 mg/kg or **32d** tended to decrease immobility, but this result was not statistically significant. Subchronic treatment of mice with **32c** at doses of 10 mg/kg did not significantly change immobility compared to the vehicle control. Under the same conditions, fluoxetine (10 mg/kg) did cause significantly decreased immobility in the FST. The lack of pronounced antidepressant effect for **32c** and **32d** is likely not due to brain penetration because the *C*Log*P* values for **32c** and **32d** were 2.2. Further, the calculated total polar surface area (tPSA) for **32c** and **32d** were 44.5 Å^3 and this value is well below the value of 70 Å^3 that is generally used as a limit on ready blood brain penetration. It is possible that the lack of in vivo efficacy was due to relatively rapid metabolism of the primary amine to inactive metabolites, or possibly that the amount and duration of the dose of the test compound was not large enough. Future chronic in vivo studies will address this issue.

4. Experimental

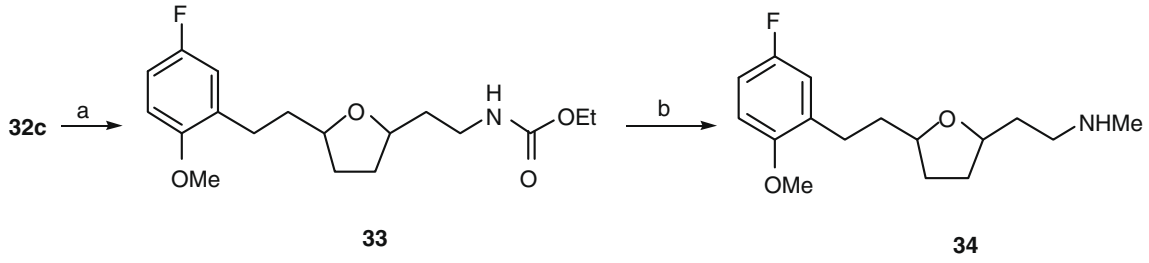
4.1. General

Commercially available reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) (e.g., phenylpropanal) or VWR (San Diego, CA) and were used as received. 4-Hydroxy phenylpropanal was purchased from Otava Chemical Company (Toronto, Canada). All moisture sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) and toluene were freshly distilled from calcium hydride under an argon atmosphere. Methanol (CH_3OH) was passed through a column of neutral alumina and stored over 3 Å molecular sieves prior to use.

Analytical thin-layer chromatography (TLC) was done on K6F Silica Gel 60 Å (Whatman) glass-backed plates. Compounds were detected using UV absorption at 254 nm and/or stained with I_2 (iodine). Flash chromatography was done on Merck (60 Å) pore silica. NMR spectra were recorded at 500 MHz by NuMega Resonance Labs, Inc., (San Diego, CA) or at 300 MHz at the Human BioMolecular Research Institute using the solvent specified. Chemical shifts were reported in parts per million (ppm, δ) using residual solvent signals as internal standards. Low resolution mass spectroscopy (LRMS) was done with an HP 1100 mass spectrometer at HT Laboratories (San Diego, CA) using electrospray ionization (ESI) or at the Human BioMolecular Research Institute on a Hitachi M-8000



Scheme 7. Reagents and conditions: (a) 1-butenylmagnesium bromide, THF, 0 °C, 15 min, 44–94% yield; (b) NBS, CH_2Cl_2, 0 °C to room temperature, 12 h, 44–72% yield; (c) potassium phthalimide, NaI, DMSO, 70 °C, 12 h, 47–72% yield; (d) NH_2NH_2, MeOH, room temperature, 12 h, 30–95% yield; (e) KCN, NaI, DMSO, 70 °C, 12 h, 18–86% yield ; (f) Raney Ni, H_2, 1 M NH_3/MeOH, room temperature, 48 h, 41–54% yield.



Scheme 8. Reagents and conditions: (a) ethyl chloroformate, K_2CO_3, THF, 0 °C to room temperature, 3 h; (b) $LiAlH_4$, THF, 0 °C to room temperature, 4 h, 66% yield.

3DQMS (ion trap) mass spectrometer using ESI. High resolution mass spectroscopy (HRMS) was done with a Micromass LCT time of flight mass spectrometer at the University of California, Irvine (Irvine, CA) or at the University of Montana Mass Spectrometry Facility (Missoula, MT) using ESI.

The 2,5-disubstituted tetrahydrofuran analogues were characterized by ^{1}H NMR, LRMS, HRMS and their purities (>98%) were determined by HPLC in two distinct solvent systems. Analytical HPLC measurements were run on a Hitachi L-6200 system equipped with a Hitachi L-7400 UV detector. Separations were done (straight-phase) with an Axxi-chrom silica column (4.6 mm × 250 mm, 5 μM) or (reverse-phase) with a Supelco HS F5 pentafluorophenyl column (4.6 mm × 250 mm, 5 μM). Standard conditions utilized an isocratic, ternary-solvent system consisting of solvents A (methanol), B (isopropanol), C (acetonitrile), and D ($HClO_4$) set at a flow rate of 1.5 mL/min (straight-phase), or A, E (water) and F (HCO_2H) set at a flow rate of 1.0 mL/min (reverse-phase), λ = 254 nm with retention times (t_R) determined in minutes. Typical analyses involved two distinct isocratic elutions per compound of interest. Solvent conditions for the isocratic elutions

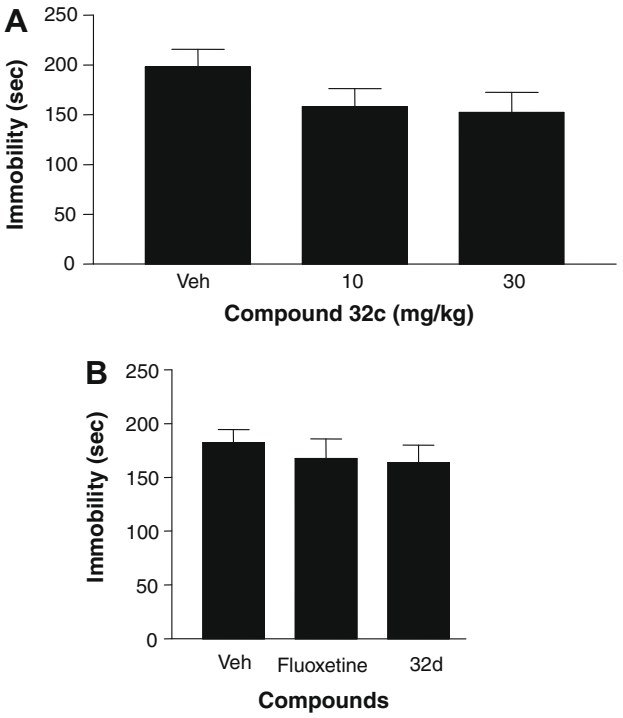


Figure 3. (A) Effect of acute treatment of compound **32c** on immobility in the forced-swim test in ICR mice. Vehicle (Veh) or compound **32c** (10 or 30 mg/kg) was injected ip 30 min prior to the test. $N = 9–11$. (B) Effect of acute treatment of fluoxetine (20 mg/kg) or compound **32d** (10 mg/kg), on immobility in the forced-swim test in Balb/c mice. Vehicle or compound **32d** were injected ip 30 min prior to the test. $N = 10–11$.

were varied depending on the compound and its specific chromatographic properties. ^{1}H NMR and mass spectra were consistent with the assigned structures.

4.2. Transporter binding and re-uptake inhibition assays

For [^{125}I]RTI-55 binding studies and [^{3}H]neurotransmitter uptake assays, the HEK-hDAT, -hSERT, or hNET cells were grown and experiments were conducted as described previously.[4,17] Two (in cases where K_i or IC_{50} values exceeded 10,000 nM) or at least three independent experiments were conducted with duplicate (radioligand binding) or triplicate (re-uptake) determinations. GraphPad Prism was used to analyze the data with IC_{50} values in radioligand binding assays converted to $K_i \pm$ SEM values using the Cheng–Prusoff equation. For uptake inhibition assays, Krebs-HEPES and test compound were added to cells and the assay was initiated by addition of [^{3}H] neurotransmitter (20 nM final concentration). Specific uptake or binding was defined as the difference in uptake or binding observed in the presence and absence of 5 μM mazindol or 5 μM imipramine (i.e., for the hSERT). Filtration of membranes or whole cells through filters and calculation of IC_{50} values were conducted as previously described.[17]

4.3. Animal testing

Forty Balb/c male mice weighing 22.4 ± 0.1 g were used in the experiment and were housed in a temperature-controlled room (22–23 °C) and maintained on a 12-h on/12-h off light cycle (lights on at 6:00 AM). The study was conducted according to a standard operating procedure and in accordance with all Federal regulations. Water and food were freely available in the home cages. The mice were randomly divided into four groups: Vehicle (saline containing 5% DMSO), (B) fluoxetine 20 mg/kg, (C) **32c** (*trans:cis* 2:1)10 mg/kg and **32d** (*trans:cis* 2.5:1) 10 mg/kg. The forced-swim test (FST) was carried out as described previously.[19] Mice were given a swimming pretest session, once a day for two successive days. Twenty-four hours after the last session, mice were injected ip with vehicle or the lower dose of each drug 30 min prior to the FST. During the pretest and test sessions, each mouse was placed for 6 min in a plastic cylinder (45 cm high × 20 cm diameter), that was filled to a depth of 28 cm with water (23 ± 1 °C). The duration of immobility, which was defined as floating in an upright position without additional activity other than that necessary for the animal to keep its head above water, was recorded. For the subchronic administration tests, the animals were separated as above and vehicle or chemicals were given by ip administration 23, 5 and 1 h before the FST. The subchronic experiments were done similar to the study described above except for the pretest training that was not carried out.

4.4. Mouse and rat liver microsome stability assay

A typical assay mixture contained either mouse or rat liver microsomes (0.5 mg of protein), 100 mM potassium phosphate buffer (pH 7.4), 40 μM test compounds, 0.5 mM $NADP^+$, 0.5 mM glucose-6-phosphate, 5 IU/mL glucose-6-phosphate dehydrogenase, 1 mg/mL diethylenetriaminepentaacetic acid (DETAPAC) and 5 mM $MgCl_2$ in a final incubation volume of 0.1 mL. After 0, 10, 25, 40 and 60 min, the incubations were stopped by the addition of 1 mL CH_2Cl_2/2-propanol (3:1 v:v). The mixture was centrifuged at 12,000*g* for 1 min, and the organic layer was separated from the aqueous fraction. The organic fraction was evaporated with a stream of argon and the residue was taken up in methanol (200 μL) and injected into the HPLC system described above.

4.5. Chemical synthesis

4.6. General procedure to synthesize 8

4.6.1. Ethyl 3-(1′-naphthyl)-2-propenoate (8i)

To a suspension of carbethoxymethyltriphenylphosphonium chloride (10.0 g, 30.0 mmol) in THF (30 mL) under Ar was added NaH (60% in mineral oil, 1.2 g, 30 mmol) and then heated to reflux for 1 h. The orange colored suspension was cooled to 0 °C and the requisite benzaldehyde (**7**) (4.2 g, 26.0 mmol) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was then poured into a separatory funnel containing ammonium chloride aqueous solution (satd NH_4Cl/H_2O, 1:1, v:v, 100 mL). The organic material was extracted with ethyl acetate (3 × 80 mL) and the combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo and the crude product (**8**) obtained was dissolved in acetone (50 mL). H_2SO_4 (1 M, 1.5 mL) was added and the mixture obtained was heated to reflux for 6 h with stirring. The reaction was then cooled to room temperature and the solvent was removed in vacuo to obtain the crude product that was then purified by flash column chromatography ($R_f = 0.15$, EtOAc/hexane, 10:90, v:v) to afford the product as an oil (14.3 g, 98.4%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, $J = 15.9$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.88 (t, $J = 7.5$ Hz, 2H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.58 (t, $J = 5.6$ Hz, 1H), 7.53 (t, $J = 7.0$ Hz, 1H), 7.47 (t, $J = 7.8$ Hz, 1H), 6.53 (d, $J = 15.6$ Hz, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H).

The following compounds were prepared in a similar fashion as that for compound **8i**.

4.6.2. Ethyl 3-pentafluorophenyl-2-propenoate (8j)

The product (94% yield) was obtained by chromatography on silica as an oil; ($R_f = 0.39$, EtOAc/hexane, 6:94, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, $J = 16.6$ Hz, 1H), 6.73 (d, $J = 16.5$ Hz, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.2$ Hz, 3H).

4.6.3. Ethyl-3-(3-pyridine) 2-propenoate (8k)

The product as an oil (quantitative yield) was obtained by chromatography on silica; (R_f = 0.24, EtOAc/hexane, 50:50, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 1.9 Hz, 1H), 8.55 (t, J = 5.2 Hz, 1H), 7.79 (d, J = 9.8 Hz, 1H), 7.63 (d, J = 18.9 Hz, 1H), 7.28 (dd, J = 5.3, 4.7 Hz, 1H), 6.45 (d, J = 15.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H).

4.6.4. Ethyl 3-(4′-fluoro-3′-methylphenyl)-2-propenoate (8b′)

The product as an oil (99% yield) was obtained by chromatography on silica; (R_f = 0.54, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 16.2 Hz, 1H), 7.34–7.28 (m, 2H), 6.98 (t, J = 9.3 Hz, 1H), 6.31 (d, J = 16.2 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H).

4.6.5. Ethyl 3-(4′-methoxy-1′-naphthyl)-2-propenoate (8c′)

The product as an oil (92% yield) was obtained by chromatography on silica; (R_f = 0.55, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 15.6 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.63–7.5 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.02 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H).

4.6.6. Ethyl 3-(2′-methoxy-1′-naphthyl)-2-propenoate (8d′)

The product as an oil (93% yield) was obtained by chromatography on silica; (R_f = 0.54, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 15.8 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 9.1Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.52 (m, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.8Hz, 1H), 6.76 (d, J = 15.6 Hz, 1H), 3.95 (s, 3H), 3.42 (t, J = 7.7 Hz, 3H), 2.74 (td, J = 7.7, 1.9Hz, 3H).

4.7. General procedure for the synthesis of 9

4.7.1. Ethyl-3-(1′-naphthyl)-propanoate (9i)

To a solution of **8i** (6.0 g, 27.0 mmol) in ethanol (200 proof, 40 mL) under Ar was added 10% Pd/C (250 mg). The flask containing the mixture was then evacuated and purged with H_2 three times. In an H_2 gas environment the reaction was allowed to stir for 15 h at room temperature. The reaction mixture was filtered through Celite with ethanol and the crude product obtained after removal of the solvent in vacuo was purified by flash column chromatography (R_f = 0.27, EtOAc/hexane, 10:90, v:v) to give the product as an oil (12.4 g, 86.2% yield); (R_f = 0.5, EtOAc/hexane, 20:80, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.5 (t, J = 6.9 Hz, 1H), 7.42 (t, J = 7.3Hz, 1H), 7.37 (d, J = 6.8 Hz, 1H), 4.18 (t, J = 7.1 Hz, 2H), 3.45 (t, J = 8.0 Hz, 2H), 2.78 (q, J = 8.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H).

