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Investigation into the structure–activity relationship of novel concentration dependent, dual action T-type calcium channel agonists/antagonists

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Abstract—This paper describes the synthesis and biological evaluation of a series of straight chain analogs of a compound (**1**) that was previously synthesized in our research program. These compounds, which are T-type calcium channel antagonists, exhibits potent anti-proliferative activity against a variety of cancer cells. A structure–activity relationship of these analogs against a variety of cancer cells has provided insight into a logical pharmacophore for this series of compounds. Furthermore, this series of compounds has presented itself as a set of novel, concentration dependent, dual action agonists/antagonists for the T-type calcium channel.

1. Introduction

The cell cycle and calcium influx have an intimate relationship.[1–3] Calcium is known to regulate many processes within the cell cycle via changes in the intracellular calcium concentration.[4–6] Therefore, regulation of intracellular calcium concentrations directs certain aspects of the cell cycle which, in turn, lead to inhibition of cellular proliferation. Thus, inhibition of calcium influx could be an important tool in the fight against a variety of disease states where the cell cycle has become aberrant, such as cancer.

T-type calcium channels, also known as low voltage activated (LVA) calcium channels, have been weakly associated with cancer for some time.[7] In fact, T-type currents are recorded from a variety of cancer cell lines.[7] They are also the only calcium current recorded from a human medullary thyroid carcinoma cell line.[8–10] Furthermore, we have shown, in our laboratories that inhibiting calcium influx into the cell leads to inhibition of cellular proliferation in certain types of cancer cells.[11] A T-type calcium channel, which will be discussed in more detail shortly, has recently been shown to be the ion channel that is responsible for this link between calcium influx and cellular proliferation.

Of all the calcium channel subtypes, the T-type has been the least studied and is the least understood.[7] There is no single reason for this lack of understanding. However, the need for a selective antagonist for LVA channels has definitely hampered investigations into this subtype of ion channels. Most of what is known about LVA channels has come from the over-expression of cloned channels and the isolation of endogenous T-type currents via pharmacological and electrophysiological methods.[7]

We have recently described the synthesis and biological activity of a novel set of T-type calcium channel antagonists[11] and provided a link between chemical blockade of a T-type calcium channel and inhibition of cellular proliferation. We have further described a brief SAR of this series of compounds on inhibition of cellular proliferation via calcium channel blockade. This study has produced the lead compound (**1**) shown in Figure 1. Figure 2 shows the typical dose–response curve exhibited by compound **1** on the inhibition of calcium influx.

Keywords: T-type calcium channels; Concentration dependent dual antagonist/agonist; Cancer.
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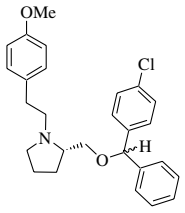


Figure 1. Structure of T-type calcium channel antagonist **1**.

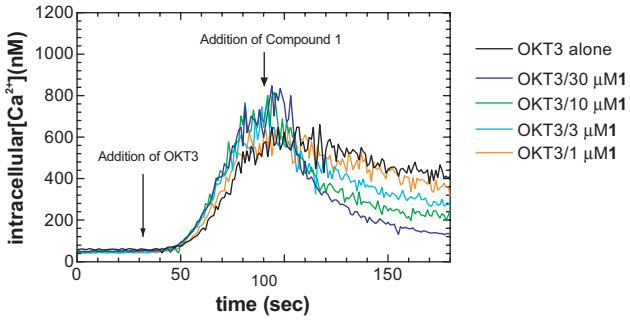


Figure 2. Dose–response curve of compound **1** against intracellular calcium concentration.

We have also recently shown that a T-type calcium channel subtype is responsible for the biological activity that is elicited by compound **1** and its structural analogs.[12] These subtypes include Cav3.2 and its variants. In this study we were able to inhibit cellular proliferation of cancer cells that presented the Cav3.2 or one of its variants, as well as cancer cell lines that were transfected with the Cav3.2 subtype. However, a cancer cell line that is known to utilize a different subtype of LVA calcium channels shows resistance to the biological effects of our compounds.

In this paper we describe the synthesis and biological evaluation of a variety of straight chain analogs of compound **1** as well as two conformationally restricted analogs. We provide further evidence that calcium channel antagonism, via chemical means, is a viable way to cytostatically inhibit cellular proliferation. Representative biological data is provided to establish a clearly defined link between calcium channel antagonism and inhibition of cellular proliferation. We will also provide a proposed pharmacophore for the antagonist activity.

We will also provide proof of a concentration dependent dual action agonism/antagonism of T-type calcium channels exhibited by these compounds. There are several examples of dual action agonist/antagonist for calcium channels in the literature.[13] However, none of these examples have been shown to display this type of activity on T-type calcium channels. Therefore, to the best of our knowledge we believe this to be the first example of such activity for T-type calcium channels.

2. Chemistry

Compound **2** displayed in Table 1 was synthesized according to Scheme 1. Synthesis began with the typical Williamson ether synthesis to afford the ether **2a** from the diol. Then the alcohol was treated with NaH, followed by condensation with *p*-methoxybenzyl chloride (PMB-Cl) affording the final diether product **2**.

Compounds **3**, **5**, and **9** displayed in Table 1 were synthesized as described in Scheme 2. Synthesis began with an acid catalyzed reductive amination, which lead to the aminoalcohols **3a**, **5a**, and **9a**. Coupling of the aminoalcohols with 4-chlorobenzhydrol via Williamson ether synthesis conditions afforded the final products **3**, **5**, and **9**.[14]

Compound **4** displayed in Table 1 was synthesized according to Scheme 3. Synthesis began with the coupling reaction of *p*-anisidine with succinic anhydride to afford the amide acid **4a**.[15] Reduction of the amide acid afforded the aminoalcohol **4b**, which was then coupled to 4-chlorobenzhydrol using the standard Williamson ether synthesis conditions already mentioned to afford the final product **4**.

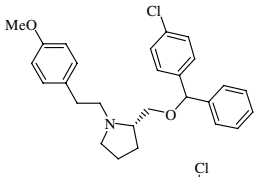
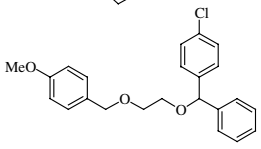
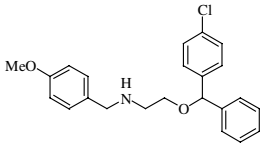
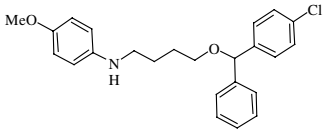
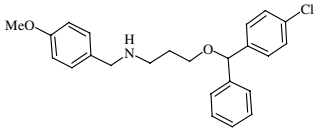
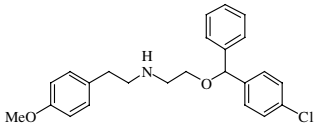
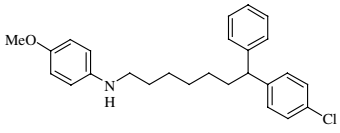
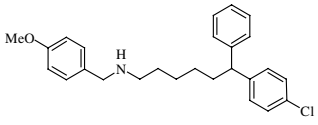
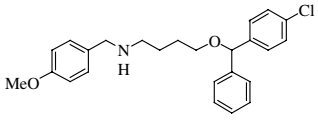
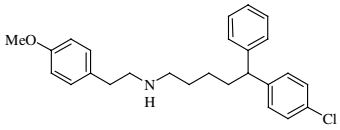
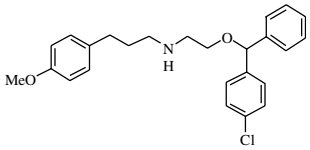
Compounds **6** and **11** displayed in Table 1 were synthesized as described in Scheme 4. Synthesis started with the coupling of 4-methoxyphenyl acetic acid or 4-methoxyphenyl propanoic acid to *tert*-butyl dimethyl silyl protected ethanolamine to afford the amides **6a** and **11a**. Deprotection of the silyl ether afforded the amide alcohols **6b** and **11b**, which were reduced to the aminoalcohols **6c** and **11c**.[16] Coupling of the alcohols **6c** and **11c** to 4-chlorobenzhydrol afforded the final products **6** and **11**.