4.7.2. Ethyl-3-pentafluorophenyl-2-propanoate (9j)

The product as an oil (96% yield) was obtained by chromatography on silica; (R_f = 0.65, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J = 7.2 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H), 2.6 (q, J = 8.0 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H).

4.7.3. Ethyl-3-(3′-pyridine)propanoate (9k)

The product as an oil (quantitative yield) was obtained by chromatography on silica; (R_f = 0.33, EtOAc/hexane, 40:60, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.46, (d, J = 4.7 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.21 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H).

4.7.4. Ethyl-3-(4′-fluoro-3′-methylphenyl)-2-propanoate (9b′)

The product as an oil (95% yield) was obtained by chromatography on silica; (R_f = 0.54, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ *7.0–6.86* (m, 3H), 4.11 (q, J = 7.2 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 2.23 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H).

4.7.5. Ethyl 3-(4′-methoxy-1′-naphthyl)-2-propanoate: (9c′)

The product as an oil (94% yield) was obtained by chromatography on silica; (R_f = 0.22, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.54 (m, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.34 (t, J = 8.0 Hz, 2H), 2.72 (t, J = 7.9 Hz, 2H), 1.25 (t, J = 7.2 Hz , 3H).

4.7.6. Ethyl 3-(2′-methoxy-1′-naphthyl)-2-propanoate (9d′)

The product as an oil (91% yield) was obtained by chromatography on silica; (R_f = 0.54, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.5 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.26 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 3.42 (t, J = 7.7 Hz, 2H), 2.61 (m, 2H), 1.26 (m, 3H).

4.8. General procedure for the synthesis of 10

4.8.1. 3-(1′-Naphthyl) propanal (10i)

To a solution of **9i** (5.8 g, 25.7 mmol) in dry toluene (40 mL) under Ar was added DIBAL solution (1 M in toluene, 30 mL, 30 mmol) at −78 °C. The reaction was then stirred at this temperature for 2 h. Methanol (2 mL) was added to the reaction mixture and the reaction was allowed to warm to 0 °C. The reaction mixture was then poured into a separatory funnel containing a HCl solution (1 N, 100 mL). The organic material was extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were washed with brine (80 mL) and dried over sodium sulfate. The crude product obtained after removal of the solvent in vacuo was purified by flash column chromatography (R_f = 0.1, EtOAc/hexane, 10:90, v:v) to give the product as an oil (74% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 7.41 (t, J = 7.3 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 3.43 (t, J = 7.8 Hz, 2H), 2.91 (t, J = 8.1 Hz, 2H).

The following compounds were prepared in a similar manner to **10i**.

4.8.2. 3-Pentafluorophenylpropanal (10j)

The product as an oil (30% yield) was obtained by chromatography on silica; (R_f = 0.3, EtOAc/hexane, 5:95, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 3.02 (t, J = 7.3 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H).

4.8.3. 3-(3-Pyridine) propanal (10k)

The product as an oil (67% yield) was obtained by chromatography on silica; (R_f = 0.29, EtOAc/hexane, 20:80, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.48 (s, 1H), 8.46 (d, J = 4.7 Hz, 1H), 7.52 (d, J = 7.8Hz, 1H), 7.22 (m, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5Hz, 2H).

4.8.4. 3-(4′-Fluoro-3′-methylphenethyl)propanal (10b′)

The product as an oil (77% yield) was obtained by chromatography on silica; (R_f = 0.37, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.0–6.88 (m, 3H), 2.89 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 7.2Hz, 2H), 2.24 (s, 3H).

4.8.5. 3-(4′-Methoxy-1′-naphthyl) propanal (10c′)

The product as an oil (84% yield) was obtained by chromatography on silica; (R_f = 0.33, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.55 (m, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 6.74 (d, J = 7.9Hz, 1H), 3.99 (s, 3H), 3.34 (t, J = 7.6 Hz, 2H), 2.74 (m, 2H).

4.8.6. 3-(2′-Methoxy-1′-naphthyl) propanal (10d′)

The product as an oil (94% yield) was obtained by chromatography on silica; (R_f = 0.43, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.9Hz, 1H), 7.49 (m 1H), 7.35 (m, 1H), 7.27 (d, J = 9.2 Hz, 1H), 3.95 (s, 3H), 3.41 (m, 2H), 2.74 (td, J = 7.7, 1.9 Hz, 2H).

4.9. General procedure for synthesis of 11

4.9.1. 5-Phenyl-1-penten-5-ol (11a)

To a solution of the aldehyde **10a** (3.0 g, 19.5 mmol) in THF (20 mL) at 0 °C was added a solution 1-butenylmagnesium bromide (0.5 M in THF, 45 mL, 22.5 mmol) dropwise for 15 min. The reaction mixture was then poured into a separatory funnel containing a solution of saturated ammonium chloride (80 mL). The organic fraction was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent then was removed in vacuo and the crude product was purified by flash column chromatography (R_f = 0.36, EtOAc/hexane, 20:80, v:v); on silica to afford the product as a yellow oil (82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.36–7.27* (m, 5H), 5.83 (m, 1H), 5.04 (dt, J = *1*5.7, 1.8 Hz, 1H), 4.98 (d, J = 10.4 Hz, 1H), 4.7 (t, J = 6.5 Hz, 1H), 2.21–1.80 (m, 5H).

The following compounds were prepared in a similar manner as **11a**.

4.9.2. 5-(4′-Chlorophenyl)-1-penten-5-ol (11b)

The product (43% yield) was obtained as an oil by chromatography on silica; (R_f = 0.43, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ *7.34–7.27* (m, 4H), 5.9–5.66 (m, 1H), 5.04 (d, J = 17.4 Hz, 1H), 4.99 (d, J = 9.9 Hz, 1H), 4.69 (m, 1H), 2.17–2.08 (m, 2H), 1.91–1.75 (m, 2H).

4.9.3. 5-(4′-Bromophenyl)-1-penten-5-ol (11c)

The product (94% yield) was obtained as an oil by chromatography on silica; (R_f = 0.40, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.82 (m, 1H), 5.01 (m,2H), 4.66 (t, J = 6.6 Hz, 1H), 2.16–2.05 (m, 2H), 1.92–1.74 (m, 2H).

4.9.4. 5-(4′-Methoxyphenyl)-1-penten-5-ol (11d)

The product (93% yield) was obtained as an oil by chromatography on silica; (R_f = 0.15, DCM/hexane, 80:20, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.83 (m, 1H), 4.98 (m, 2H), 4.65 (t, J = 6.6 Hz, 1H), 3.81 (s 3H), 2.17–2.04 (m, 2H), 2.03–1.67 (m, 2H).

4.9.5. 5-(4′-*t*-Butylphenyl)-1-penten-5-ol (11e)

The product (76% yield) was obtained as an oil by chromatography on silica; (R_f = 0.35, DCM/hexane, 80:20, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.84 (m, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.98 (d, J = 10.0 Hz, 1H), 2.2–2.06 (m, 2H), 1.96–1.75 (m, 2H), 1.31 (s, 9H).

4.9.6. 5-(2′-Naphthyl)-1-penten-5-ol (11f)

The product (71% yield) was obtained as an oil by chromatography on silica; (R_f = 0.32, DCM/hexane, 80:20, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *7.86–7.78* (m, 4H), 7.5–7.46 (m, 3H), 5.85 (m, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.99 (d, J = 10.0 Hz, 1H), 4.88 (t, J = 6.9 Hz, 1H), 2.22–2.09 (m, 2H), 2.05–1.85 (m, 2H).

4.9.7. 5-(1′-Naphthyl)-1-penten-5-ol (11g)

The product (23% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.87 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.5 (m, 3H), 5.89 (m, 1H), 5.49 (m, 1H), 5.04 (dd, J = 1.8, 15.6 Hz, 1H), 4.99 (dd, J = 1.8, 10.2 Hz, 1H), 2.3–2.24 (m, 2H), 2.06–1.97 (m, 2H).

4.9.8. 7-Phenyl-1-hepten-5-ol (11h)

The product (58% yield) was obtained as an oil by chromatography on silica; (R_f = 0.43, EtOAc/hexane, 25:75, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ *7.29–7.19* (m, 5H), 5.85 (m, 1H), 5.04 (td, J = 2.2, 14.0 Hz, 1H), 4.97 (dd, J = 1.7, 10.4 Hz, 1H), 3.67 (m, 1H), 2.8 (m, 1H), 2.68 (m, 1H), 2.22–2.13 (m, 2H), 1.83–1.73 (m, 2H), 1.62–1.54 (m, 3H).

4.9.9. 7-(1′-Naphthyl)-1-hepten-5-ol (11i)

The product (56% yield) was obtained as an oil by chromatography on silica; (R_f = 0.12, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.54–7.33 (m, 4H), 5.84 (m, 1H), 5.04 (dd, J = 1.8, 17.4 Hz, 1H), 4.99 (dd, J = 2.1, 10.2 Hz, 1H), 3.75 (m, 1H), 3.47–3.25 (m, 1H), 3.16–3.06 (m, 1H), 2.24–2.13 (m, 2H), 1.94–1.85 (m, 2H), 1.65–1.55 (m, 2H).

4.9.10. 7-Pentafluorophenyl-1-hepten-5-ol (11j)

The product (48% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.05 (dd, J = 1.8, 15.8 Hz, 1H), 4.98 (dd, J = 1.3, 10.3 Hz, 1H), 3.64 (m, 1H), 2.91–2.75 (m, 2H), 2.24–2.11 (m, 2H), 1.78–1.65 (m, 2H), 1.63–1.55 (m, 3H).

4.9.11. 7-(3′-Pyridinyl)-1-hepten-5-ol (11k)

The product (52% yield) was obtained as an oil by chromatography on silica; (R_f = 0.15, EtOAc/hexane, 60:40, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.42 (d, J = 4.2 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.2 (dd, J = 4.9, 7.8 Hz, 1H), 5.82 (m, 1H), 5.03 (d, J = 16.0 Hz, 1H), 4.96 (d, J = 10.3 Hz, 1H), 3.65 (m, 1H), 2.81 (m, 1H), 2.68 (m, 1H), 2.23–2.11 (m, 2H), 1.94 (br s, 1H), 1.81–1.72 (m, 2H), 1.63–1.56 (m, 2H).

4.9.12. 6-Phenylhex-1-en-5-ol (11′a′)

The product (95% yield) was obtained as an oil by chromatography on silica; (R_f = 0.12, EtOAc/hexane, 10:90, v:v); ^{1}H NMR: (500 MHz,$CDCl_3$) δ *7.33–7.20* (m, 5H), 5.04 (m, 1H), 5.0 (m, 2H), 3.85 (m, 1H), 2.84 (m, 1H), 2.69–2.65 (m, 1H), 2.29–2.16 (m, 2H), 1.67–1.58 (m, 2H).

4.9.13. 7-(4′-Fluoro-3′-methylphenyl)-1-hepten-5-ol (11″b′)

The product (38% yield) was obtained as an oil by chromatography on silica; (R_f = 0.41, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.00–6.88* (m, 3H), 5.88–5.8 (m, 1H), 4.05 (dt, J = 1.9, 15.7 Hz, 1H), 4.99–4.95 (m, 1H), 3.67–3.62 (m, 1H), 2.74–2.70 (m, 1H), 2.64–2.57 (m, 1H), 2.25 (s, 3H), 2.24–2.05 (m, 2H), 1.77–1.7 (m, 2H), 1.63–1.53 (m, 3H).

4.9.14. 7-(4′-Methoxy-1′-naphthyl)-1-hepten-5-ol (11″c′)

The product (41% yield) was obtained as an oil by chromatography on silica; (R_f = 0.10, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 88.33 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.53 (m, 2H), 7.26 (d, J = 7.8 Hz, 1H), 6.76 (d, J = 6.0 Hz, 1H), 5.87 (m, 1H), 5.04 (dd, J = 1.8, 15.3 Hz, 4.99 (dd, J = 1.2, 10.2 Hz, 1H), 4.01 (s, 3H), 3.77 (m, 1H), 3.28–3.18 (m, 1H), 3.11–3.01 (m, 1H), 2.26–2.16 (m, 2H), 1.84–1.84 (m, 2H), 1.67–1.57 (m, 2H).

4.9.15. 7-(2′-Methoxy-1′-naphthyl)-1-hepten-5-ol (11″d′)

The product (43% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.36–7.24 (m, 2H), 5.81

(m, 1H), 5.0 (m, 2H), 3.93 (s 3H), 3.45 (m, 1H), 3.09 (t, J = 8.2 Hz, 2H) 2.14–2.07 (m, 2H), 1.89–1.82 (m, 2H), 1.78–1.73 (m, 2H).

4.9.16. 7-(*p*-(*t*-Butyldimethylsilyloxy)phenyl)-1-hepten-5-ol (11″e′)

The product (52% yield) was obtained as an oil by chromatography on silica; (R_f = 0.41, EtOAc/hexane, 25:75, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 5.85–5.08 (m, 1H), 5.5 (dd, J = 1.8, 15.8 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 3.66–3.62 (m, 1H), 2.75–2.68 (m, 1H), 2.64–2.57 (m, 1H), 2.21–2.12 (m, 2H), 1.77–1.71 (m, 2H), 1.6–1.52 (m, 2H), 0.98 (s, 9H), 0.18 (s, 6H).

4.9.17. 5-(2′-Furanyl)pent-1-en-5-ol (11f′)

The product (85% yield) was obtained as an oil by chromatography on silica; (R_f = 0.19, EtOAc/hexane, 15:85, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (s, 1H), 6.33 (t, J = 2.2 Hz. 1H), 6.24 (d, J = 3.2 Hz, 1H), 5.83 (m, 1H), 5.04 (d, J = 12.3 Hz, 1H), 4.99 (d, J = 9.6 Hz, 1H), 4.71 (t, J = 6.8 Hz, 1H), 2.17 (m, 2H), 1.96 (q, J = 7.2Hz, 2H), 1.89 (br s, 1H).

4.10. General procedure for the synthesis of 12

4.10.1. Bromomethyl-5-phenyltetrahydrofuran (12a)

To a solution of **11a** (3.24 g, 18.0 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added *N*-bromosuccinimide (NBS, 3.56 g, 20.0 mmol) portion wise and the reaction was warmed to room temperature for 12 h. The solvent was then removed in vacuo and the remaining residue was purified by flash column chromatography to afford the product (94% yield); (R_f = 0.45, EtOAc/hexane, 25:75, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz):δ 7.38–7.24 (m, 5H), 5.09 (t, J = 6.9 Hz, 0.66H), 4.95 (m, 0.33H), 4.47 (m, 0.66H), 4.34 (m, 0.33H), 3.58–3.44 (m, 2H), 2.46–1.87 (m, 4H).

The following compounds were prepared in a similar manner as **12a.**

4.10.2. 5-Bromomethyl-2-(4′-chlorophenyl)tetrahydrofuran (12b)

The product (23% yield) was obtained as an oil by chromatography on silica as a mixture of *cis* and *trans* isomers (*cis*:*trans*, 2:1); (R_f = 0.4, EtOAc/hexane, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (m, 4H), 5.06 (dd, J = 1.8, 7.8 Hz, 0.67H), 4.91 (dd, J = 2.1, 8.4 Hz, 0.33H), 4.47 (m, 0.67H), 4.33 (m, 0.33H), 3.5 (m, 2H), 2.44–2.14 (m, 2H), 1.99–1.78 (m, 2H).