Compounds **7**, **8**, and **10** displayed in Table 1 were synthesized according to Scheme 5. These syntheses began with terminal alkynyl alcohols of varying chain lengths between butynyl and hexynyl. The alkynyl alcohols were coupled to 4-chlorobenzophenone to afford **7a**, **8a**, and **10a** in good yields in all three cases. Dual hydrogenation/hydrogenolysis of the alkynyl groups/benzylic alcohol afforded the corresponding reduced alcohols **7b**, **8b**, and **10b**. Oxidation of the primary alcohols afforded the aldehydes **7c**, **8c**, and **10c**.[17] Finally compounds **7c** and **8c** were coupled to 4-methoxybenzyl amine and 4-methoxyphenethyl amine, respectively, to afford the final products **7** and **8** as shown. Reductive amination was attempted at this point on **10c** with *p*-anisidine, however in our hands this could not be accomplished. Therefore, the aldehyde was converted into the corresponding acid **10d**.[18] A PyBOP coupling reaction with *p*-anisidine ensued to form the amide **10e**,[19] which then underwent a reduction to afford the amine **10**.

Synthesis of compound **12** in Table 1 was accomplished according to Scheme 6. Synthesis started with a Wittig reaction to couple 4-chlorobenzophenone with (3-benzyloxypropyl)triphenylphosphonium bromide to form the alkene **12a**.[20] A dual hydrogenation/hydrogenolysis of the alkene/protected alcohol lead to the production of the reduced, unprotected alcohol, which was oxidized to the aldehyde **12b** using Dess–Martin periodinane.[21]

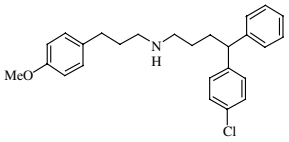
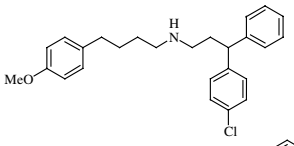
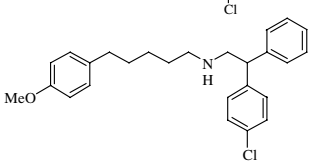
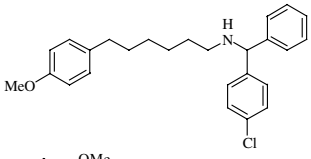
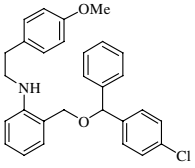
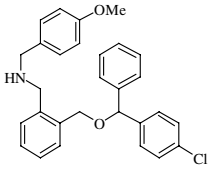
Next, 4-methoxycinnaminitrile was reduced to the corresponding amine followed by hydrogenation of the

Table 1. Antagonist data for all of the compounds

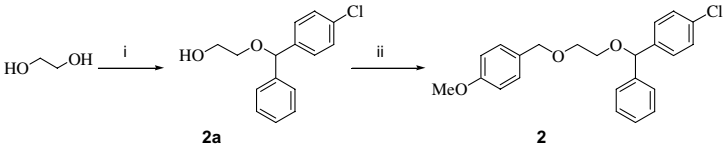
Compound	Structure	IC_{50} (μM)					
		Jurkat		LNCaP		MDA-231	
		Cellular proliferation	Calcium influx	Cellular proliferation	Calcium influx	Cellular proliferation	Calcium influx
1		6	7	4	4	40	35
2		100	10	100	NE	>100	60
3		3.8	3	1.6	3	11.7	10
4		30	30	100	NE	NE	NE
5		4	7	4	5	11	10
6		7.6	10	3.5	10	8	10
7		>100	30	>100	30	NE	30
8		4	10	3.5	10	8	10
9		3	3	2	5	10	8
10		4	10	3	10	6	10
11		3.7	3	5.5	15	4	20

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	IC_{50} (μM)					
		Jurkat		LNCaP		MDA-231	
		Cellular proliferation	Calcium influx	Cellular proliferation	Calcium influx	Cellular proliferation	Calcium influx
12		70	60	42	NE	>100	100
13		30	30	7	NE	15	30
14		13	3	9	NE	25	10
15		30	NE	100	NE	NE	NE
16		>300	NE	>1 mM	NE	1	NE
17		5.4	3.3	3.3	NE	11.6	20

NE = no effect at the concentration tested; IC_{50} values are in μM concentrations.

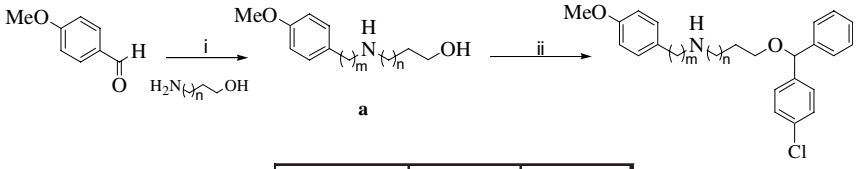


Scheme 1. Synthesis of diether **2**. Reagents and conditions: (i) 4-chlorobenzhydrol, *p*-TsOH, toluene, reflux; (ii) NaH, DMF, then add PMB-Cl.

double bond leading to the corresponding reduced amine **12c**. Coupling of the amine to the previously formed aldehyde **12b** using reductive amination conditions yielded the final product **12**.

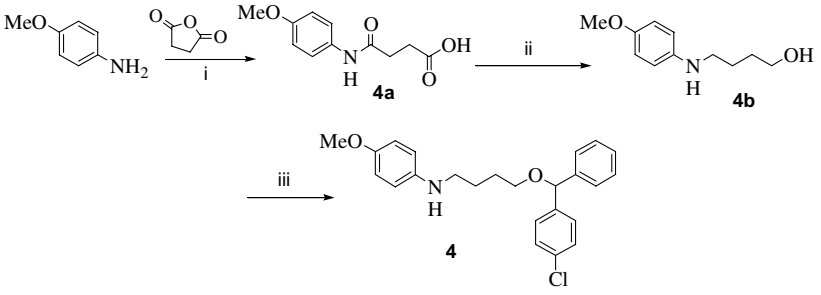
Synthesis of compound **13** in Table 1 was accomplished as described in Scheme 7. The synthesis began with the oxidation of 4-(4-methoxyphenyl)-1-butanol to the aldehyde **13a**. Next, a Wittig reaction on 4-chlorobenzophenone using (triphenylphosphoranylidene) acetonitrile formed the α,β-unsaturated nitrile **13b**.[22] Reduction of the nitrile resulted in the β,γ-unsaturated amine **13c**, which was then coupled with the aldehyde **13a** to form the secondary amine **13d**. Hydrogenation of the double bond resulted in the reduced amine **13**.

Synthesis of compound **14** in Table 1 is described as shown in Scheme 8. The reaction sequence started with a Friedel–Crafts acylation of anisole with glutaric anhydride to form the δ-ketoacid **14a**.[23] Reduction of the

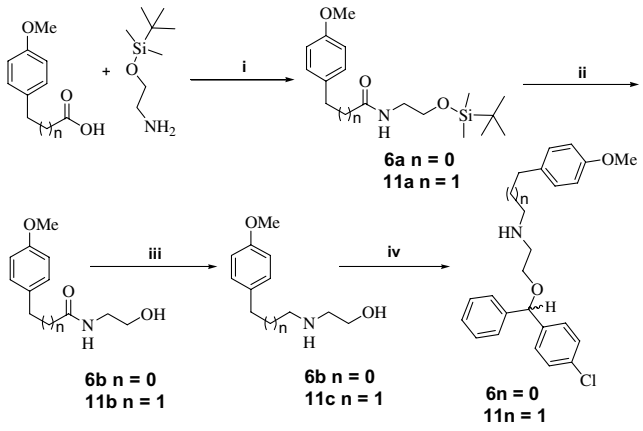


Compound	m	n
3	1	0
5	1	1
9	1	2

Scheme 2. Synthesis of several straight chain analogs **3**, **5**, and **9**. Reagents and conditions: (i) AcOH or $ZnCl_2$, MeOH, then add $NaBH_3CN$; (ii) 4-chloro-benzhydrol, *p*-TsOH, toluene, heat.



Scheme 3. Synthesis of straight chain analog **4**. Reagents and conditions: (i) THF; (ii) $LiAlH_4$, $AlCl_3$, THF, 0 °C; (iii) 4-chlorobenzhydrol, *p*-TsOH, toluene, reflux.



Scheme 4. Synthesis of compounds **6** and **11**. Reagents and conditions: (i) DCC, TEA, CH_2Cl_2; (ii) TBAF, THF, 25 °C, 1 h; (iii) $LiAlH_4$, THF; (iv) 4-chlorobenzhydrol, *p*-TsOH, toluene, 110 °C.

ketoacid resulted in the acid (not shown), which was coupled to *N*,*O*-dimethylhydroxyamine to form the Weinreb amide **14c**. The Weinreb amide was then reduced to the aldehyde **14d**.[24] The aldehyde was coupled to the β-aminoalcohol **14f** to form the secondary amine. The benzylic alcohol (not shown in scheme) was reduced to yield the final product **14**.

The β-aminoalcohol **14f** was formed when 4-chlorobenzophenone was reacted with trimethylsilylcyanide to form the cyanohydrin **14e**.[25] Reduction of the cyanohydrin was undertaken immediately, due to the instability of the molecule, to the β-aminoalcohol, which was used as previously mentioned.

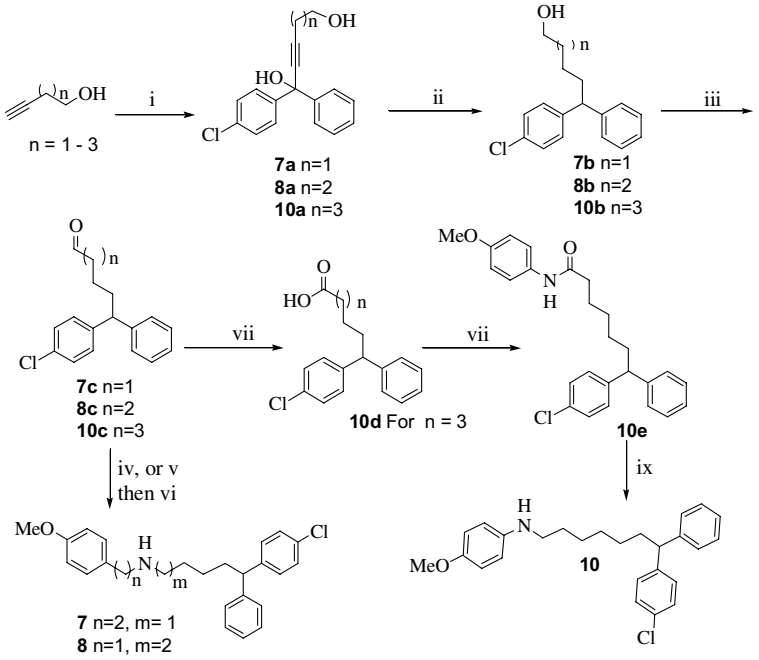
Synthesis of compound **15** in Table 1 was accomplished as described in Scheme 9. First, a Sonogashira coupling of 4-iodoanisole with 5-hexyn-1-ol formed the aryl alcohol **15a**.[26] Next, a hydrogenation produced the reduced alcohol **15b**, which was then oxidized to the aldehyde **15c** using typical Swern conditions. Reductive amination of the aldehyde with 4-chlorobenzhydrylamine hydrochloride formed the final product **15**.

Synthesis of compound **16** in Table 1 was accomplished according to Scheme 10. First, 2-cyanobenzaldehyde was reduced to form the amino alcohol **16a**. Then reductive amination of 4-methoxybenzaldehyde and **16a** provided **16b**. A condensation reaction between **16b** and 4-chlorobenzhydrol afforded **16**.

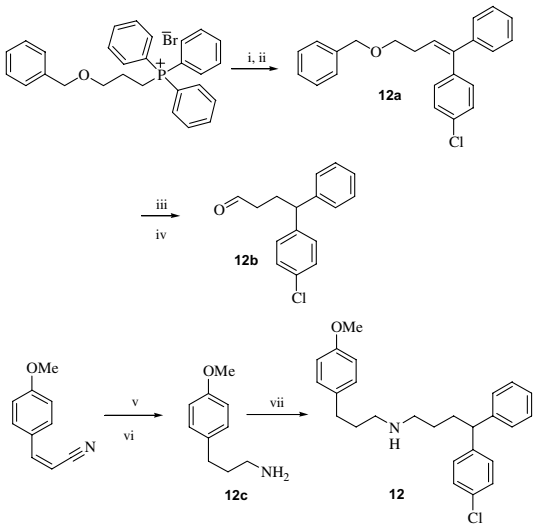
Synthesis of compound **17** in Table 1 was accomplished according to Scheme 11. First, the alcohol of 2-aminobenzyl alcohol was protected with a *tert*-butyldimethylsilyl group to form **17a**[27] then PyBOP mediated coupling of **17a** and 4-methoxyphenylacetic acid generated amide **17b**. The silyl protecting group was then removed with TBAF to provide the free alcohol **17c**. Reduction of the amide yielded amine **17d**. The free alcohol of **17d** was then reacted with NaH and condensed with 4-chloro bromobenzhydrol to afford the final product **17**.

3. Biological data

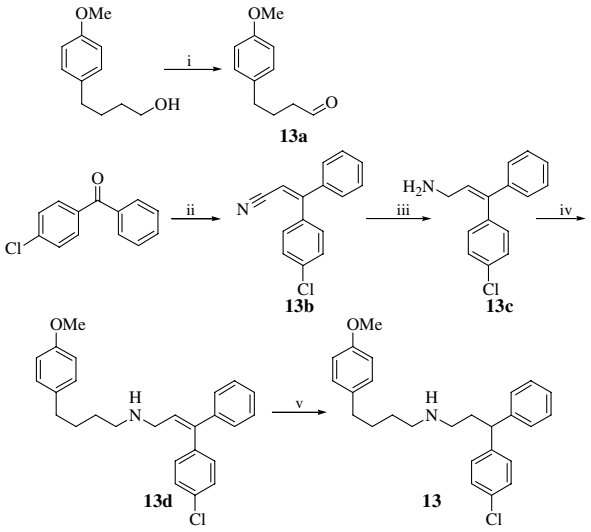
Table 1 illustrates the calcium influx and cellular proliferation[28] data exhibited by the compounds. Most of the straight chain analogs of compound **1** that contain both the nitrogen and the oxygen seem to display some degree



Scheme 5. Synthesis of compounds **7**, **8**, and **10**. Reagents and conditions: (i) 2 equiv *n*-BuLi, THF, −78 °C, then add 4-chlorobenzophenone; (ii) Pd/C, H_2, formic acid, EtOH; (iii) $(ClCO)_2$, DMSO, DIEA, CH_2Cl_2; (iv) HCl, *p*-methoxybenzyl amine; (v) HCl, *p*-methoxyphenethyl amine; (vi) $NaCNBH_3$; (vii) NaClO, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH; (viii) PyBOP, DIEA, CH_2Cl_2, *p*-anisidine; (ix) $LiAlH_4$, THF.