4.10.3. 2-Bromomethyl-5-(4′-bromophenyl)tetrahydrofuran (12c)

The product (55% yield) was obtained as an oil by chromatography on silica; (R_f = 0.49, DCM/hexane, 50:50, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 (d, J = 8.1 Hz, 2H), 7.2 (d, J = 8.1 Hz, 2H), 5.04 (dd, J = 1.8, 7.8 Hz, 0.67H), 4.90 (dd, J = 1.8, 8.1 Hz, 0.33H), 4.47 (m, 0.67H), 4.34 (m, 0.33H), 3.5 (m, 2H), 2.44–2.13 (m, 2H), 2.0–1.71 (m, 2H).

4.10.4. 2-Bromomethyl-5-(4′-methoxyphenyl)tetrahydrofuran (12d)

The product (81% yield) was obtained as an oil by chromatography on silica; (R_f = 0.36, DCM/hexane, 50:50, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.3 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.02 (dd, J = 1.8, 7.8 Hz, 0.67H), 4.88 (dd, J = 2.7, 8.4 Hz, 0.33H), 4.45 (m, 0.67H), 4.3 (m, 0.33H), 3.78 (s, 3H), 3.49 (m, 2H), 2.37–2.14 (m, 2H), 2.0–1.83 (m, 2H).

4.10.5. 2-(Bromomethyl)-5-(4′-(*t*-Butylphenyl)tetrahydrofuran (12e)

The product (87% yield) was obtained as an oil by chromatography on silica; (R_f = 0.54, DCM/hexane, 50:50, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (m, 4H), 5.05 (dd, J = 1.5, 7.8 Hz, 0.67H), 4.91 (dd, J = 1.8, 8.1 Hz, 0.33H), 4.45 (m, 0.67H), 4.32 (m, 0.33H), 3.48 (m, 2H), 2.43–2.21 (m, 2H), 1.98–1.87 (m, 2H), 1.3 (s, 12H).

4.10.6. 2-Bromomethyl-5-(2′-naphthyl)tetrahydrofuran (12f)

The product (65% yield) was obtained as an oil by chromatography on silica; (R_f = 0.37, DCM/hexane, 50:50, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (m, 4H), 7.44 (m, 3H), 5.27 (m, 0.7H), 5.12 (m, 0.3H), 4.57 (m, 0.7H), 4.4 (m, 0.3H), 3.55 (m, 2H), 2.53–2.22 (m, 2H), 2.07–1.94 (m, 2H).

4.10.7. 2-Bromomethyl-5-(1′-naphthyl)tetrahydrofuran (12″g)

The product (93% yield) was obtained as an oil by chromatography on silica; (R_f = 0.5, DCM/hexane, 50:50, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.95–7.85* (m, 3H), 7.76 (d, J = 8.1 Hz, 1H), 7.64–7.44 (m, 3H), 5.85 (t, J = 6.7 Hz, 0.3H), 5.71 (t, J = 6.9 Hz, 0.7H), 4.62 (m, 0.3H), 4.43 (m, 0.7H), 3.62 (m, 2H), 2.67–2.55 (m, 1H), 2.33–2.23 (m, 1H), 2.08–1.92 (m, 2H).

4.10.8. 2-Bromomethyl-5-phenethyltetrahydrofuran (12″h)

The product (74% yield) was obtained as an oil by chromatography on silica as a mixture of isomers; *trans:cis* = 2:1; (R_f = 0.26, EtOAc/hexane, 20:80, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.28–7.19* (m, 5H), 4.26 (m, 0.66H), 4.15 (m, 0.33H), 4.06 (m, 0.66H), 3.94 (m, 0.33H), 3.47–3.44 (m, 1H), 3.37–3.34 (m, 1H), 2.77–2.63 (m, 2H), 2.19–1.76(m, 5H), 1.62–1.58 (m, 1H).

4.10.9. 2-Bromomethyl-5-naphthylethyltetrahydrofuran (12i)

The product (71% yield) was obtained as an oil by chromatography on silica as a mixture of isomers; *trans:cis* = 2:1; (R_f = 0.3, EtOAc/hexane, 20:80, v:v); ^{1}H NMR: (500 MHz,$CDC1_3$) δ *8.09–7.34* (m, 7H), 4.31 (m, 0.5H), 4.2–4.1 (m, 1H), 4.05 (m, 0.5H), 3.5–3.47 (m, 1H), 3.47–3.37 (m, 1H), 3.28–3.22 (m, 1H), 3.13–3.07 (m, 1H), 2.21–1.77 (m, 5H), 1.67–1.60 (m, 1H)

4.10.10. 2-Bromomethyl-2-(pentafluorophenyl)tetrahydrofuran (12″j)

The product (65% yield) was obtained as an oil by chromatography on silica; (R_f = 0.17, EtOAc/hexane, 3:97, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24 (m, 1H), 4.04 (m, 1H), 3.43 (dd, J = 5.2, 15.3 Hz, 1H), 3.35 (dd, J = 6.5, 10.3 Hz, 1H), 2.83 (m, 1H), 2.73 (1H), 2.19–2.11 (m, 2H), 1.83–1.57 (m, 4H).

4.10.11. 2-Bromomethyl-5-(3′-pyridinylethyl)tetrahydrofuran (12″k)

The product (81% yield) was obtained as a yellow oil by chromatography on silica; (R_f = 0.28, EtOAc/hexane,60:40, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.49 (d, J = 4.6 Hz, 1H), 7.75 (m, 1H), 7.38 (m, 1H), 4.25 (m, 0.6H), 4.14 (m, 0.4H), 4.02 (m, 0.6H), 3.92 (m, 0.4H), 3.45–3.33 (m, 2H), 2.85–2.72 (m, 2H), 2.17–2.04 (m, 2H), 1.91–1.77 (m, 3H), 1.59 (m, 1H).

4.10.12. 2-Benzyl-5-bromomethyltetrahydrofuran (12′a′)

The product (65% yield) was obtained as an oil by chromatography on silica; (R_f = 0.55, DCM/hexane, 50:50, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ *7.20–7.29* (m, 5H), 4.15–4.33 (m, 1H), 3.27–3.45 (m, 2H), 2.96 (dd, J = 5.6, 13.5 Hz, 1H), 2.70–2.79 (m, 1H), 1.91–2.11 (m, 2H), 1.63–1.78 (m, 3H).

4.10.13. 2-(Bromomethyl)-5-(4′-fluoro-3′-methylphenethyl)-tetrahydrofuran (12″b′)

The product (30% yield) was obtained as an oil by chromatography on silica; (R_f = 0.3, EtOAc/hexane, 20:80, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.0–6.87* (m, 3H), 4.27–3.9 (m, 2H), 3.46–3.42 (m, 1H), 3.37–3.32 (m, 1H), 2.69–2.57 (m, 2H), 2.24 (s, 3H), 2.23–1.56 (m, 6H).

4.10.14. 2-Bromomethyl-5-(4′-methoxy-1′-naphthethyl)-tetrahydrofuran (12″c′)

The product (88% yield) was obtained as an oil by chromatography on silica; (R_f = 0.3, DCM/hexane, 50:50, v:v); ^{1}H NMR: (300 MHz,$CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4Hz, 1H), 7.67–7.38 (m, 2H), 4.41–4.26 (m, 1H), 4.21–4.02 (m, 1H), 3.99 (s, 3H), 3.83 (m, 2H), 2.22–1.71 (M, 8H).

4.10.15. 2-Bromomethyl-5-(2′-methoxy-1′-naphthethyl)tetrahydrofuran (12″d′)

The product (97% yield) was obtained as an oil by chromatography on silica; (R_f = 0.5, EtOAc/hexane, 25:75, v:v); ^{1}H NMR: (500 MHz,$CDCl_3$) δ *8.32–6.74* (m, 6H), 4.3 (m, 0.67H), 4.19 (m, 0.33H), 4.12 (m, 0.67H), 4.03 (m, 0.33H), 3.99 (s, 3H), 3.5–3.47 (m, 1H), 3.41–3.37 (m, 1H), 3.19–3.13 (m, 1H), 3.05–2.99 (m, 1H), 2.18–1.76 (m, 5H), 1.66–1.59 (m, 1H).

4.10.16. 2-(Bromomethyl)-5-(*p*-(*t*-butyldimethylsilyloxy-phenethyl)-tetrahydrofuran (12″e′)

The product (70% yield) was obtained as an oil by chromatography on silica; (R_f = 0.47, EtOAc/hexane, 15:85, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 4.28–4.13 (m, 1H), 4.05–3.9 (m, 1H), 3.46–3.42 (m, 1H), 3.36–3.32 (m, 1H), 2.67–2.56 (m, 2H), 2.16–1.55 (m, 6H), 0.98 (s, 9H), 0.18 (s, 6H).

4.10.17. 2-Bromomethyl-5-(1′-furanyl)tetrahydrofuran (12f′)

The product (50% yield) was obtained as an oil by chromatography on silica; (R_f = 0.2, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (s, 1H), 6.32 (s, 1H), 6.27 (dd, J = 3.2, 8.3 Hz, 1H), 5.1 (t, J = 6.8Hz, 0.5H), 5.0 (t, J = 6.7 Hz, 0.5H), 4.39 (m, 0.5H), 4.29 (m, 0.5H), 3.51–3.35 (m, 2H), 2.32–1.89 (m, 4H).

4.11. General procedure for synthesis of 13

4.11.1. 2-Phenyl-5-(*N*-phthlimidomethyl)tetrahydrofuran (13a)

To a vial under Ar was added **12a** (1.28 g, 4.44 mmol), NaI (100 mg), potassium phthalimide (2.05 g, 11.1 mmol), and dry DMSO (10 mL). The reaction was heated to 70 °C and stirred under Ar for 12 h. After it was cooled to room temperature, the reaction mixture was poured into a separatory funnel containing sodium bicarbonate aqueous solution (satd $NaHCO_3/H_2O$ = 1:1, 70 mL). The organic material was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford crude product as an oil which was purified by flash column chromatography (1.42 g, 74% yield) as a mixture of the *trans:cis* = 2:1 isomers; (R_f = 0.16, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (m, 2H), 7.71 (m, 2H), 7.39–7.21 (m, 5H), 5.1 (t, J = 6.9 Hz, 0.66H), 4.90 (t, J = 7.2 Hz, 0.33H), 4.64 (m, 0.66H), 4.46 (m, 0.33H), 4.01 (dd, J = 7.3, 13.5 Hz, 0.33H), 3.95 (dd, J = 8.2, 14.3 Hz, 0.66H), 3.82 (dd, J = 5.2, 13.5 Hz, 0.66H), 2.46–2.12 (m, 2H), 1.92–1.81 (m, 2H).

The following compounds were prepared in a similar manner as **13a.**

4.11.2. 2-(4′-Chlorophenyl)-5-(*N*-phthalimidomethyl)tetrahydrofuran (13b)

The product (99% yield) was obtained as an oil by chromatography on silica; (R_f = 0.38, EtOAc/hexane, 40:60, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz); δ *7.86–7.84* (m, 2H), 7.72–7.69 (m, 2H), 7.3–7.22 (m, 4H), 5.06 (t, J = 6.9 Hz, 0.67H), 4.85 (t, J = 7.2 Hz, 0.33H), 4.61 (m, 0.67H), 4.44 (m, 0.33H), 3.9 (m, 0.66H), 3.8 (m, 1.34H), 2.44–2.25 (m, 1H), 2.22–2.08 (m, 1H), 1.88–1.74 (m, 2H).

4.11.3. 2-(4′-Bromophenyl)-5-(*N*-phthalimidomethyl) tetrahydrofuran (13c)

The product (74% yield) was obtained as an oil by chromatography on silica; (R_f = 0.69, EtOAc/hexane, 40:60, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz); δ *7.85–7.68* (m, 4H), 7.45–7.39 (m, 2H), 7.26–7.14 (m, 2H), 5.04 (t, J = 6.9 Hz, 0.67H), 4.84 (t, J = 7.2 Hz, 0.33H), 4.61 (m, 0.67H), 4.44 (m, 0.33H), 3.89 (m, 0.66H), 3.8 (m, 1.34H), 2.45–2.37 (m, 1H), 2.21–2.11 (m, 1H), 1.88–1.77 (m, 2H).

4.11.4. 2-(4′-Methoxyphenyl)-5-(*N*-phthalimidomethyl)tetrahydrofuran (13d)

The product (99% yield) was obtained as an oil by chromatography on silica; (R_f = 0.4, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz); δ *7.87–7.67* (m, 4H), 7.31–7.2 (m, 2H), 6.87–6.8 (m, 2H), 5.03 (t, J = 6.9 Hz, 0.67H), 4.83 (t, J = 7.1 Hz, 0.33H), 4.6 (m, 0.67H), 4.43 (m, 0.33H), 3.88 (m, 0.66H), 3.79 (m, 1.34H), 3.76 (s, 3H), 2.41–2.31 (m, 1H), 2.26–2.11 (m, 1H), 1.92–1.75 (m, 2H).

4.11.5. 2-(4′-*t*-Butylphenyl)-5-(phthalimidomethyl)tetrahydrofuran (13e)

The product (68% yield) was obtained as an oil by chromatography on silica; (R_f = 0.52, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 300 MHz); δ *7.86–7.81* (m, 2H), 7.71–7.67 (m, 2H), 7.36–7.21 (m, 4H), 5.06 (t, J = 6.9 Hz, 0.67H), 4.87 (t, J = 7.1 Hz, 0.33H), 4.61 (m, 0.67H), 4.44 (m, 0.33H), 3.99 (m, 0.33H), 3.93 (m, 0.67H), 3.8 (m, 0.33H), 3.67 (m, 0.67H), 2.44–2.24 (m, 1H), 2.42–2.06 (m, 1H), 1.96–1.78 (m, 2H) 1.28 (s, 9H).

4.11.6. 2-(2′-Naphthyl)-5-(phthalimidomethyl)tetrahydrofuran (13f)

The product (77% yield) was obtained as an oil by chromatography on silica; (R_f = 0.49, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz); δ *7.87–7.68* (m, 7H), 7.48–7.37 (m, 4H), 5.27 (t, J = 6.9 Hz, 0.53H), 5.08 (t, J = 6.9 Hz, 0.47H), 4.71 (m, 0.53H), 4.52 (m, 0.47H), 3.97 (m, 0.94H), 3.85 (m, 1.06H), 2.55–2.33 (m, 1H), 2.25–2.12 (m, 1H), 2.02–1.83 (m, 2H).

4.11.7. 2-(1′-Naphthyl)-5-(*N*-phthlimidomethyl) tetrahydrofuran (13g)

The product (79% yield) was obtained as an oil by chromatography on silica; (R_f = 0.53, EtOAc/hexane, 30:70, v:v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 87.86 (m, 4H), 7.72 (m, 4H), 7.48 (m, 3H), 5.86 (t, J = 6.5 Hz, 0.3H), 5.64 (t, J = 7.1 Hz, 0.7H), 4.78 (m, 0.3H), 4.53 (m, 0.7H), 4.04 (m, 1.4H), 3.91 (m, 0.6H), 2.73–2.56 (m, 1H), 2.25–2.14 (m, 1H), 2.07–1.78 (m, 2H).