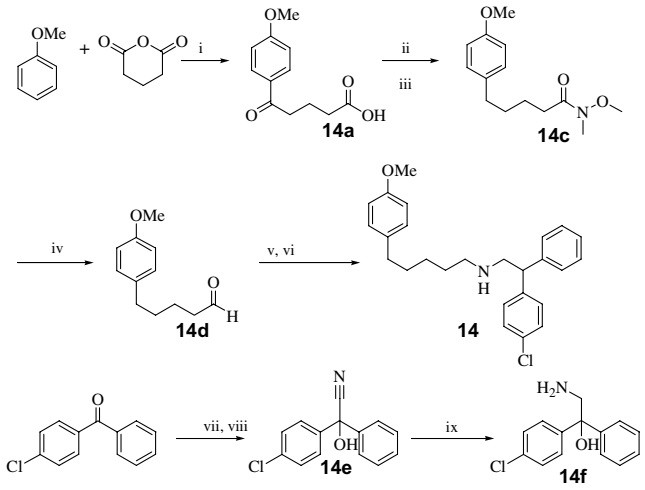
Scheme 6. Synthesis of compound **12**. Reagents and conditions: (i) K–O^{t}Bu, THF, 67 °C; (ii) 4-chlorobenzophenone; (iii) 10% Pd/C, H_2, formic acid; (iv) Dess–Martin periodinane, CH_2Cl_2; (v) $LiAlH_4$, $AlCl_3$, THF; (vi) 10% $Pd(OH)_2$/C, H_2; (vii) HCl, **12b**, followed by $NaCNBH_3$.



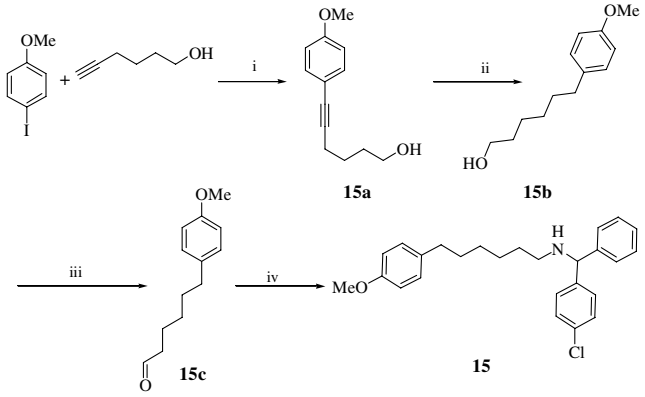
Scheme 7. Synthesis of compound **13**. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2; (ii) (triphenylphosphoranylidene)acetonitrile, neat, 100 °C; (iii) $LiAlH_4$, $AlCl_3$, THF; (iv) **13a**, HCl (cat), followed by $NaCNBH_3$; (v) 10% $Pd(OH)_2$/C, MeOH.

of biological activity (compounds **3**, **5**, **6**, **9**, and **11**). The importance of the nitrogen atom for the biological activity exhibited by the compounds seems to be very clear and will be discussed shortly. However, the importance of the oxygen atom seems to be slightly more convoluted. The importance of the oxygen atom, for biological activity, seems to be conditional based on the position of the nitrogen atom. For example, the omission of the oxygen atom is less important on the overall biological activity exhibited in compounds **8** and **10**, and to some extent **14**, compared to compounds **7**, **12**, **13**, and **15**. The reason for this variance is still unclear. However, when the nitrogen is omitted from the chain an apparent loss in both inhibition of calcium influx and cellular proliferation is realized (compound **2** compared to compound **3**).

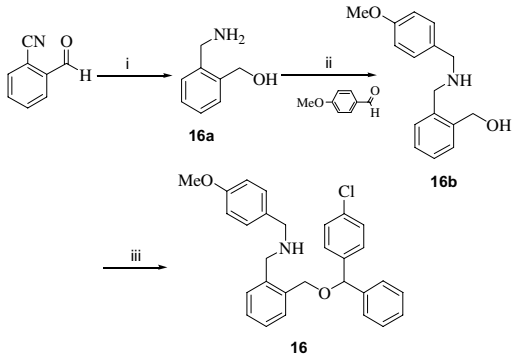
Both location and basicity of the nitrogen play an important role in whether an analog will exhibit biological activity. Varying the location of the nitrogen, when the oxygen is omitted, has a dramatic effect on the activ-



Scheme 8. Synthesis of compound **14**. Reagents and conditions: (i) neat, $AlCl_3$; (ii) H_2, 10% Pd/C, 3:1 EtOH–AcOH; (iii) *N*,*O*-dimethylhydroxyamine hydrochloride, PyBOP, DIEA, CH_2Cl_2; (iv) $LiAlH_4$, THF, −78 °C; (v) HCl (cat), **14f**, followed by $NaCNBH_3$; (vi) H_2, 10% Pd/C (cat), formic acid (cat), EtOH; (vii) TMS–Cl, KCN (cat), 18-crown-6 (cat); (viii) 15% HCl, THF; (ix) $LiAlH_4$, Et_2O.



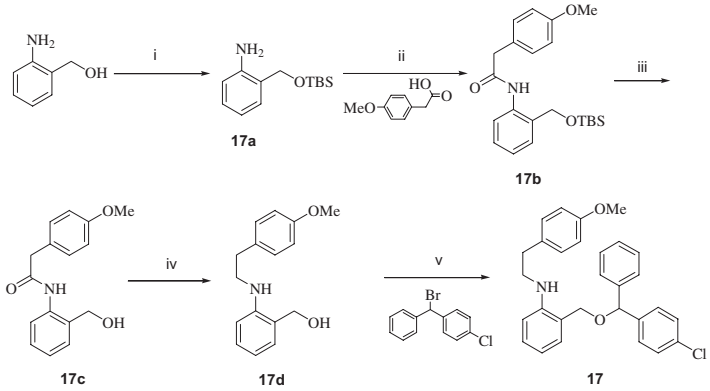
Scheme 9. Synthesis of compound **15**. Reagents: (i) $Pd(dba)_2$, PPh_3, CuI, THF, DIEA; (ii) H_2, Pd/C, formic acid, EtOH; (iii) $(ClCO)_2$, DMSO, DIEA, CH_2Cl_2; (iv) TEA, $TiCl_4$, CH_2Cl_2, 4-chlorobenzhydrylamine hydrochloride, followed by $NaBH_3CN$.



Scheme 10. Synthesis of compound **16**. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C; (ii) HCl, MeOH, then add $NaBH_3CN$; (iii) 4-chlorobenzhydrol, *p*-TsOH, toluene, reflux.

ity of the compound. There are several positions along the chain that lead to an increase in biological activity displayed by the compound. These locations are the 2, 3, and 6 positions of the chain (Fig. 3), relative to the 4-methoxyphenyl group, as opposed to all other locations (compounds **8**, **10**, and **14**, respectively, compared to compounds **12**, **13**, and **15**). Basicity of the nitrogen also plays an important role in whether the compound will display biological activity. The best examples for this are a comparison of the biological activity of compounds **8** versus **17** and then compounds **10** versus **16**. In both comparisons the nitrogen atom resides in the same position in the chain; but in the first example, **8** and **17**, both compounds have nitrogen atoms that display comparable basicities. However, in the second example the basicity of compound **16** is decreased, because of the inductive effect of the aromatic ring on the nitrogen, in respect to the nitrogen atom of compound **10**. This reduction in basicity leads to a decrease in the biological activity exhibited by compound **16** when compared to compound **10**, a decrease that is not observed when comparing compounds **8** and **17**.

The length of the chain linking the two aryl regions together has little effect on biological activity. For example, compounds **3**, **5**, and **9** are all analogs differing by one carbon homologations in between the nitrogen



Scheme 11. Reagents and conditions: (i) TBSCl, DMF, imidazole; (ii) PyBOP, DiEA, CH_2Cl_2; (iii) TBAF, THF; (iv) $LiAlH_4$, $AlCl_3$, THF, 0 °C, then reflux; (v) NaH, DMF, 0 °C, then add bromobenzhydryl.