4.11.8. 2-Phenethyl-5-(*N*-phthlimidomethyl)tetrahydrofuran-(13″h 14i)

The product (95% yield) was obtained as an oil by chromatography on silica; (R_f = 0.49, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (m, 2H), 7.71 (m, 2H), 7.25–7.17 (m, 5H), 4.39 (m, 0.66H), 4.27 (m, 0.33H), 4.05 (m, 0.66H), 3.88 (m, 0.33H), 3.86–3.8 (m, 1H), 3.71 (dd, J = 5.3, 13.6 Hz, 0.33H), 3.61 (dd, J = 5.2, 13.5 Hz, 0.66H), 2.72–2.57 (m, 2H), 2.17–1.53 (m, 4H).

4.11.9. 2-(1′-Naphthethyl)-5-(*N*-phthlimidomethyl) tetrahydrofuran(13″i)

The product (65% yield) was obtained as an oil by chromatography on silica; (R_f = 0.54, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *8.09–8.01* (m, 1H), 7.88–7.81 (m, 3H), 7.74–7.68 (m, 3H), 7.53–7.31 (m, 4H), 4.43 (m, 0.65H), 4.33 (m, 0.35H), 4.16 (m, 0.65H), 3.97 (m, 0.35H), 3.81 (m, 0.7H), 3.76 (m, 1.3H), 3.19 (m, 1H), 3.04 (m, 1H), 2.17–1.53 (m, 6H).

4.11.10. 2-(Pentafluorophenethyl)-5-(*N*-phthlimidomethyl)-tetrahydrofuran (13″j)

The product (58% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (dd, *J* = Hz, 2H), 7.72 (dd, *J* = Hz, 2H), 4.38 (m, 1H), 4.04 (quintet, *J* = Hz, 1H), 3.8 (dd, *J* = Hz, 1H), 3.59 (dd, *J* = Hz, 1H), 2.73 (m, 2H), 2.17–2.05 (m, 2H), 1.76–1.53 (m, 4H).

4.11.11. 5-(*N*-Phthalimidomethyl)-2-(3′-pyridinylethyl)-tetrahydrofuran (13″k)

The product (26% yield) was obtained as an oil by chromatography on silica as a mixture of diastereomers, *trans:cis* = 1.5:1; (R_f = 0.24, EtOAc/hexane, 60:40, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.44 (s, 1H), 8.41 (m, 1H), 7.85 (m, 2H), 7.72 (m, 2H), 7.5 (m, 1H), 7.17 (m, 1H), 4.39 (m, 0.6H), 4.28 (m, 0.4H), 4.03 (m, 0.6H), 3.86 (m, 0.4H), 3.86–3.80 (m, 1H), 3.72 (dd, *J* = 5.2, 13.5 Hz, 0.4H), 3.62 (dd, *J* = 4.5, 13.5 Hz, 0.6H), 2.73–2.58 (m, 2H), 2.12–2.06 (m, 2H), 1.8–1.54 (m, 4H).

4.12. General procedure for synthesis of 14

4.12.1. 2-Aminomethyl-5-(phenyl)tetrahydrofuran (14a)

To a vial under Ar was added **13a** (225 mg, 0.63 mmol), hydrazine hydrate (150 mg, 4.9 mmol), and methanol (10 mL). The mixture was stirred at room temperature for 12 h. The solvent was then removed in vacuo and the crude product was purified by column flash chromatography to yield the pure product as an oil (R_f = 0.1, methanol/DCM, 10:90, v:v) (65% yield) ^{1}H NMR:($CDCl_3$, 500 MHz): δ 7.33 (m, 5H), 4.97 (m, 0.66H), 4.9 (t, *J* = 7.7 Hz, 0.34H), 4.25 (m, 0.66H), 4.06 (m, 0.34H), 2.93–2.78 (m, 2H), 2.35 (m, 1H), 2.09 (m, 1H), 1.96–1.7 (m, 2H), 1.62 (br s, 2H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{15}NO$ 178 found 178; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1151.

The following compounds were prepared in a similar manner as **14a**.

4.12.2. 2-Aminomethyl-5-(*p*-chlorophenyl)tetrahydrofuran (14b)

The product (71% yield) was obtained as an oil by chromatography on silica; (R_f = 0.14, methanol/DCM, 15:85, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ *7.34–7.27* (m, 4H), 4.95 (t, *J* = 6.9 Hz, 0.66H), 4.83 (t, *J* = 6.7 Hz, 0.34H), 4.35 (m, 0.66H), 4.15 (m, 0.34H), 3.40 (br s, 2H), 2.99–2.81 (m, 2H), 2.32 (m, 1H), 2.08 (m, 1H), 1.84–1.68 (m, 2H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{14}ClNO$ 212 found 212; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{14}ClNO$ 211.0764, found 211.0759.

4.12.3. 2-Aminomethyl-5-(*p*-bromophenyl)tetrahydrofuran (14c)

The product (48% yield) was obtained as an oil by chromatography on silica; (R_f = 0.13, methanol/DCM, 15:85, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ *7.42–7.2* (m, 4H), 4.95 (t, *J* = 6.9 Hz, 0.66H), 4.86 (t, *J* = 6.7 Hz, 0.34H), 4.26 (m, 0.66H), 4.08 (m, 0.34H), 2.83–2.79 (m, 2H), 2.38–1.71 (m, 6H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{14}BrNO$ 256 found 256; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{11}H_{14}BrNO$ 255.0259, found 255.0265.

4.12.4. 2-Aminomethyl-5-(*p*-methoxyphenyl)tetrahydrofuran (14d)

The product (55% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 15:85, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ 7.27 (m, 2H), 6.87 (m, 2H), 4.92 (m, 0.66H), 4.83 (t, *J* = 6.7 Hz, 0.34H), 4.26 (m, 0.66H), 4.07 (m, 0.34H), 3.79 (s, 1H), 3.78 (s, 2H), 2.92–2.78 (m, 2H), 2.57 (br s, 2H), 2.29 (m, 1H), 2.1, m, 1H), 1.88–1.69 (m, 2H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{12}H_{17}NO_2$ 208 found 208; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1258.

4.12.5. 2-Aminomethyl-5-(*p*-*t*-butylphenyl)tetrahydrofuran (14e)

The product (54% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ *7.36–7.24* (m, 4H), 4.96 (m, 0.66H), 4.86 (m, 0.34H), 4.46 (br s, 2H), 4.34 (m, 0.66H), 4.13 (m, 0.34H), 3.00–2.8 (m, 2H), 2.29 (m, 1H), 2.1 (m, 1H), 1.97–1.68 (m, 2H), 1.3 (s, 9H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{23}NO$ 234 found 234; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1786.

4.12.6. 2-(Aminomethyl)-5-(2′-naphthyl)tetrahydrofuran (14f)

The product (66% yield) was obtained as an oil by chromatography on silica; (R_f = 0.14, methanol/DCM, 15:85, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.84–7.78* (m, 4H), 7.47–7.41 (m, 3H), 5.14 (t, *J* = 7.2 Hz, 0.33H), 5.04 (t, *J* = 7.4 Hz, 0.67H), 4.38–4.33 (m, 0.33H), 4.16–4.14 (m, 0.66H), 3.01–2.83 (m, 2H), 2.6 (br s, 2H), 2.42–2.34 (m, 1H), 2.16–2.07 (m, 1H), 1.97–1.86 (m, 1H), 1.79–1.72 (1H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{17}NO$ 228 found 228; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1304.

4.12.7. 2-(Aminomethyl)-5-(1′-naphthyl)tetrahydrofuran (14g)

The product (85% yield) was obtained as an oil by chromatography on silica; (R_f = 0.13, methanol/DCM, 15:85, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.96–7.93* (m, 1H), 7.89–7.85 (1H), 7.76–7.74 (m, 1H), 7.71–7.69 (m, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.5–7.43 (m, 3H), 5.74 (t, *J* = 7.0 Hz, 0.33H), 5.61 (t, *J* = 7.3 Hz, 0.67H), 4.38–4.28 (m, 0.33H), 4.19–4.16 (m, 0.67H), 3.02–2.88 (m, 1H), 2.62–2.52 (m, 1H), 2.15 (br s, 2H), 2.14–1.71 (m, 3H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{17}NO$ 228 found 228; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1314.

4.12.8. 2-(Aminomethyl)-5-phenethyltetrahydrofuran (14″h)

The product (55% yield) was obtained as an oil by chromatography on silica; (R_f = 0.12, methanol/DCM, 15:85, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.27–7.19* (m, 5H), 4.01–3.85 (m, 2H), 2.83–2.62 (m, 4H), 2.03–1.5 (m, 8H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{13}H_{19}NO$ 206 found 206; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1460.

4.12.9. 2-(Aminomethyl)-5-(1′-naphthethyl)tetrahydrofuran (14″i)

The product (52% yield) was obtained as an oil by chromatography on silica; (R_f = 0.13, methanol/DCM, 15:85, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *8.08–8.06* (m, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.52–7.45 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 6.8 Hz, 1H), 4.05–3.90 (m, 2H), 3.25 (m, 1H), 3.11 (m, 1H), 2.86–2.7 (m, 2H), 2.07–1.89 (m, 4H), 1.63–1.55 (m, 2H), 1.48 (br s, 2H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{17}H_{21}NO$ 256 found 256; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1626.

4.12.10. 2-Aminomethyl-5-(pentafluorophenethyl)tetrahydrofuran (14″j)

The product (53% yield) was obtained as an oil by chromatography on silica; (R_f =0.14, methanol/DCM, 15:85, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ 4.05 (m, 0.6H), 3.92 (m, 1H), 3.86 (m, 0.4H), 2.89–2.7 (m, 2H), 2.74 (m, 2H), 2.63 (br s, 2H), 2.08–1.99 (m, 2H), 1.82–1.54 (m, 4H); LRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{13}H_{14}F_5NO$ 296 found 296; HRMS (ESI) $[M+H]^+$ *m*/*z* calcd for $C_{13}H_{14}F_5NO$ 295.0996, found 295.0991.

4.12.11. 2-(Aminomethyl)-5-(3′-pyridinylethyl)tetrahydrofuran (14″k)

The product (35% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 15:85, v:v); ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.42 (d, J = 4.1 Hz, 1H), 7.51 (m, 1H), 7.19 (dd, J = 4.8, 7.7 Hz, 1H), 4.02–3.83 (m, 2H), 2.82–2.63 (m, 4H), 2.07–1.53 (m, 8H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{18}N_2O$ 207 found 207; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{18}N_2O$ 206.1419, found 206.1414.

4.13. General procedure for synthesis of 15

4.13.1. 2-Benzyl-5-cyanomethyltetrahydrofuran (15′a′)

To a vial under Ar was added 12′a′ (1.23 g, 4.3 mmol), NaI (100 mg), potassium cyanide (0.7 g, 10.6 mmol), and dry DMSO (15 mL). The mixture was heated to 70°C and stirred under Ar for 12 h. After it was cooled to room temperature, the reaction mixture was poured into a separatory funnel containing sodium bicarcarbonate aqueous solution (satd $NaHCO_3/H_2O$ = 1:1, 80 mL). The organic fraction was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (R_f = 0.2, EtOAc/hexane, 20:80, v:v) The product (0.33 g, 74%) was obtained as an oil by chromatography on silica as a mixture of *trans:cis* = 2:1 isomers; (R_f = 0.5, EtOAc/hexane, 25:75, v:v); ^{1}H NMR: (300 MHz,$CDCl_3$) δ *7.3–7.18* (m, 5H), 4.28–4.24 (m, 0.67H), 4.15–4.08 (m, 1H), 3.91–3.89 (m, 0.33H), 2.78–2.53 (m, 4H), 2.68–2.25 (m, 4H).

The following compounds were prepared in a similar manner as **15′a′**.

4.13.2. 2-Cyanomethyl-5-(4′-fluoro-3′-methylphenethyl)tetrahydrofuran (15″b′)

The product (85% yield) was obtained as an oil by chromatography on silica; (R_f = 0.25, EtOAc/hexane, 20:80, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.0–6.88* (m, 3H), 4.28–3.87 (m, 2H), 2.7–2.56 (m, 4H), 2.24 (s, 3H), 2.23–1.58 (m, 6H).

4.13.3. 2-Cyanomethyl-5-(4′-methoxy-1′-naphthethyl)tetrahydrofuran (15″c′)

The product (45% yield) was obtained as an oil by chromatography on silica; TLC (SiO_2) R_f = 0.30, 25% EtOAc/hexanes; ^{1}H NMR: (300 MHz,$CDCl_3$) δ *8.1–7.27* (m, 6H), 4.4–4.24 (m, 1H), 4.21–4.03 (m, 1H), 3.99 (s, 3H), 3.15 (m, 2H), 2.64–1.24 (m, 8H).

4.13.4. 2-Cyanomethyl-5-(2′-methoxy-1′-naphthethyl)tetrahydrofuran (15″d′)

The product (56% yield) was obtained as an oil by chromatography on silica; (R_f = 0.31, EtOAc/hexane, 25:75, v:v); ^{1}H NMR: (500 MHz,$CDCl_3$) δ *8.0–7.27* (m, 6H), 4.31 (m, 0.5H), 4.18 (m, 0.5H), 4.01 (m, 0.5H), 3.95 (s, 3H), 3.72 (m, 0.5H), 3.22–3.08 (m, 2H), 2.64–2.55 (m, 1H), 2.24–2.16 (m, 2H), 1.91–1.65 (m, 3H), 1.58 (br s, 1H), 1.24 (t, J = 7.1 Hz, 1H).

4.13.5. 2-(Cyanomethyl)-5-(4′-hydroxyphenethyl)tetrahydrofuran (15″e′)

The product (78% yield) was obtained as an oil by chromatography on silica; (R_f = 0.31, EtOAc/hexane, 50:50, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.76–7.73* (m, 2H), 7.05–7.03 (m, 2H), 5.27 (m, 2H), 4.27–4.09 (m, 1H), 4.08–3.88 (m, 1H), 2.69–2.53 (m, 4H), 2.13–2.09 (m, 2H), 1.86–1.57 (m, 4H).

4.13.6. 2-Cyanomethyl-5-(2′-furanyl)tetrahydrofuran (15f′)

The product (43% yield) was obtained as an oil by chromatography on silica as a mixture of *trans:cis* = 1:1 isomers; (R_f = 0.2, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 6.33–6.25 (m, 2H), 5.15 (t, J = 6.8 Hz, 0.5H), 4.98 (t, J = 6.7 Hz, 0.5H), 4.38 (m, 0.5H), 4.3 (m, 0.5H), 2.66 (m, 2H), 2.38–1.9 (m, 4H).

4.14. General procedure for the synthesis of 16

4.14.1. 2-(2′-Aminoethyl)-5-benzyltetrahydrofuran (16′a′)

To a vial under Ar was added Raney Ni that was previously washed with ethanol (200 proof, 3 times) and **15′a′** (80 mg, 0.35 mmol) that was treated with a small amount of Raney Ni in ethanol. The vial was then evacuated and purged with H_2 three times. An H_2 environment was added to the flask and the reaction was stirred for 48 h at room temperature. The reaction mixture was then filtered through a plug of Celite and the crude product obtained after the removal of the solvent was purified by flash column chromatography (R_f = 0.1, methanol–DCM, 10:90, v:v) to afford the pure product. The product (133 mg, 34%) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ *7.29–7.2* (m, 5H), 4.19 (quintet, J = 6.6 Hz, 0.66H), 4.04 (m, 1H), 3.91 (m, 0.34H), 2.94 (dd, J = 5.8, 13.4 Hz, 1H), 2.81 (br s, 2H), 2.7 (dd, J = 7.1, 13.4 Hz, 1H), 2.17–1.48 (m, 6H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{17}NO$ 192 found 192; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1316.

The following compounds were prepared in a similar manner as **16′a′.**

4.14.2. 2-Aminoethyl-5-(4′-fluoro-3′-methylphenethyl)tetrahydrofuran (16″b′)

The product (45% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *7.0–6.87* (m, 3H), 4.08–3.79 (m, 1H), 3.28–3.25 (m, 1H), 3.14–3.09 (m, 1H), 2.63–2.52 (m, 2H), 2.23 (m, 1H), 2.06–1.48 (m, 8H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{22}FNO$ 252 found 252; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{22}FNO$ 251.1685, found 251.1681.

4.14.3. 2-Aminoethyl-5-(4′-methoxy1–1′-naphthethyl)tetrahydrofuran (16″c′)

The product (35% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (br s, 2H), 7.3 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.69 (m, 1H), 7.5 (m, 1H), 7.2 (m, 1H), 6.73 (m, 1H), 4.05 (m, 1.3H), 3.96 (s, 1H), 3.95 (s, 2H), 3.9 (m, 0.7H), 3.29 (m, 1H), 3.16–2.92 (m, 3H), 2.06–1.77 (m, 7H), 1.52 (m, 1H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{25}NO_2$ 300 found 300; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{25}NO_2$ 299.1885, found 299.1878.

4.14.4. 2-Aminoethyl-5-(2′-methoxy1–1′-naphthethyl)tetrahydrofuran (16″d′)

The product (56% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (br s, 2H), 7.92 (d, J = 8.6 Hz, 1H), 7.75 (m, 1H), 7.69 (m, 1H), 7.50 (m, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 4.05 (m, 1.3H), 3.94 (s, 1H), 3.93 (s, 2H), 3.85 (m, 0.7H), 3.28 (m, 1H), 3.14–3.07 (m, 3H), 2.04–1.8 (m, 7H), 1.52 (m, 1H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{25}NO_2$ 300 found 300; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{19}H_{25}NO_2$ 299.1885, found 299.1888.

4.14.5. 2-Aminoethyl-5-(4′-hydoxyphenethyl)tetrahydrofuran (16″e′)

The product (32% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, methanol/DCM, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = *8.3* Hz, 2H), 6.78 (d, J = 8.2 Hz, 2H), 3.98–3.94 (M, 1H), 3.9–3.82 (m, 1H), 2.99–2.94 (m, 1H), 2.88–2.84 (m, 1H), 2.64–2.58 (m, 2H), 2.03–1.93 (m, 2H), 1.84–1.67 (m, 4H), 1.51–1.48 (m, 2H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}NO_2$ 236 found 236; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}NO_2$ 235.1572, found 235.1571.

4.14.6. 2-(2′-Aminoethyl)-5-(2″-furyl)tetrahydrofuran (16f′)

The product (40% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 7.34 (d, J = 1.2 Hz, 1H), 6.31(t, J = 2.1 Hz, 1H), 6.24(dd, J = 3.2, 6.6Hz, 1H), 5.01(t, J = 7.0 Hz, 0.5H), 4.89 (t, J = 7.0 Hz, 0.5H), 4.17 (m, 0.5H), 4.06 (m, 0.5H), 2.85 (m, 2H), 2.30–1.7 (m, 6H), 2.09 (s, 2H); LRMS (ESI) $[M+H]^+$ m/z calcd for $C_{10}H_{15}NO_2$ 182 found 182; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1109.

4.14.7. 5-Fluoro-2-methoxyphenylacetaldehyde (18)

To a suspension of methoxymethyltriphenylphosphonium chloride (10.0 g, 30.0 mmol) in THF (30 mL) under Ar was added NaH (60% in mineral oil, 1.2 g, 30 mmol) and then heated to reflux for 1 h. The orange colored suspension was cooled to 0 °C and 5-fluoro-2-methoxybenzaldehyde (**17**) (4.2 g, 26.0 mmol) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was then poured into a separatory funnel containing ammonium chloride aqueous solution (satd NH_4Cl/H_2O, 1:1, v:v, 100 mL). The organic material was extracted with ethyl acetate (3 × 80 mL) and the combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo and the crude product (**18**) obtained was dissolved in acetone (50 mL). H_2SO_4 (1 M, 1.5 mL) was then added and the mixture obtained was heated to reflux for 6 h while stirring. The reaction was then cooled to room temperature and the solvent was removed in vacuo to obtain the crude product that was then purified by flash column chromatography (R_f = 0.15, EtOAc/hexane, 10:90, v:v) to afford the product (2.63 g, 66%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.68 (s, 1H), 6.97 (dt, J = 3.1, 8.7 Hz, 1H), 6.89 (dd, J = 3.1, 8.7 Hz, 1H), 6.83 (dd, J = 4.3, 8.7 Hz, 1H), 3.8 (s, 3H), 3.63 (d, J = 1.7 Hz, 2H).

4.14.8. Ethyl-3-(5′-fluoro-2′-methoxyphenyl)-2-propenoate (19)

To a solution of 5-fluoro-2-methoxybenzaldehyde (4.3 g, 28.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added portionwise carbethoxymethylenetriphenylphosphorane (10.7 g, 30.1 mmol). The mixture was then warmed to room temperature and stirred for 12 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (R_f = 0.2, EtOAc/hexane, 10:90, v:v) to provide the product (6.0 g, 95%) as oil in a 4:1 mixture of *trans:cis* isomers; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (d, J = 16.2 Hz, 0.8H), 7.33 (dd, J = 3.1, 9.2 Hz, 0.2H), 7.21 (dd, J = 3.1, 9.2, Hz, 0.8H), 7.08 (d, J = 12.5 Hz, 0.2H), 7.03 (dt, J = 3.0, 8.8 Hz, 0.8H), 6.99 (dt, J = 3.0, 8.8 Hz, 0.2H), 6.84 (dd, J = 3.1, 8.6 Hz, 0.8H), 6.79 (dd, J = 3.3, 9.1 Hz, 0.2H), 6.47 (d, J = 16.2 Hz, 0.8H), 5.99 (d, J = 12.5 Hz, 0.2H), 4.25 (q, J = 7.1 Hz, 1.6H), 4.15 (q, J = 7.0 Hz, 0.4H), 3.86 (s, 2.4H), 3.81 (s, 0.6H), 1.34 (t, J = 7.1 Hz, 2.4H), 1.22 (t, J = 7.0 Hz, 0.6H).

4.14.9. Ethyl-4-(5′-fluoro-2′-methoxyphenyl)propanoate (20)

To a solution of **19** (6.0 g, 27.0 mmol) in ethanol (200 proof, 40 mL) under Ar was added 10% Pd/C (250 mg). The flask containing the mixture was then evacuated and purged with H_2 three times. An environment of H_2 gas was added to the flask and the reaction was allowed to stir for 15 h at room temperature. The reaction mixture was then filtered through Celite with ethanol. The crude product obtained after removal of the solvent in vacuo was purified by flash column chromatography (R_f = 0.27, EtOAc/hexane, 10:90, v:v) to give the product as an oil (5.8 g, 95%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.89–6.84* (m, 2H), 6.74 (dd, J = 4.7, 9.8 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.91 (t, J = 7.7 Hz, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).

4.14.10. 3-(5′-Fluoro-2′-methoxyphenyl)propanal (21)

To a solution of ethyl-3-(5′-fluoro-2′-methoxyphenyl)propanoate (5.8 g, 25.7 mmol) in dry toluene (40 mL) under Ar was added DIBAL solution (1 M in toluene, 30 mL, 30 mmol) at −78 °C. The reaction was then stirred at this temperature for 2 h. Methanol (2 mL) was added to the reaction mixture and the reaction was allowed to warm to 0 °C. The reaction mixture was then poured into a separatory funnel containing an HCl solution (1 N, 100 mL). The organic material was extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were washed with brine (80 mL) and dried over sodium sulfate. The crude product obtained by removal of the solvent in vacuo was purified by flash column chromatography (R_f = 0.1, EtOAc/hexane, 10:90, v:v) to give the product (3.1 g, 66%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.8 (s, 1H), 6.88–6.86 (m, 2H), 6.75 (dd, J = 4.6, 8.6 Hz, 1H), 3.79 (s, 3H), 2.91 (t, J = 7.4 Hz, 2H), 2.72 (t, J = 7.4 Hz, 2H).

4.14.11. 1-(5′-Fluoro-2′-methoxyphenyl)-4-ethylenedioxy-1-butene (22)

To a suspension of 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (5.0 g, 11.3 mmol) in THF (30 mL) under Ar was added NaH (60% in mineral oil, 0.48 g, 11.3 mmol). The reaction was heated to reflux for 1 h. The resulting orange colored suspension was cooled to 0 °C and 5-fluoro-2-methoxybenzaldehyde (1.54 g, 10.0 mmol) was added and the reaction was stirred for 12 h at room temperature. The mixture was poured to a separatory funnel containing ammonium chloride aqueous solution (satd NH_4Cl/H_2O = 1:1, v:v, 30 mL). The organic material was extracted with EtOAc (3 × 80 mL) and the combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and product was purified by flash column chromatography (R_f = 0.15, EtOAc/hexane, 7:93, v:v) to result in the product (2.63 g, 66%) as a mixture of *cis* and *trans* diastereomers (*cis:trans* = 4:1): ^{1}H NMR (the major isomer): ($CDCl_3$, 500 MHz): δ 7.08 (dd, J = 3.1, 8.7 Hz, 1H), 6.93 (dt, J = 3.1, 8.7 Hz, 1H), 6.78 (dd, J = 4.3, 8.7 Hz, 1H), 6.63 (d, J = 11.9 Hz, 1H), 5.83 (td, J = 7.3 Hz, 11.9 Hz, 1H), 4.99 (t, J = 4.6 Hz, 1H), 4.02–3.99 (m, 2H), 3.9–3.87 (m, 2H), 3.8 (s, 3H), 2.64–2.62 (m, 2H).

4.14.12. 4-(5′-Fluoro-2′-methoxyphenyl)-1-ethylenedioxy-butane (23)

To a solution **22** (1.75 g, 7.3 mmol) in ethanol (200 proof, 80 mL) under Ar was added Pd/C (10%, 300 mg). The flask containing the mixture was evacuated and purged with H_2 three times. An H_2 environment was added to the flask and the reaction was stirred for 72 h at room temperature. The reaction mixture was then filtered through a pad of Celite eluted with EtOH. The crude product was obtained by removal of the solvent in vacuo. ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.87–6.72* (m, 3H), 4.87 (t, J = 3.8 Hz, 1H), 3.97–3.95 (m, 2H), 3.86–3.83 (m, 2H), 3.79 (s, 3H), 2.64–2.62 (m, 2H), 2.44 (td, J = 1.7, 7.2 Hz, 2H), 1.92 (quintet, J = 7.5 Hz, 2H).

4.14.13. 4-(5′-Fluoro-2′-methoxyphenyl)butyraldehyde (24)

To a solution of **23** (1.7g, 7.0 mmol) in THF (60 mL) was added HCl (1 N, 3 mL) and the reaction was stirred at room temperature for 48 h. The reaction mixture was then poured into a separatory funnel containing water (60 mL). The organics were extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (80 mL) and dried over Na_2SO_4. The crude product obtained by removal of the solvent in vacuo was purified by flash column chromatography (R_f = 0.1, EtOAc/hexane, 10:90, v:v) to give the product (1.03 g, 53% yield) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.76 (s, 1H), 6.88–6.83 (m, 2H), 6.75 (dd, J = 4.6, 8.6 Hz, 1H), 3.79 (s, 3H), 2.63 (t, J = 7.4 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.92 (quintet, J = 7.4 Hz, 2H).

4.14.14. 5-(5′-Fluoro-2′-methoxyphenyl)-1-pentene methyl ether (25)

To a suspension of methoxymethyltriphenylphosphonium chloride (2.0 g, 5.8 mmol) in THF (20 mL) under Ar was added NaH (60%

in mineral oil, 0.27 g, 6.7 mmol). The reaction was heated to reflux for 1 h. The resulting orange colored suspension was cooled to 0 °C and 4-(5′-fluoro-2′-methoxyphenyl)butyraldehyde (**24**) (0.92 g, 4.7 mmol) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into a separatory funnel containing ammonium chloride aqueous solution (satd NH_4Cl/H_2O = 1:1, 50 mL). The organic material was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was then removed in vacuo and crude product was purified by flash column chromatography on silica (R_f = 0.3, EtOAc/hexane, 5:95, v:v) to afford the product (0.46, 43% yield) as an oil and a mixture of *cis* and *trans* isomers (*cis*:*trans* = 1:2): ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.87–6.72(m, 3H),* 6.30 (d, *J* = 12.5 Hz, 0.66H), 5.9 (d, *J* = 6.2 Hz, 0.33H), 4.75 (td, *J* = 7.2, 12.5 Hz, 0.66H), 4.36 (m, 0.33H), 3.79 (s, 3H), 3.59 (s, 1H), 3.51 (s, 2H), 2.61–2.57 (m, 2H), 2.11 (q, *J* = 7.2 Hz, 0.66H), 1.97 (q, *J* = 7.2 Hz, 1.34H), 1.65–1.58 (m, 2H).

4.14.15. 5-(5′-Fluoro-2′-methoxyphenyl)pentanal (26)

To a solution of **25** (0.46 g, 2.0 mmol) in acetone (20 mL) was added H_2SO_4 (5%, 2 mL) and the mixture was heated to reflux for 1.6 h. After the reaction was cooled to room temperature, the solvent was then removed in vacuo. A solution of $NaHCO_3$ (satd 40 mL) was added and the organic material was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The crude product obtained after removal of the solvent in vacuo was purified by flash column chromatography on silica (R_f = 0.1, EtOAc/hexane, 10:90, v:v) to give the product (0.2 g, 50%) as oil; ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 9.76 (s, 1H), 6.88–6.82 (m, 2H), 6.74 (dd, *J* = 4.6, 8.6 Hz, 1H), 3.79 (s, 3H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.45 (m, 2H), 1.69–1.6 (m, 4H).