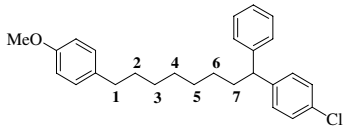


Figure 3. Possible locations for the nitrogen atom on the chain.

atom and the oxygen atom and all seem to exhibit relatively similar biological activities. Also compounds **3**, **6**, and **11** all maintain the two carbon ethanol–amine linker; however, they vary in the number of carbon atoms in the chain between the nitrogen and the 4-methoxyphenyl group. In this case, as in the previous example, there is no real difference in biological activity exhibited by the compounds in all three of the chain lengths shown.

Two conformationally restricted analogs (**16** and **17**) were made. Compound **17** is a rigid analog of compound **9** with an aniline heterocyclic core. Both compound **16** and **17** contain aromatic functionality within the carbon chain that links the 4-methoxyphenyl region to the benzhydrol region. The *ortho* attachments to the previously mentioned aromatic functionality positions both ends of the chain in closer proximity to each other than what is believed in the non-restricted analogs. Both of these modifications limit the degrees of rotation and conformations that these compounds can adopt. There is no advantage in terms of additional biological activity exhibited by these conformationally restricted analogs to that of their unrestricted counterparts.

4. Updated pharmacophore

Based on all of the above information a pharmacophore has been proposed (Fig. 4). It includes a straight chain linking two regions of aromaticity together. X can either be an oxygen atom or a carbon atom, however, if X is a carbon atom then the nitrogen atom must be located in the 2, 3, or 6 position from the 4-methoxyphenyl region as designated in Figure 3. The chain can be either 6, 7, or 8 bonds long. The nitrogen atom is crucial for biological activity of the compound. Not only does it have to be present, but it must also be basic. The need for the aryl rings and the positioning of their substituents has been previously addressed[11] and they are an absolute necessity for biological activity.

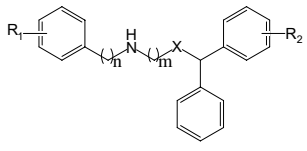


Figure 4. Proposed pharmacophore: (i) a basic nitrogen is required for activity; (ii) X = O, CH_2. If X = CH_2 then nitrogen atom must be in the 2, 3, or 6 position of the chain as designated by Figure 3; (iii) R_2 requires an electronegative group, which is comparable in size to that of chlorine, or smaller. Larger groups are detrimental to activity; (iv) the length of the chain is limited so that it should have 6–8 atoms total.

5. Calcium channel agonism

During the course of this investigation it was discovered that some of the straight chain analogs were observed to cause an influx of extracellular calcium rather than prevent it. At first, it was thought that this occurrence was localized to a few compounds, however as new compounds were made and subsequently submitted for biological activity the incidence of increased calcium influx was observed repeatedly. It was not that these compounds only displayed an ability to cause calcium influx into the cell, they also effectively blocked calcium influx at lower concentrations of the drug. Thus a concentration dependent dual action agonist/antagonist for T-type calcium channels was discovered.

Figure 2 displays the concentration dependent antagonist activity that was exhibited by the lead compound up until this study. This is a typical dose–response curve for many of the prolinol and piperidine type compounds that were synthesized and provided in our previous paper, albeit not as potent. Figure 5 displays the calcium channel agonism data for one of the straight chain analogs. As can be seen, there is no antagonism of calcium influx exhibited at this concentration of the drug and the relative agonistic effect is not affected by the addition of OKT3.[29,30] However, the intensity of the agonist effect is affected, the reason for this occurrence is still unclear. When compound **12** is added to the cells alone, without any external stimulus to induce calcium influx, there is still an increase in intracellular calcium concentrations (red line). The delayed response of OKT3 on calcium influx is typical for an entity that initiates calcium influx via the calcium influx pathway (black line). We believe that our compounds are acting on the calcium channels directly to allow calcium influx. Thus there is no delayed onset of calcium influx after the compound is administered to the cell (red line).

The structural requirements needed to elicit this agonism of calcium influx are yet to be optimized. However, Table 2 displays the intensity of calcium channel agonism that the compounds exhibit and the structures that evoked this response. What appears to be clear as of now is that placement of the nitrogen atom plays an important role in whether the compound will exhibit agonistic activity toward calcium channels. For example, when the nitrogen atom is placed in the 2 and 3 position (compounds **8** and **10**), as described in Figure 3,

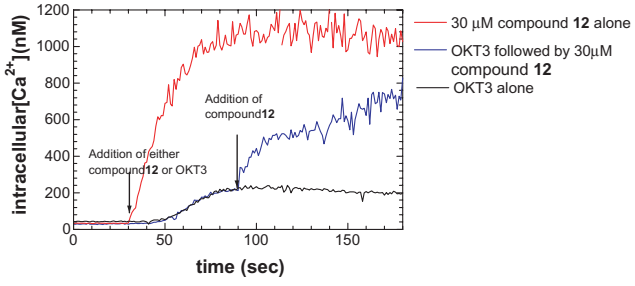
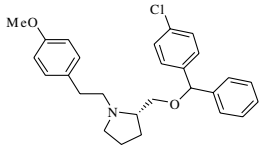
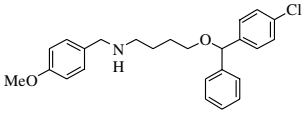
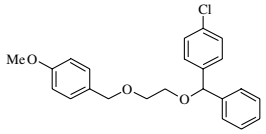
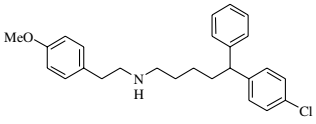
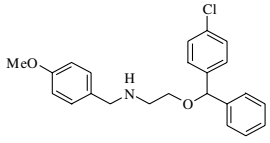
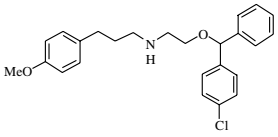
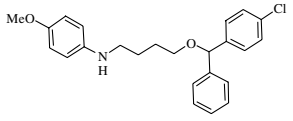
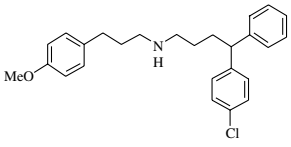
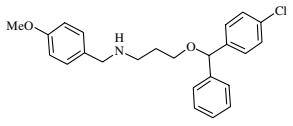
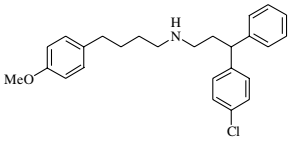
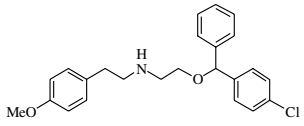
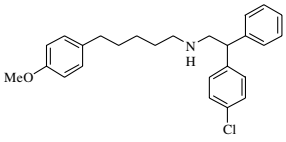
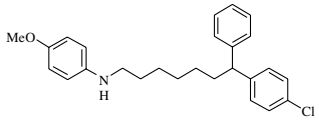
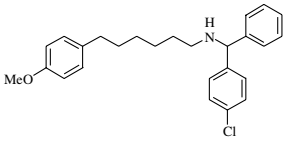
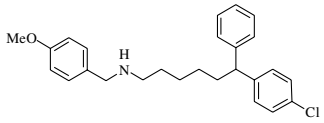


Figure 5. Agonist action of straight chain analogs.

Table 2. Calcium influx data

Compound	Structure	Intracellular calcium concentration (μM) taken at 100 μM of drug[a]	Compound	Structure	Intracellular calcium concentration (μM) taken at 100 μM of drug[a]
1		30	**9**		1000
2		0	**10**		1500[b]
3		400	**11**		1300
4		N/T	**12**		0
5		N/T	**13**		1000
6		500	**14**		200
7		200	**15**		0
8		1400[b]			

N/T = not tested for overall increase in intracellular calcium concentrations, but was tested to see if this effect is present.
[a] Intracellular calcium concentrations were obtained in the Jurkat cell line.
[b] Calcium influx data was obtained at 30 μM concentration of drug.

the compound elicits the greatest agonism that has been seen in this lab to date. However, if the nitrogen atom is moved down the chain to the 4 position (compound **12**) all activity is lost. Then if it is moved farther down to the 5 and 6 positions (compounds **13** and **14**) the agonism starts to rebound then drops off again as it is placed in the 7 position (compound **15**), including the oxygen atom allows some variability to the agonism activity elicited by the compounds compared to non-oxygenated analogs. For example, compound **11** displays good agonism data, compared to compound **12**. However, there is a reverse in this trend when comparing compounds **10** and **11**. Obviously, there are a lot of unknown factors that need to be discovered in order to fully map out the structural requirements needed to elicit this biological effect. And there is a lot more work that is needed in this area.