4.14.16. 1-(2′-Methoxy-5′-fluorophenyl)pent-4-en-1-ol (27a)

To a solution of 2-methoxy-5-fluorobenzaldehyde (3.0 g, 19.5 mmol) in THF (20 mL) at 0 °C was added a solution 1-butenylmagnesium bromide (0.5 M in THF, 45 mL, 22.5 mmol) dropwise for 15 min. The reaction mixture was then poured into a separatory funnel containing a solution of saturated ammonium chloride (80 mL). The organic material was extracted with EtOAc (3 × 60 mL) and the combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (R_f = 0.11, EtOAc/hexane, 10:90, v:v) to afford the product as an oil (3.27 g, 93%); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.07 (dd, *J* = 3.1, 9.2 Hz, 1H), 6.91 (dt, *J* = 3.1, 9.0 Hz, 1H), 6.79 (dd, *J* = 4.2, 8.5 Hz, 1H), 5.85 (m, 1H), 5.04 (d, *J* = 18.0 Hz, 1H), 4.97 (d, *J* = 13.5 Hz, 1H), 4.9 (t, *J* = 6.3 Hz, 1H), 3.83 (s, 3H), 2.42 (br s, 1H), 2.23–2.13 (m, 2H), 1.84 (q, *J* = 7.7 Hz, 2H).

4.14.17. 1-(2′-Methoxy-5′-fluorophenyl)hex-5-en-2-ol (27b)

The product (74% yield) was obtained as an oil by chromatography on silica; (R_f = 0.18, EtOAc/hexane, 12:88, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.9–6.88* (m, 2H), 6.79 (dd, *J* = 4.7, 9.8 Hz, 1H), 5.83 (m, 1H), 5.04 (d, *J* = 17.1 Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 3.85 (m,1H), 3.81 (s, 3H), 2.85 (dd, *J* = 4.0, 13.7 Hz, 1H), 2.69 (dd, *J* = 8.1, 13.7 Hz, 1H), 2.26 (m, 1H), 2.17 (m, 1H), 1.82 (br s, 1H), 1.60 (m, 2H).

4.14.18. 7-(5′-Fluoro-2′-methoxyphenyl)hept-1-en-5-ol (27c)

The product (94% yield) was obtained as an oil by chromatography on silica; (R_f = 0.2, EtOAc/hexane, 15:85, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.86–6.82* (m, 2H), 6.76 (dd, *J* = 4.6, 8.6 Hz, 1H), 5.82 (m, 1H), 5.04 (d, *J* = 17.3 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 3.81 (s, 3H), 3.55 (m, 1H),2.75–2.69 (m, 2H), 2.2 (m, 1H), 2.1 (m, 1H), 1.96 (br s, 1H), 1.73–1.68 (m, 2H), 1.6–1.53 (m, 3H).

4.14.19. 8-(5′-Fluoro-2′-methoxyphenyl)oct-1-en-5-ol (27d)

The product (61% yield) was obtained as an oil by chromatography on silica; (R_f = 0.15, EtOAc/hexane, 12:88, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.86–6.82* (m, 2H), 6.74 (dd, *J* = 4.6, 8.6 Hz, 1H), 5.85 (m, 1H), 5.04 (d, *J* = 17.3 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.66 (m, 1H), 2.6 (m, 2H), 2.22–2.10 (m, 2H), 1.74–1.47 (m, 7H).

4.14.20. 9-(5′-Fluoro-2′-methoxyphenyl)non-1-en-5-ol (27e)

The product (71% yield) was obtained as an oil by chromatography on silica; (R_f = 0.25, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.85–6.81* (m, 2H), 6.74 (dd, *J* = 4.6, 8.6 Hz, 1H), 5.84 (m, 1H), 5.04 (dd, *J* = 15.8, 1.9 Hz, 1H), 4.98 (d, *J* = 10.2, 1.3Hz, 1H), 3.79 (s, 3H), 3.63 (m, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.23–2.11 (m, 2H), 1.62–1.36 (m, 9H).

4.14.21. 2-(Bromomethyl)-5-(2′-methoxy-5′-fluorophenyl)-tetrahydrofuran (28a)

To a solution of 1-(2′-methoxy-5′-fluorophenyl)pent-4-en-1-ol (3.24 g, 18.0 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added *N*-bromosuccinimide (NBS, 3.56 g, 20.0 mmol) portion-wise and the mixture was warmed to room temperature for 12 h. The solvent was then removed in vacuo and the remaining residue was purified by flash column chromatography (R_f = 0.28, EtOAc/hexane, 10:90, v:v) to afford the product (2.28 g, 44%) as oil; ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.15 (dd, *J* = 3.1, 9.2 Hz, 1H), 6.88 (dt, *J* = 3.1, 9.0 Hz, 1H), 6.76 (dd, *J* = 4.2, 8.5Hz, 1H), 5.3 (t, *J* = 7.0 Hz, 0.65H). 5.18 (t, *J* = 7.0 Hz, 0.35H), 4.48 (p, *J* = 6.6 Hz, 0.65H), 4.31 (p, *J* = 6.6 Hz, 0.35H), 3.79 (s, 3H), 3.56 (m, 1H), 3.44 (m, 1H), 2.51–2.42 (m, 1H), 2.18 (m, 1H), 1.9 (m, 1H), 1.78–1.7 (m, 1H).

4.14.22. 2-(Bromomethyl)-5-(2′-methoxy-5′-fluorobenzyl)-tetrahydrofuran *(trans* **28b**; *cis* **28b**)

The *cis* (***cis* 28b**, 238 mg, 13%) and *trans* product (***trans* 28b**, 663 mg, 36%) were separated as oils by chromatography on silica; (R_f = 0.12, EtOAc/hexane, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) ***cis* 28b**: 6.93 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.86 (dt, *J* = 3.1, 9.1 Hz, 1H), 6.74 (dd, *J* = 4.7, 9.0 Hz, 1H), 4.33 (p, *J* = 6.7 Hz, 1H), 4.26 (m, 1H), 3.78 (s, 3H), 3.45 (dd, *J* = 4.4, 9.9 Hz, 1H), 3.33 (dd, *J* = 7.0, 10.2 Hz, 1H), 2.92 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.71 (dd, *J* = 6.9, 13.5 Hz, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.66 (m, 1H); ^{1}H NMR ($CDCl_3$, 500 MHz) ***trans* 28b**: 6.94 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.87 (dt, *J* = 3.1, 9.1 Hz, 1H), 6.75 (dd, *J* = 4.7, 9.0 Hz, 1H), 4.21 (p, *J* = 6.7 Hz, 1H), 4.16 (p, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.43 (dd, *J* = 5.1, 10.2 Hz, 1H), 3.31 (dd, *J* = 6.5, 10.2 Hz, 1H), 2.91 (dd, *J* = 6.2, 13.5 Hz, 1H), 2.78 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.03 (m, 1H), 1.93 (m, 1H), 1.82 (m, 1H), 1.66 (m, 1H).

4.14.23. 2-(Bromomethyl)-5-(2′-methoxy-5′-fluorophenethyl)-tetrahydrofuran (28c)

The product (0.45 g, 72%) was obtained as an oil by chromatography on silica as a mixture of *trans:cis* isomers = 2:1; (R_f = 0.1, EtOAc/hexane, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.86–6.81* (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.22 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.44 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.34 (dd, *J* = 6.4, 9.7 Hz, 1H), 2.6 (t, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.67–1.46 (m, 5H).

4.14.24. 2-(Bromomethyl)-5-(2′-methoxy-5′-fluoro-phenethyl)tetrahydrofuran (*trans* **28c**; *cis* **28c**)

The *cis* (**cis 28c**, 0.74 g, 20 %) and *trans* isomers (*trans,* **28c,** 1.38 g, 42%) were separated as oils by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) ***cis* 28c**: *δ 6.86–6.81* (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.22 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.44 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.34 (dd, *J* = 6.4, 9.7 Hz, 1H), 2.6 (t, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 2.05

(m, 1H), 1.75 (m, 1H), 1.67–1.46 (m, 5H); 1H NMR ($CDCl_3$, 500 MHz) ***trans* 28c**: *δ 6.88–6.82* (m, 2H), 6.73 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.25 (m, 1H), 4.04 (quintet, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 3.45 (dd, *J* = 4.2, 9.5 Hz, 1H), 3.34 (dd, *J* = 6.4, 9.5 Hz, 1H), 2.70 (m, 1H), 2.6 (m, 1H), 2.13 (m, 1H), 2.05 (m, 1H), 1.87–1.56 (m, 4H).

4.14.25. *trans*-2-(Bromomethyl)-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-propyl)tetrahydrofuran (*trans* 28d)

The product (530 mg, 40%) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.86–6.81* (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.22 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.44 (dd, *J* = 4.3, 9.7 Hz, 1H), 3.34 (dd, *J* = 6.4, 9.7 Hz, 1H), 2.6 (t, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.67–1.46 (m, 5H).

4.14.26. *cis*-2-(Bromomethyl)-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-propyl)tetrahydrofuran (*cis* 28d)

The product (110 mg, 10%) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.86–6.81* (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.13 (m, 1H), 3.93 (m, 1H), 3.78 (s, 3H), 3.42 (m, 1H), 3.32 (m, 1H), 2.6 (t, *J* = 7.3 Hz, 2H), 2.06–1.96 (m, 2H), 1.8–1.51 (m, 6H).

4.14.27. *trans*-2-(Bromomethyl)-5-(4′-(2″-methoxy-5″-fluorophenyl)-1′-butyl)tetrahydrofuran (*trans* 28e)

The product (80 mg, 32%) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 4:96, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 6.84–6.8* (m, 2H), 6.73 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.22 (m, 1H), 4.01 (m, 1H), 3.78 (s, 3H), 3.44 (dd, *J* = 5.1, 10.3 Hz, 1H), 3.34 (dd, *J* = 7.1, 10.3 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.15 (m, 1H), 2.06 (m, 1H), 1.75 (m, 1H), 1.65–1.37 (m, 7H).

4.14.28. 2-(*N*-Phthilimidomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (29a)

To a vial under Ar was added 2-(bromomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (1.28 g, 4.44 mmol), NaI (100 mg), potassium phthalimide (2.05 g, 11.1 mmol), and dry DMSO (10 mL). The reaction was heated to 70 °C and stirred under Ar for 12 h. After it was cooled to room temperature, the reaction mixture was poured into a separatory funnel containing sodium bicarbonate aqueous solution (satd $NaHCO_3/H_2O$ = 1:1, 70 mL). The organic material was extracted with EtOAc (3 × 60 mL) and the combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to afford crude product that was purified by flash column chromatography (R_f = 0.12, EtOAc/hexane, 20:80, v:v) to yield pure product (a 2:1 mixture of *trans:cis* isomers, 1.14 g, 72%) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 7.88–7.84* (m, 2H), 7.73–7.69 (m, 2H), 7.36 (dd, *J* = 3.1, 9.4 Hz, 0.35H), 7.07 (dd, *J* = 3.1, 9.4 Hz, 0.65H), 6.85 (dt, *J* = 3.1, 8.5 Hz. 0.35H), 6.83 (dt, *J* = 3.1, 8.5 Hz. 0.65H), 6.72 (dd, *J* = 4.2, 9.1 Hz, 1H), 5.31 (t, *J* = 6.8 Hz, 0.65H), 5.09 (t, *J* = 7.2 Hz, 0.35H), 4.63 (m, 0.65H), 4.39 (m, 0.35H), 4.02 (dd, *J* = 7.4, 13.7 Hz, 0.35H), 3.92 (dd, *J* = 8.1 13.7 Hz, 0.65H), 3.87 (dd, *J* = 7.4, 13.7 Hz, 0.35H), 3.85 (s, 1.95H), 3.78 (s, 1.05H), 3.7 (dd, *J* = 8.1 13.7 Hz, 0.65H), 2.5 (m, 0.65H), 2.41 (m, 0.35H), 2.11–2.04 (m, 1H), 1.84–1.68 (m, 2H).

4.14.29. *trans*-2-(*N*-phthilimidomethyl)-5-(2′-methoxy-5′-fluorobenzyl)tetrahydrofuran (*trans* 29b)

The product (385 mg, 70% yield) was obtained as a white solid by chromatography on silica; (R_f = 0.5, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 7.85–7.84* (m, 2H), 7.72–7.7 (m, 2H), 6.91 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.82 (dt, *J* = 3.1, 9.1 Hz. 1H), 6.72 (dd, *J* = 4.7, 9.1 Hz, 1H), 4.41 (m, 1H), 4.34 (p, *J* = 6.7 Hz, 1H), 3.83 (dd, *J* = 8.1, 13.5 Hz, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 5.3 13.5 Hz, 1H), 2.85 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.7 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.03 (m, 2H), 1.64 (m, 2H).

4.14.30. *cis*-2-(*N*-Phthilimidomethyl)-5-(2′-methoxy-5′-fluorobenzyl)tetrahydrofuran (*cis* 29b)

The product (138 mg, 47% yield) was obtained as a white solid by chromatography on silica; (R_f = 0.52, EtOAc/hexane, 30:70, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 7.87–7.85* (m, 2H), 7.71–7.7 (m, 2H), 6.94 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.8 (dt, *J* = 3.1, 9.1 Hz. 1H), 6.71 (dd, *J* = 4.7, 9.1Hz, 1H), 4.25 (m, 1H), 4.11 (p, *J* = 6.7 Hz, 1H), 3.84 (dd, *J* = 8.1, 13.8 Hz, 1H), 3.75 (s, 3H), 3.68 (dd, *J* = 5.2 13.8 Hz, 1H), 2.84 (d, *J* = 6.3 Hz, 2H), 1.98–1.92 (m, 2H), 1.73–1.67 (m, 2H).

4.14.31. *trans*-2-(5′-Fluoro-2′-methoxyphenethyl)-5-(phthalimidomethyl)tetrahydrofuran (*trans* 29c)

The product (0.7 g, 57% yield) was obtained as a white solid by chromatography on silica; (R_f = 0.2, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 7.85–7.84* (m, 2H), 7.72–7.71 (m, 2H), 6.86 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.8 (dt, *J* = 3.1, 9.1 Hz. 1H), 6.71 (dd, *J* = 4.7, 9.1Hz, 1H), 4.38 (m, 1H), 4.05 (quintet, *J* = 6.6 Hz, 1H), 3.83 (dd, *J* = 8.0, 13.8 Hz, 1H), 3.76 (s, 3H), 3.62 (dd, *J* = 5.1 13.8 Hz, 1H), 2.67–2.52 (m, 2H), 2.11–2.04 (m, 2H), 1.79–1.54 (m, 4H).

4.14.32. *cis*-2-(5′-Fluoro-2′-methoxyphenethyl)-5-(phthalimidomethyl)tetrahydrofuran (*cis* 29c)

The product (0.26 g, 63% yield) was obtained as a white solid by chromatography on silica; (R_f = 0.2, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ 7.86–7.85* (m, 2H), 7.72–7.7 (m, 2H), 6.86 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.81 (dt, *J* = 3.1, 9.1 Hz. 1H), 6.71 (dd, *J* = 4.7, 9.1 Hz, 1H), 4.27 (quintet *J* = 6.1 Hz, 1H), 3.88 (quintet, *J* = 6.6 Hz, 1H), 3.82 (dd, *J* = 8.0, 13.8 Hz, 1H), 3.77 (s, 3H), 3.72 (dd, *J* = 5.1 13.8 Hz, 1H), 2.65–2.58 (m, 2H), 2.04–1.97 (m, 2H), 1.83–1.58 (m, 4H).