6. Conclusion

In summary, we have provided additional evidence linking the inhibition of calcium influx to the cessation of cellular proliferation. We have provided another

structural class of compounds to strengthen this conclusion, as well as a proposed pharmacophore.

We have also provided evidence of a concentration dependent dual action agonist/antagonist to T-type calcium channels. We believe this to be the first example in the literature of such a concentration dependent dual action agonist/antagonist.

7. Experimental

7.1. General procedure A: reductive amination

7.1.1. Method 1: acetic acid catalyzed. A solution of amine (4 equiv) in anhydrous MeOH (0.4 M aldehyde) was acidified to pH 6 with glacial acetic acid. The aldehyde (1 equiv) was added slowly via syringe and this mixture was allowed to stir for 2 h. (Note: If the aldehyde is a solid, dissolve it in a minimum amount of MeOH to add it via syringe.) At this time, sodium cyanoborohydride (0.6 equiv), dissolved in a minimum amount of MeOH, was added slowly via syringe, and the reaction was allowed to stir for 12–48 h. At its completion, methanol was removed under reduced pressure and the crude oil was made basic (pH 8) with saturated $NaHCO_3$. The aqueous layer was extracted repeatedly (five times or more) with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography.

7.1.2. Method 2: zinc chloride catalyzed. To a solution of amine (2 equiv) and aldehyde (1 equiv) in anhydrous MeOH (0.25 M aldehyde) was added dropwise a solution of sodium cyanoborohydride (1 equiv) and zinc chloride (0.5 equiv) dissolved in a minimal amount of MeOH. At the completion of the reaction (6 h), methanol was removed under reduced pressure and enough 0.1 N NaOH was added to dissolve any inorganic salts. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography.

7.1.3. Method 3: hydrochloric acid catalyzed. To a mixture of amine (2 equiv) and aldehyde (1 equiv) in anhydrous MeOH (0.1 M aldehyde) was added one drop of concentrated HCl (catalytic). After 2 h, sodium cyanoborohydride (1 equiv) was added and the reaction was allowed to stir for 6 h. Methanol was removed under reduced pressure and saturated $NaHCO_3$ was added to the resulting oil. This mixture was extracted three times with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure.

7.2. General procedure B: reductions using lithium aluminum hydride ($LiAlH_4$)

A solution of $LiAlH_4$ (1.5 equiv) was prepared in THF (0.5 M amide). This mixture was allowed to stir until the reagents dissolved and a dark gray solution remained. The mixture was cooled to 0 °C and the amide (1 equiv), dissolved in a minimum amount of THF, was added slowly via syringe. The reaction mixture was allowed to stir overnight, then cooled to 0 °C, and slowly quenched with water. The reaction was diluted with water (approximately twice the reaction volume) and was allowed to stir until completely quenched. Then the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography.

7.3. General procedure C: ether synthesis using *p*-toluenesulfonic acid (*p*-TsOH)

To a solution of alcohol (1 equiv) in toluene (0.1 M alcohol) was added the benzhydrol (1 equiv) and dry *p*-TsOH (1 equiv). This mixture was refluxed using a Dean–Stark trap for 6 h. The reaction was diluted with ethyl acetate and extracted two times with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography. Note: Dry *p*-TsOH was obtained by refluxing *p*-TsOH monohydrate in toluene under Dean–Stark conditions for 6 h. This mixture was then concentrated under reduced pressure and placed under vacuum to afford brown solid. Place under vacuum for 30 min before each use.

7.4. General procedure D: Swern oxidation

To a solution of oxalyl chloride (1.5 equiv) in dichloromethane was added a solution of dimethylsulfoxide (3 equiv) in dichloromethane at −78 °C. Reaction mixture was allowed to stir for 10 min before addition of the alcohol to be oxidized (1 equiv) in dichloromethane. The reaction was stirred for an additional 30 min and then diisopropylethylamine (6 equiv) was added, stirring continued for 10 min before the mixture was allowed to warm to room temperature. Cold 10% hydrochloric acid was added until the reaction mixture was slightly acidic and then the mixture was extracted with dichloromethane (3×). The organic layer was washed with saturated sodium bicarbonate solution (3×) and then dried over anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure.

7.5. General procedure E: Pd/C reductions

To a solution of the substrate to be reduced in ethanol under nitrogen was added a catalytic amount of 10% palladium on carbon and formic acid. The reaction mixture was then placed under a hydrogen atmosphere for 18 h. Reaction was then filtered through Celite to remove palladium and then concentrated under reduced pressure.

7.6. General procedure F: coupling of alkynyl alcohols to 4-chlorobenzophenone

To a solution of alkynyl alcohol (1 equiv) in THF at −78 °C was added *n*-butyl lithium (2.2 equiv), and the reaction mixture was allowed to warm up to room tem-

perature and was stirred for 1 h. The reaction was then cooled back down to −78 °C then a solution of 4-chlorobenzophenone (1 equiv) in THF was carefully added. The reaction was warmed up to 0 °C and stirred for 3 h and then carefully quenched with a saturated solution of ammonium chloride. Next, the mixture was extracted with ethyl acetate (3×), dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure.

7.7. General procedure G: TBAF deprotection

To a solution of protected alcohol (1 equiv) in THF was added tetra butyl ammonium fluoride (1.1 equiv). Reaction was allowed to stir for 1 h at room temperature. Then the reaction was quenched with water, and extracted three times with EtOAc. Solution was dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

7.7.1. 2-[(4-Chloro-phenyl)-phenyl-methoxy]-ethanol (2a). To a solution of ethylene glycol (0.51 mL, 9.15 mmol) in 9 mL toluene was added 4-chlorobenzhydrol (0.20 g, 0.915 mmol) and *p*-TsOH (0.174 g, 0.915 mmol). This mixture was refluxed under Dean–Stark conditions for 30 min. The reaction was diluted with ethyl acetate and extracted two times with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (80% ether/hexanes, $R_f = 0.2$) afforded a yellow oil (0.218 g, 91%). ^{1}H NMR (acetone-d_6): δ 7.39–7.07 (m, 9H), 5.40 (s, 1H), 3.72–3.55 (m, 2H), 3.42 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (acetone-d_6): δ 142.90, 142.44, 132.78, 128.90, 128.71, 128.61, 127.78, 127.24, 83.00, 71.07, 61.61.

7.7.2. [(4-Chloro-phenyl)-phenyl-methyl]-(4-methoxy-benzyl)-ethane-1,2-diether (2). To a slurry of NaH (60% dispersion in mineral oil, 0.015 g, 0.381 mmol) in 4 mL of DMF at 0 °C was added **2a**, dissolved in a minimum volume of DMF, slowly via syringe. After 30 min, 4-methoxybenzyl chloride (0.06 mL, 0.419 mmol) was added dropwise at 0 °C. After 12 h, the reaction was diluted with ether and extracted twice with saturated LiBr. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (25% ether/hexanes, $R_f = 0.35$) afforded a pale yellow oil (0.060 g, 41%). ^{1}H NMR (acetone-d_6): δ 7.36–7.08 (m, 11H), 6.79 (d, $J = 8.9$ Hz, 2H), 5.41 (s, 1H), 4.37 (s, 2H), 3.67 (s, 3H), 3.59–3.47 (m, 4H). ^{13}C NMR (acetone-d_6): δ 159.66, 142.83, 142.37, 132.81, 131.26, 129.43, 128.90, 128.72, 128.65, 127.81, 127.25, 113.95, 82.99, 72.65, 69.57, 68.75, 55.02. MS (CI) *m*/*z* 382.9 (M^+). Anal. Calcd for $C_{23}H_{23}ClO_3$: C, 72.15; H, 6.05. Found: C, 72.21; H, 6.09.

7.7.3. 2-(4-Methoxy-benzylamino)-ethanol (3a). This compound was prepared according to general procedure A (method 1). Flash chromatography (30% MeOH/$CHCl_3$) afforded a yellow oil (0.126 g, 38%). ^{1}H NMR ($CDCl_3$): δ 7.22 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 3.79 (s, 3H), 3.73 (s, 2H), 3.63 (t, $J = 5.2$ Hz, 2H), 2.77 (t, $J = 5.0$ Hz, 2H), 2.51–2.43 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ 159.27, 132.48, 129.86, 114.37, 61.33, 55.78, 53.38, 50.96. MS (CI) *m*/*z* 181.9 (M^+).

7.7.4. {2-[(4-Chloro-phenyl)-phenyl-methoxy]-ethyl}-(4-methoxy-benzyl)-amine (3). This compound was prepared from **3a** and 4-chlorobenzhydrol according to general procedure C. Flash chromatography (5% MeOH/$CHCl_3$) afforded an orange oil (0.188 g, 71%). ^{1}H NMR (acetone-d_6): δ 7.36–7.07 (m, 11H), 6.75 (d, $J = 8.1$ Hz, 2H), 5.36 (s, 1H), 3.65 (s, 3H), 3.60 (s, 2H), 3.45 (t, $J = 5.4$ Hz, 2H), 2.69 (t, $J = 5.4$ Hz, 2H). ^{13}C NMR (acetone-d_6): δ 159.06, 142.93, 142.43, 133.47, 132.82, 129.49, 128.87, 128.77, 128.66, 127.83, 127.21, 113.89, 83.02, 69.02, 54.97, 53.15, 48.89. MS (CI) *m*/*z* 382.1 (M^+). Anal. Calcd for $C_{23}H_{24}ClNO_2$: C, 72.34; H, 6.33; N, 3.67. Found: C, 72.17; H, 6.56; N, 3.62.

7.7.5. 3-[*N*-(4-Methoxyphenyl)carbamoyl]propanoic acid (4a). Succinic anhydride (0.081 g, 0.812 mmol) was dissolved in a minimum volume of THF (≈1.5 mL) and then was diluted to 3 mL with ether. To this solution, *p*-anisidine (0.100 g, 0.812 mmol), dissolved in 6 mL of ether, was added slowly via cannula. The white product precipitate was filtered and washed with cold ethyl acetate. The filtrate was concentrated under reduced pressure and the resulting beige solid was dissolved in hot ethyl acetate and stored in a cold room (4 °C) to induce crystallization. The crystals were collected by filtration and rinsed with cold ethyl acetate. The initial precipitate and the second batch of crystals were combined to afford a white solid (0.164 g, 91%) as the desired product ($R_f = 0.5$ in 40% MeOH/$CHCl_3$). ^{1}H NMR (methanol-d_4): δ 7.35 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 4.94–4.80 (br s, 1H), 3.69 (s, 3H), 2.61–2.55 (m, 5H). ^{13}C NMR (methanol-d_4): δ 175.40, 171.64, 156.87, 131.90, 122.05, 113.96, 54.89, 31.24, 29.17. MS (CI) *m*/*z* 224.1 (M^+).

7.7.6. 4-[(4-Methoxyphenyl)amino]butan-1-ol (4b). This compound was prepared from **4a** according to general procedure B. However, 3 equiv of $LiAlH_4$ and 1 equiv of $AlCl_3$ were used. In addition, this reaction was conducted at 0.1 M in THF with respect to the amide/acid (due to its low solubility in THF). Flash chromatography (100% ether, $R_f = 0.3$) afforded a dark orange oil (0.079, 55%). ^{1}H NMR ($CDCl_3$): δ 6.78 (d, $J = 8.8$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 3.75 (s, 3H), 3.67 (t, $J = 5.9$ Hz, 2H), 3.10 (t, $J = 6.6$ Hz, 2H), 2.75–2.59 (br s, 2H), 1.77–1.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 152.87, 142.93, 115.42, 115.12, 63.13, 56.33, 45.66, 31.06, 26.90. MS (CI) *m*/*z* 196.2 (M^+).

7.7.7. {4-[(4-Chlorophenyl)phenylmethoxy]butyl}(4-methoxyphenyl)amine (4). This compound was prepared from **4b** and 4-chlorobenzhydrol according to general procedure C. Flash chromatography afforded (50% ether/hexanes, $R_f = 0.25$) an orange oil (0.096 g, 83%). ^{1}H NMR (acetone-d_6): δ 7.35–7.09 (m, 9H), 6.61 (d, $J = 8.9$ Hz, 2H), 6.44 (d, $J = 8.9$ Hz, 2H), 5.34 (s, 1H), 4.38–4.23 (br s, 1H), 3.56 (s, 3H), 3.38 (t, $J = 5.6$ Hz, 2H), 2.96 (t, $J = 6.4$ Hz, 2H), 1.71–1.54 (m, 4H). ^{13}C NMR

(acetone-d_6): δ 151.92, 143.93, 143.03, 142.57, 132.77, 128.82, 128.74, 128.65, 127.78, 127.16, 115.00, 113.78, 82.84, 68.91, 55.35, 44.47, 27.72, 26.57. MS (CI) *m/z* 396.5 (M^+). Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.81; H, 6.62; N, 3.54. Found: C, 72.63; H, 6.60; N, 3.55.

7.7.8. 3-{[(4-Methoxyphenyl)methyl]amino}propan-1-ol (5a). This compound was prepared according to general procedure A (method 1). Flash chromatography (30% MeOH/$CHCl_3$) afforded a yellow oil (1.03 g, 72%). ^1H NMR ($CDCl_3$): δ 7.22 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 3.84–3.77 (m, 5H), 3.74 (s, 2H), 3.17–2.97 (br s, 2H), 2.90 (t, J = 5.8 Hz, 2H), 1.73 (q, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 159.28, 132.10, 129.86, 114.37, 64.75, 55.77, 53.82, 49.69, 31.24. MS (ESI) *m/z* 196.0 (M^+).

7.7.9. {3-[(4-Chlorophenyl)phenylmethoxy]propyl}[(4-methoxyphenyl)methyl]amine (5). This compound was prepared from **3a** and 4-chlorobenzhydrol according to general procedure C. Flash chromatography (5% MeOH/$CHCl_3$) afforded an orange oil (0.321 g, 79%). ^1H NMR (acetone-d_6): δ 7.31–7.07 (m, 11H), 6.74 (d, J = 8.5 Hz, 2H), 5.32 (s, 1H), 3.65 (s, 3H), 3.58 (s, 2H), 3.42 (t, J = 6.2 Hz, 2H), 2.61 (t, J = 6.6 Hz, 2H), 2.53–2.37 (br s, 1H), 1.70 (q, J = 6.6 Hz, 2H). ^{13}C NMR (acetone-d_6): δ 159.06, 143.00, 142.54, 133.24, 132.75, 129.59, 128.81, 128.72, 128.64, 127.76, 127.15, 113.83, 82.86, 67.56, 54.96, 53.30, 46.52, 30.36. MS (CI) *m/z* 396.3 (M^+). Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.81; H, 6.62; N, 3.54. Found: C, 72.52; H, 6.60; N, 3.55.