4.14.33. *trans*-2-(3′-(2″-Methoxy-5″-fluorophenyl)-1′-propyl)-5-(*N*-phthilimidomethyl) tetrahydrofuran (*trans* 29d)

The product (0.15 g, 62% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 15:85, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.84 (m, 2H), 7.7 (m, 2H), 6.84–6.79 (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.37 (m, 1H), 4.05 (m, 1H), 3.82 (dd, *J* = 8.3, 13.5 Hz, 1H), 3.76 (s, 3H), 3.59 (dd, *J* = 5.0, 13.5 Hz, 1H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.06 (m, 2H), 1.68–1.45 (m, 6H).

4.14.34. *cis*-2-(3′-(2″-Methoxy-5″-fluorophenyl)-1′-propyl)-5-(*N*-phthilimidomethyl) tetrahydrofuran (*cis* 29d)

The product (95 mg, 73% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 15:85, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.84 (m, 2H), 7.7 (m, 2H), 6.84–6.8 (m, 2H), 6.72 (dd, *J* = 4.6, 8.6 Hz, 1H), 4.25 (m, 1H), 3.86 (m, 1H), 3.81 (dd, *J* = 8.3, 13.5 Hz, 1H), 3.77 (s, 3H), 3.68 (dd, *J* = 5.0, 13.5 Hz, 1H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.0–1.95 (m, 2H), 1.74–1.49 (m, 6H).

4.14.35. *trans*-2-(3′-(2″-Methoxy-5″-fluorophenyl)-1′-butyl)-5-(*N*-phthilimidomethyl) tetrahydrofuran (*trans* 29e)

The product (67 mg, 69% yield) was obtained as an oil by chromatography on silica; (R_f = 0.15, EtOAc/hexane, 20:80, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.84 (m, 2H), 7.7 (m, 2H), 6.83–6.79 (m, 2H), 6.72 (dd, *J* = 4.3, 8.3 Hz, 1H), 4.36 (m, 1H), 4.01 (m, 1H), 3.81 (dd, *J* = 8.3, 13.5 Hz, 1H), 3.77 (s, 3H), 2.55 (, *J* = 7.8 Hz, 2H), 2.07 (m, 2H), 1.68–1.39 (m, 8H).

4.14.36. 2-Aminomethyl-5-(2′-methoxy-5′-fluorophenyl) tetrahydrofuran (30a)

To a vial under Ar was added 2-(*N*-phthalimidomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (225 mg, 0.63 mmol), hydrazine hydrate (150 mg, 4.9 mmol), and methanol (10 mL). The mixture was stirred at room temperature for 12 h. The solvent

was then removed in vacuo and the crude product was purified by column flash chromatography to yield the product (R_f = 0.1, methanol/DCM, 10:90, v:v) (90 mg, 60%, *trans:cis* isomers = 1.5:1) as a viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (m 1H), 6.87(m 1H), 6.75(m 1H), 5.2 (t, J = 7.1 Hz, 0.58H), 5.11 (t, J = 7.1 Hz, 0.42H), 4.24 (m, 0.58H), 4.04 (m, 0.42H), 2.93–2.78 (m, 2H), 2.41 (m, 1H), 2.03 (m, 1H), 1.79 (s, 2H), 1.75–1.63 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{17}FNO_2$ 226.1243, found 226.1255; HPLC >96% (t_R = 4.4 min, 40(A):55(B):5(C):0.01(D); t_R = 5.1 min, 20(A):75(B):5(C):0.01(D)).

4.14.37. *trans*-2-Aminomethyl-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (*trans* 30a)

The product (41 mg, 30% yield, *trans:cis* isomers = 95:5) was obtained as an oil by chromatography on silica; (R_f = 0.08, methanol/DCM, 10:90, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ 7.18 (dd, J = 3.1, 9.4 Hz, 1H), 6.87(dt, J = 3.1, 8.5 Hz. 1H), 6.75(dd, J = 4.2, 9.1 Hz, 1H), 5.2 (t, J = 7.1 Hz, 1H), 4.24 (m, 1H), 2.82 (m, 2H), 2.44 (m, 1H), 2.04 (m, 1H), 1.71–1.69 (m, 2H), 1.67 (s, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{12}H_{17}FNO_2$ 226.1243, found 226.1257; HPLC >96% (t_R = 4.3 min, 40(A):55(B):5(C):0.01(D); t_R = 5.04 min, 20(A):75(B):5(C):0.01(D)).

4.14.38. *trans*-2-Aminomethyl-5-(2′-methoxy-5′-fluorophenylmethyl)tetrahydrofuran (*trans* 30b)

The product (54 mg, 60%) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.93 (dd, J = 3.1, 8.8 Hz, 1H), 6.86 (dt, J = 3.1, 8.8 Hz, 1H), 6.75 (dd, J = 3.1, 8.8 Hz, 1H), 4.23 (m, 1H), 4.08 (m 1H), 3.79 (s, 3H), 2.91 (dd, J = 13.5, 6.5 Hz, 2H), 2.78 (m, 1H), 2.72 (m, 1H), 2.18 (br s, 2H), 2.02–1.92 (m, 2H), 1.64 – 1.55 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{19}FNO_2$ 240.1400, found 240.1423; HPLC >98% (t_R = 4.68 min, 40(A):55(B):5(C):0.01(D); t_R = 5.04 min, 20(A):75(B):5(C):0.01(D)).

4.14.39. *cis*-2-Aminomethyl-5-(2′-methoxy-5′-fluorophenylmethyl)tetrahydrofuran (*cis* 30b)

The product (26 mg, 73% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.93 (dd, J = 3.1, 8.8 Hz, 1H), 6.86 (dt, J = 3.1, 8.8 Hz, 1H), 6.77 (dd, J = 3.1, 8.8 Hz, 1H), 4.15 (m, 1H), 3.97 (m 1H), 3.79 (s, 3H), 2.91 (dd, J = 13.5, 6.6 Hz, 2H), 2.76 (dd, J = 13.5, 6.6 Hz, 2H), 2.43 (br s, 2H), 1.93 (m, 2H), 1.63 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{19}FNO_2$ 240.1400, found 240.1423; HPLC >98% (t_R = 4.69 min, 40(A):55(B):5(C):0.01(D); t_R = 5.06 min, 20(A):75(B):5(C):0.01(D)).

4.14.40. *trans*-2-(Aminomethyl)-5-(2′-methoxy-5′-fluorophenethyl)tetrahydrofuran (*trans* 30c)

The product (197 mg, 85% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.87 (dt, J = 3.0, 8.9 Hz, 1H), 6.82 (dd, J = 3.0, 8.5Hz, 1H), 6.74 (dd, J = 4.3, 8.5 Hz, 1H), 4.01 (m, 1H), 3.93 (quintet, J = 6.8 Hz, 1H), 3.78 (s, 3H), 2.76–2.67 (m, 3H), 2.6 (m, 1H), 2.06–1.99 (m, 2H), 1.84 (m, 1H), 1.78 (br s, 2H), 1.7 (m, 1H), 1.59–1.54 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}FNO_2$ 254.1556, found 254.1573; HPLC >98% (t_R = 4.48 min, 40(A):55(B):5(C):0.01(D); t_R = 5.76 min,20(A):75(B):5(C):0.01(D)).

4.14.41. *cis*-2-(Aminomethyl)-5-(2′-methoxy-5′-fluorophenethyl)tetrahydrofuran (*cis* 30c)

The product (125 mg, 73% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.87 (dt, J = 3.0, 8.9 Hz, 1H), 6.82 (dd, J = 3.0, 8.5 Hz, 1H), 6.72 (dd, J = 4.3, 8.5 Hz, 1H), 3.91–3.87 (m, 2H), 3.79 (s, 3H), 2.83–2.57 (m, 4H), 2.0–1.52 (m, 6H) 1.84 (br s, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}FNO_2$ 254.1556, found 254.1551; HPLC >98% (t_R = 4.50 min, 40(A):55(B):5(C):0.01(D); t_R = 5.81 min, 20(A):75(B):5(C):0.01(D)).

4.14.42. *trans*-2-Aminomethyl-5-((2″-methoxy-5″-fluorophenyl)-3′-propyl)tetrahydrofuran (*trans* 30d)

The product (42 mg, 87% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.86–6.8* (m, 2H), 6.74 (dd, J = 4.7, 8.8 Hz, 1H), 4.01 (p, J = 6.2 Hz, 1H), 3.93 (p, J = 7.2 Hz, 1H), 3.78 (s, 3H), 2.85–2.67 (m, 2H), 2.6 (t, J = 7.2 Hz, 2H), 2.34 (br s, 2H), 2.03–1.98 (m, 2H), 1.68–1.46 (m, 6H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{23}FNO_2$ 268.1713, found 268.1709; HPLC >95% (t_R = 4.70 min, 40(A):55(B):5(C):0.01(D); t_R = 5.1 min, 10(A):85(B):5(C):0.01(D)).

4.14.43. *cis*-2-Aminomethyl-5-(3′-(2″-methoxy-5″-fluorophenyl)-3′-propyl)tetrahydrofuran (*cis* 30d)

The product (42 mg, 87% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.85 (dd, J = 3.0, 9.6, Hz, 1H), 6.82 (dd, J = 3.0, 8.3 Hz, 1H), 6.73 (dd, J = 4.7, 8.9 Hz, 1H), 3.94 (m, 1H), 3.85 (m, 1H), 3.78 (s, 3H), 3.0–2.60 (m, 4H), 2.6 (t, J = 7.2 Hz, 2H),1.98–1.92 (m, 2H), 1.68–1.46 (m, 6H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{23}FNO_2$ 268.1713, found 268.1702; HPLC >98% (t_R = 4.71 min, 40(A):55(B):5(C):0.01(D); t_R = 5.10 min, 10(A):85(B):5(C):0.01(D)).

4.14.44. *trans*-2-Aminomethyl-5-(5″-fluoro-2″-methoxyphenyl-4′-butyl)tetrahydrofuran (*trans* 30e)

The product (33 mg, 95% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.85–6.80* (m, 2H), 6.72 (dd, J = 4.7, 8.9 Hz, 1H), 4.02 (m, 1H), 3.92 (m, 1H), 3.78 (s, 3H), 2.9–2.7 (bm, 2H), 2.58 (t, J = 7.6 Hz, 2H), 2.32 (br s, 2H), 2.02 (m, 1H), 1.64–1.35 (m, 9H); MS: 282 (MH^+), 264, 139; HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{16}H_{25}FNO_2$ 282.2869, found 282.1889; HPLC >98% (t_R = 4.83 min, 40(A):55(B):5(C):0.01(D); t_R = 5.17 min, 10(A):85(B):5(C):0.01(D)).

4.14.45. *trans*-2-(Cyanomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (*trans* 31a) and *cis*-2-(cyanomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (*cis* 31a)

To a vial under Ar was added 2-(bromomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (1.23 g, 4.3 mmol), NaI (100 mg), potassium cyanide (0.7 g, 10.6 mmol), and dry DMSO (15 mL). The mixture was heated to 70°C and stirred under Ar for 12 h. After it was cooled to room temperature, the mixture was poured into a separatory funnel containing sodium bicarcarbonate aqueous solution (satd $NaHCO_3$:H_2O = 1:1, 80 mL). The organic material was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (R_f = 0.2, EtOAc/hexane, 20:80, v:v) A careful analysis and collection of early fractions afforded the *trans* isomer (***trans 31a***, 0.55 g, 55% yield): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11 (dd, J = 3.1 9.2 Hz, 1H), 6.89 (dt, J = 3.1, 9.0 Hz, 1H), 6.76 (dd, J = 4.2, 8.5 Hz, 1H), 5.33 (t, J = 7.1 Hz, 1H), 4.49 (p, J = 6.1 Hz, 1H), 3.79 (s, 3H), 2.69 (dd, J = 6.1, 16.7 Hz, 1H), 2.66 (dd, J = 6.1 16.7 Hz, 1H), 2.57 (m, 1H), 2.25 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H); The rest of the fractions were collected and upon removal of the solvent a white colored solid formed. Further purification of this solid by triturating with hexane resulted in the *cis* isomer (***cis 31a***, 250 mg, 25% yield); δ 7.24 (dd, J = 3.1 9.2 Hz, 1H), 6.9 (dt, J = 3.1, 9.0 Hz, 1H), 6.76 (dd, J = 4.2, 8.5 Hz, 1H), 5.14 (t, J = 7.4 Hz, 1H), 4.28 (p, J = 6.1 Hz, 1H), 3.8 (s, 3H), 2.73 (d, J = 5.8 Hz, 1H), 2.46 (m, 1H), 2.24 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H);

4.14.46. *trans*-2-(Cyanomethyl)-5-(2′-methoxy-5′-fluorobenzyl)tetrahydrofuran (*trans* 31b) and *cis*-2-(cyanomethyl)-5-(2′-methoxy-5′-fluorobenzyl)tetrahydrofuran (*cis* 31b)

The products were obtained as oils by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); *trans* isomer (***trans* 31b**, 170 mg, 27% yield): ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.89 (dt, J = 3.1, 9.0 Hz, 1H), 6.86 (dd, J = 3.1 9.2 Hz, 1H), 6.76 (dd, J = 4.2, 8.5 Hz, 1H), 4.38 (p, J = 6.8 Hz, 1H), 4.27 (p, J = 6.1 Hz, 1H), 3.79 (s, 3H), 2.9 (dd, J = 6.3, 13.5 Hz, 1H), 2.72 (dd, J = 6.5 13.5 Hz, 1H), 2.58 (m, 2H), 2.19 (m, 1H), 2.06 (m, 1H), 1.77 (m, 1H), 1.68 (m, 1H); *cis* isomer (***cis* 31b**, 77 mg, 12% yield); δ 6.9 (dd, J = 3.1 9.2 Hz, 1H), 6.83 (dt, J = 3.1, 9.0 Hz, 1H), 6.71 (dd, J = 4.2, 8.5 Hz, 1H), 4.14 (p, J = 6.8 Hz, 1H), 4.1 (p, J = 6.1 Hz, 1H), 3.75 (s, 3H), 2.87 (dd, J = 6.5, 13.5 Hz, 1H), 2.78 (dd, J = 6.2 13.5 Hz, 1H), 2.52 (m, 2H), 2.06 (m, 1H), 1.92 (m, 1H), 1.76–1.69 (m, 2H).

4.14.47. *trans*-2-Cyanomethyl-5-(5′-fluoro-2-methoxyphenethyl)tetrahydrofuran (*trans* 31c)

The product (0.45 g, 86% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *6.87–6.82* (m, 2H), 6.74 (dd, J = 4.3, 8.5 Hz, 1H), 4.26 (quintet, J = 6.2 Hz, 1H), 4.09 (m, 1H), 3.79 (s, 3H), 2.72–2.53 (m, 4H), 2.22–2.04 (m, 2H), 1.84–1.6 (m, 4H).

4.14.48. *cis*-2-Cyanomethyl-5-(5′-fluoro-2-methoxyphenethyl)tetrahydrofuran (*cis* 31c)

The product (0.20 g, 80% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); ^{1}H NMR (500 MHz, $CDCl_3$) δ *6.88–6.82* (m, 2H), 6.74 (dd, J = 4.3, 8.5 Hz, 1H), 4.26 (quintet, J = 6.1 Hz, 1H), 3.9 (quintet, J = 6.7 Hz, 1H), 3.79 (s, 3H), 2.73 (m, 1H), 2.59 (t, J = 5.2 Hz, 2H), 2.53 (m, 1H), 2.14–2.02 (m, 2H), 1.89–1.57 (m, 4H).

4.14.49. *trans*-2-Cyanomethyl-5-(3′-(2″-methoxy-5″-fluoro phenyl)-1′-propyl)tetrahydrofuran (*trans* 31d)

The product (71 mg, 85% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, EtOAc/hexane, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.84–6.81* (m, 2H), 6.73 (dd, J = 4.2, 8.5 Hz, 1H), 4.22 (p, J = 6.8 Hz, 1H), 4.09 (m, 1H), 3.79 (s, 3H), 2.62–2.52 (m, 4H), 2.18 (m, 1H), 2.12 (m, 1H), 1.78 (m, 1H), 1.69–1.46 (m, 3H).

4.14.50. *cis*-2-Cyanomethyl-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-propyl)tetrahydrofuran (*cis* 31d), 22 mg, 18% yield)

The product was obtained as an oil by chromatography on silica; (R_f = 0.11, EtOAc/hexane, 10:90, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.86–6.81* (m, 2H), 6.73 (dd, J = 4.2, 8.5 Hz, 1H), 4.11 (m, 1H), 3.9 (m, 1H), 3.79 (s, 3H), 2.62–2.55 (m, 4H), 2.1 (m, 1H), 2.01 (m, 1H), 1.78 (m, 1H), 1.69–1.46 (m, 3H).

4.14.51. 2-Cyanomethyl-5-(4′-(2″-methoxy-5″-fluorophenyl)-1′-butyl)tetrahydrofuran (31e)

The product (40 mg, 33% yield) was obtained as an oil by chromatography on silica; (R_f = 0.12, EtOAc/hexane, 15:85, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz): δ *6.84–6.80* (m, 2H), 6.74 (dd, J = 4.2, 8.5 Hz, 1H), 4.22 (quintet, J = 6.4 Hz, 0.5H), 4.11 (quintet, J = 6.2 Hz, 0.5H), 4.07 (m, 0.5H), 3.87 (quintet, J = 6.6 Hz, 0.5H), 3.78 (s, 3H), 2.61–2.55 (m, 4H), 2.21–1.95 (m, 2H), 2.01 (m, 1H), 1.77 (m, 1H), 1.66–1.34 (m, 6H).

4.14.52. *trans*-2-Aminoethyl-5-(2′-methoxy-5′-fluorophenyl)-tetrahydrofuran (*trans* 32a)

To a vial under Ar was added Raney Ni that was washed with ethanol (200 proof, 3 times) and *trans*-2-(cyanomethyl)-5-(2′-methoxy-5′-fluorophenyl)tetrahydrofuran (80 mg, 0.35 mmol) that was treated with a small amount of Raney Ni in ethanol. The vial was then evacuated and purged with H_2 three times. An environment of H_2 was added to the flask and the reaction was stirred for 48 h at room temperature. The reaction mixture was then filtered through a plug of Celite and the crude product obtained after the removal of the solvent was purified by flash column chromatography (R_f = 0.1, methanol/DCM, 10:90, v:v) to afford the product (43.7 mg, 52% yield); ^{1}H NMR:($CDCl_3$, 500 MHz): δ 7.15 (dd, J = 3.1, 9.4 Hz, 1H), 6.86(dt, J = 3.1, 8.5 Hz. 1H), 6.74 (dd, J = 4.2, 9.1 Hz, 1H), 5.21 (t, J = 7.1 Hz, 1H), 4.25 (m 1H), 3.78 (s, 3H), 2.91 (m, 2H), 2.46 (m, 1H), 2.08 (m, 1H), 1.73–1.66 (m, 6H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{19}FNO_2$ 240.1400, found 240.1401; HPLC >95% (t_R = 4.71 min, 40(A):55(B):5(C):0.01(D); t_R = 5.25 min, 10(A):85(B):5(C):0.01(D)).

4.14.53. *cis*-2-Aminoethyl-5-(2′-methoxy-5′-fluorophenyl)-tetrahydrofuran (32a)

The product (43 mg, 42% yield) was obtained as an oil by chromatography on silica; (R_f = 0.11, methanol/DCM, 10:90, v:v); ^{1}H NMR:($CDCl_3$, 500 MHz): δ 7.21 (dd, J = 3.1, 9.4 Hz, 1H), 6.87(dt, J = 3.1, 8.5 Hz. 1H), 6.74 (dd, J = 4.2, 9.1 Hz, 1H), 5.1 (t, J = 7.1 Hz, 1H), 4.06 (p, J = 5.8Hz, 1H), 3.79 (s, 3H), 2.92 (m, 2H), 2.36 (m, 1H), 2.04 (m, 1H), 1.88 (m, 1H), 1.79 (m, 1H), 1.65 (m, 1H), 1.56 (m, 1H), 1.46 (br s, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{13}H_{19}FNO_2$ 240.1400, found 240.1403; HPLC >96% (t_R = 4.72 min, 40(A):55(B):5(C):0.01(D); t_R = 5.27 min, 10(A):85(B):5(C):0.01(D)).

4.14.54. *trans*-2-Aminoethyl-5-(2′-methoxy-5′-fluorobenzyl)-tetrahydrofuran (*trans* 32b)

The product (41 mg, 45% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 6.92 (dd, J = 8.8. 3.1 Hz, 1H), 6.85 (dt, J = 3.1, 8.8 Hz, 1H), 6.75 (dd, J = 4.5, 8.7 Hz, 1H), 4.23 (p, J = 6.6 Hz, 1H), 4.06 (m 1H), 3.78 (s, 3H), 2.88 (dd, J = 6.4, 13.5 Hz, 1H), 2.82 (br, 2H), 2.7 (dd, J = 6.4, 13.5 Hz, 1H), 2.03 (m, 1H), 1.92 (m, 1H), 1.91 (br s, 2H), 1.69–1,48 (m, 4H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}FNO_2$ 254.1556, found 254.1548; HPLC >96% (t_R = 4.35 min, 40(A):55(B):5(C):0.01(D); t_R = 5.53 min, 20(A):75(B):5(C):0.01(D)).

4.14.55. *cis*-2-Aminoethyl-5-(2′-methoxy-5′-fluorobenzyl)-tetrahydrofuran (*cis* 32b)

The product (31 mg, 41%) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 6.95 (dd, J = 9.2. 3.1 Hz, 1H), 6.88 (dt, J = 3.1, 8.5 Hz, 1H), 6.78 (dd, J = 4.7, 9.1Hz, 1H), 4.11 (p, J = 6.8 Hz, 1H), 3.94 (p, J = 6.4 Hz, 1H), 3.81 (s, 3H), 2.91 (dd, J = 6.6, 13.5 Hz, 1H), 2.87 (br, 2H), 2.78 (dd, J = 6.6, 13.5 Hz, 1H), 1.96 (m, 2H), 1.88 (br s, 2H), 1.72 (m, 2H), 1.64–1.55 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{14}H_{21}FNO_2$ 254.1556, found 254.1546; HPLC >96% (t_R = 4.35 min, 40(A):55(B):5(C):0.01(D); t_R = 5.53 min, 20(A):75(B):5(C):0.01(D)).

4.14.56. *trans*-2-(Aminoethyl)-5-(2′-methoxy-5′-fluorophenethyl)tetrahydrofuran (*trans* 32c)

The product (192 mg, 40% yield) was obtained as an oil by chromatography on silica; (R_f = 0.12, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 6.87 (dt, J = 3.0, 8.9Hz, 1H), 6.82 (dd, J = 3.0, 8.5 Hz, 1H), 6.72 (dd, J = 4.3, 8.5 Hz, 1H), 4.03 (m, 1H), 3.96 (m, 1H), 3.78 (s, 3H), 2.84 (bm, 2H), 2.68 (m, 1H), 2.58 (m, 1H), 2.03 (m, 2H), 1.83 (br s, 2H), 1.72–1.6 (m, 4H), 1.54 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{23}FNO_2$ 268.1713, found 268.1733; HPLC >97% (t_R = 4.67 min, 40(A):55(B):5(C):0.01(D); t_R = 5.05 min, 10(A):85(B):5(C):0.01(D)).

4.14.57. *cis*-2-(Aminoethyl)-5-(2′-methoxy-5′-fluorophenethyl)tetrahydrofuran (*cis* 32c)

The product (118 mg, 54% yield) was obtained as an oil by chromatography on silica; TLC (SiO_2) R_f = 0.1, 90% DCM/MeOH; ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 6.86 (dt, J = 3.0, 8.9 Hz, 1H), 6.82 (dd, J = 3.0, 8.5 Hz, 1H), 6.73 (dd, J = 4.3, 8.5 Hz, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 2.85 (t, J = 6.9 Hz, 2H), 2.68 (m, 1H), 2.6 (m, 1H), 1.96 (m, 2H), 1.86–1.67 (m, 4H), 1.76 (br s, 2H), 1.53 (m, 2H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{15}H_{23}FNO_2$ 268.1713, found 268.1701; HPLC >96% (t_R = 4.65 min, 40(A):55(B):5(C): 0.01(D); t_R = 5.05 min, 10(A):85(B):5(C):0.01(D)).

4.14.58. *trans*-2-Aminoethyl-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-propyl)tetrahydrofuran (*trans* 32d)

The product (24 mg, 47% yield) was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ *6.86–6.80* (m, 2H), 6.73 (dd, J = 4.4, 8.5 Hz, 1H), 4.02 (m, 1H), 3.96 (m, 1H), 3.78 (s, 3H), 2.88 (b, 2H), 2.61 (br s, 2H), 2.58 (t, J = 7.0 Hz, 2H), 2.02 (m, 2H), 1.72–1.44 (m, 8H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{16}H_{25}FNO_2$ 282.1869, found 282.1875; HPLC >95% (t_R = 4.7 min, 40(A):55(B):5(C): 0.01(D); t_R = 5.09 min, 10(A):85(B):5(C):0.01(D)).

4.14.59. *cis*-2-Aminoethyl-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-propyl)tetrahydrofuran (*cis* 32d)

The product (11 mg, 46% yield) was obtained as an oil by chromatography on silica; (R_f = 0.09, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ 6.84 (dd, J = 3.1, 9.2 Hz, 1H), 6.82 (dd, J = 3.1, 8.4 Hz, 1H), 6.73 (dd, J = 4.7, 9.1 Hz, 1H), 3.92 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.09 (m, 1H), 2.99 (m, 1H), 2.6 (t, J = 7.0 Hz, 2H), 1.96 (m, 2H), 1.83–1.77 (m, 2H), 1.65–1.47 (m, 8H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{16}H_{25}FNO_2$ 282.1869, found 282.1875; HPLC >95% (t_R = 4.7 min, 40(A):55(B):5(C):0.01(D); t_R = 5.09 min, 10(A):85(B):5(C):0.01(D)).

4.14.60. 2-Aminoethyl-5-(3′-(2″-methoxy-5″-fluorophenyl)-1′-butyl)tetrahydrofuran (32e)

The product (20 mg, 46% yield) in a 1:1 *cis:trans* ratio was obtained as an oil by chromatography on silica; (R_f = 0.1, methanol/DCM, 10:90, v:v); ^{1}H NMR: ($CDCl_3$, 500 MHz): δ *6.84–6.72* (m, 2H), 6.72 (dd, J = 4.7, 9.1 Hz, 1H), 4.03 (m, 0.5H), 3.93 (m, 0.5H), 3.89 (m, 0.5H), 3.81 (m, 0.5H), 3.78 (s, 3H), 2.88 (bm, 2H), 2.57 (t, J = 7.5 Hz, 2H), 2.27 (br s, 2H), 2.17–1.93 (m, 2H), 1.73–1.33 (m, 10H); HRMS (ESI) $[M+H]^+$ m/z calcd for $C_{17}H_{27}FNO_2$ 296.2026, found 296.2015; HPLC >96% (t_R = 4.74 min, 40(A):55(B):5(C): 0.01(D); t_R = 5.17 min, 10(A):85(B):5(C):0.01(D)).

4.14.61. (2-{5-[2-(5-Fluoro-2-methoxy-phenyl)-ethyl]-tetrahydrofuran-2-yl}-ethyl)-carbamic ethyl ester (33)

In a flame dried 20 mL vial was placed K_2CO_3 (239 mg, 1.73 mmol, 6.0 equiv) and anhydrous THF (5.0 mL). The vial was purged with $Ar_{(g)}$ and then chilled in an ice bath. Ethyl chloroformate (156 mg, 1.44 mmol, 5.0 equiv) was added via syringe followed by the slow addition of **32c** (77 mg, 0.29 mmol, 1.0 equiv) dissolved in THF (1.5 mL). The reaction was stirred at 0 °C for 0.5 h and then warmed to rt and stirred for an additional 3 h. The reaction was then stopped by addition of satd $NaHCO_{3(aq)}$ and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4, filtered through paper, and concentrated under reduced pressure to yield crude product that was used in the next step of the synthesis. (R_f = 0.4, methanol/DCM, 2:98, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ *6.87–6.82* (m, 2H), 6.74–6.71 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.05–3.77 (m, 2H), 3.78 (s, 3H), 2.71–2.56 (m, 2H), 2.08–1.51 (m, 10H) 1.3 (t, J = 7.2 Hz, 3H). LRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{27}FNO_4$ 340 found 340.

4.14.62. (2-{5-[2-(5-Fluoro-2-methoxy-phenyl)-ethyl]-tetrahydrofuran-2-yl}-ethyl)-methyl-amine (34)

To a flame dried round bottom flask, purged with $Ar_{(g)}$, was placed **33** (112 mg, 0.33 mmol, 1.0 equiv) and anhydrous THF (1.6 mL). The flask was then cooled with an ice bath with stirring for 15 min. LAH (1.0 M, 1.32 mL, 1.32 mmol, 4.0 equiv) was then slowly added via syringe over a period of 5 min. The reaction was allowed to warm to rt and stirred an additional 4 h. The reaction was then stopped by addition of ice cold MeOH and then stirred at rt for an additional 15 min. The resulting solution was transferred to a beaker and acidified with 1N $HCl_{(aq)}$ and then made basic with 10 M $NaOH_{(aq)}$. The basic solution was then extracted with Et_2O (3 × 20 mL) and the organic layer was washed with brine. The Et_2O layer was dried over Mg_2SO_4 and filtered through paper and concentrated to an oil under reduced pressure to afford the crude product (68 mg, 66% yield). The oil was purified with PTLC and eluted with MeOH–CH_2Cl_2 (5:95). (R_f = 0.05, methanol/DCM, 5:95, v:v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87–6.82 (m, 2H), 6.74–6.71 (m, 1H), 4.05–3.77 (m, 2H), 3.78 (s, 3H), 2.71–2.56 (m, 5H), 2.08–1.51 (m, 10H); HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{25}FNO_2$ 282.3784, found 282.3762; HPLC >97% (t_R = 30.2 min, 100(A):0.5(D); t_R = 26.05 min, 90(A):10(C):0.5(D)).

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