7.7.10. 2-(1,1,2,2-Tetramethyl-1-silapropoxy)ethylamine. Ethanolamine (1.0 mL, 16.6 mmol), *tert*-butyldimethylsilyl chloride (2.74 g, 18.2 mmol), and triethylamine (1.31 mL, 18.2 mmol) were dissolved in CH_2Cl_2 (50 mL) and 4-dimethylaminopyridine was added (cat.). The reaction mixture was allowed to stir for 18 h. The solution was then diluted with water (50 mL) and the organic layer was washed with water (25 mL) and brine (25 mL). The organic layer was then dried ($MgSO_4$) and concentrated. The protected ethanolamine was used without need for further purification.

7.7.11. *N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-(4-methoxy-phenyl)-acetamide (6a). TBDMS protected ethanol amine (389 mg, 2.2 mmol) was added to a solution of 3-(4-methoxyphenyl)acetic acid (400 mg, 2.2 mmol) in CH_2Cl_2 and TEA (289 mg, 2.2 mmol). Reaction mixture was cooled to 0 °C and DCC (458 mg, 2.2 mmol) was added. Reaction mixture was warmed to room temperature and allowed to stir for 5 h. Reaction mixture was then filtered to remove DCU, and solvent was removed under reduced pressure. EtOAc was then added to crude product and the mixture was cooled to 4 °C. The mixture was filtered at this temperature. Product was purified by flash chromatography using 25% EtOAc in hexanes (0.443 g, 48%). ^1H NMR ($CDCl_3$): δ 7.09–7.22 (m, 4H) 3.78 (s, 3H), 3.54–3.63 (m, 2H), 3.45–3.54 (s, 2H), 3.26–3.38 (m, 2H), 0.8 (s, 9H), 0.0 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 171.86, 161.23, 131.13, 127.28, 114.99, 62.08, 55.72, 43.46, 42.10, 26.25, 18.57, −5.05; low-resolution MS (CI) *m/e* 324 (MH^+).

7.7.12. 2-[2-(4-Methoxy-phenyl)-ethylamino]-ethanol (6b). This compound was prepared from **6a** (217 mg, 0.98 mmol) according to general procedure G. Then this compound was carried on according to general procedure B. The product was purified by flash chromatography using 20% MeOH in EtOAc. Yield: 80 mg (39%). ^1H NMR ($CDCl_3$): δ 6.77–7.19 (m, 4H), 3.69 (s, 3H), 3.46–3.58 (t, J = 5.39 Hz, 2H), 2.72–3.06 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.57, 132.32, 130.11, 114.44, 61.28, 55.75, 51.56, 51.40, 35.91; low-resolution MS (CI) *m/e* 179 $(M-OH)^+$.

7.7.13. {2-[(4-Chloro-phenyl)-phenyl-methoxy]-ethyl}-[2-(4-methoxy-phenyl)-ethyl]-amine (6). Reaction was performed according to general procedure C. Flash chromatography of the organic layer (40% MeOH/60% ethyl acetate) afforded the product (0.208 g, 57%). ^1H NMR ($CDCl_3$): δ 6.75–7.57 (m, 13H), 5.31 (s, 1H), 3.79 (s, 3H), 2.58–3.64 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 158.60, 142.14, 141.29, 133.68, 132.38, 130.18, 129.03, 128.77, 128.23, 127.44, 114.44, 83.68, 68.76, 55.74, 51.58, 49.70, 35.81; low-resolution MS (CI) *m/e* 396 (MH^+). Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.81; H, 6.62; N, 3.54 Found: C, 72.61; H, 6.71; N, 3.53.

7.7.14. 1-(4-Chloro-phenyl)-1-phenyl-pent-2-yne-1,5-diol (7a). This compound was prepared according to general procedure F using 3-butyn-1-ol (500 mg, 7.13 mmol). Flash chromatography (1:1 EtOAc/hexanes) yielded the product in 26% (511 mg); R_f = 0.32. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 4H), 7.30 (m, 5H), 5.29 (s, 1H), 3.95 (s, 1H), 3.57 (m, 2H), 2.42 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 145.6, 144.7, 133.8, 128.8, 128.2, 128.1, 126.5, 85.6, 85.0, 74.4, 61.1, 23.3; [MS] (ESI) *m/z* 269.1 $[M-OH]^+$.

7.7.15. 5-(4-Chloro-phenyl)-5-phenyl-pentan-1-ol (7b). This compound was prepared from **7a** (511 mg, 1.89 mmol) according to general procedure E. Flash chromatography (3:1 hexanes/EtOAc, R_f = 0.26) afforded the product in 100% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 9H), 4.00 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 2.84 (s, 1H), 2.16 (m, 2H), 1.67 (m, 2H), 1.41 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 145.2, 144.3, 132.4, 129.9, 129.2, 129.1, 128.5, 126.8, 63.0, 51.4, 36.1, 33.2, 24.9.

7.7.16. 5-(4-Chloro-phenyl)-5-phenyl-pentanal (7c). This compound was prepared from **7b** (250 mg, 0.910 mmol) according to general procedure D. Flash chromatography (3:1 hexanes/EtOAc, R_f = 0.52) yielded the product in 82% (204 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.32 (m, 9H), 3.94 (q, J = 7.51, 10.78 Hz, 1H), 2.45 (t, J = 7.1 Hz, 2H), 2.09 (m, 2H), 1.63 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 202.8, 144.7, 143.8, 132.5, 129.8, 129.2, 129.1, 128.4, 51.2, 44.2, 35.5, 21.2.

7.7.17. [5-(4-Chloro-phenyl)-5-phenyl-pentyl]-[2-(4-methoxy-phenyl)-ethyl]-amine (7). To a solution of **7c** (100 mg, 0.367 mmol) and 4-methoxyphenethylamine (333 mg, 2.20 mmol) in dichloromethane was added titanium tetrachloride (0.184 mL, 1 M in CH_2Cl_2) via syringe. The reaction was stirred for 18 h and then

carefully quenched with a solution of methanolic sodium cyanoborohydride (23 mg, 0.367 mmol) and stirred for an additional 15 min. The reaction was then made basic to a pH of 13 with 3 N sodium hydroxide, extracted with ethyl acetate (3×), dried using magnesium sulfate, and concentrated under reduced pressure. Flash chromatography (1:9 MeOH/EtOAc, $R_f = 0.13$) yielded the product in 19% (29 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 9H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 3.80 (s, 3H), 2.79 (dd, $J = 6$ Hz, 4H), 2.59 (t, $J = 7.3$ Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 158.5, 145.6, 132.4, 130.1, 129.7, 129.0, 128.9, 128.3, 128.2, 126.8, 126.6, 114.4, 55.7, 51.8, 51.1, 50.1, 36.1, 35.8, 30.3, 26.3, 26.2; [MS] (APCI) m/z 408.2 $[MH]^+$.

7.7.18. 1-(4-Chloro-phenyl)-1-phenyl-hex-2-yne-1,6-diol (8a). This compound was prepared according to general procedure F using 4-pentyn-1-ol (500 mg, 5.94 mmol). Flash chromatography (1:1 EtOAc/hexanes, $R_f = 0.44$) yielded the product in 33% (562 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 4H), 7.27 (m, 5H), 3.60 (t, $J = 6.1$, 2H), 2.36 (t, $J = 6.9$, 2H), 1.69 (t, $J = 6.5$, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 145.8, 144.9, 133.7, 128.1, 126.5, 87.9, 84.0, 74.3, 61.7, 31.4, 16.0; [MS] (ESI) m/z 283.2 $[M-OH]^+$.

7.7.19. 6-(4-Chloro-phenyl)-6-phenyl-hexan-1-ol (8b). This compound was prepared from **8a** (562 mg, 1.97 mmol) according to general procedure E. Flash chromatography (3:1 hexanes/EtOAc, $R_f = 0.31$) afforded the product in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 9H), 3.60 (t, $J = 6.4$ Hz, 2H), 2.09 (m, 2H), 1.54 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 145.2, 144.3, 132.3, 129.8, 129.1, 129.0, 128.4, 126.9, 126.6, 63.3, 51.9, 36.3, 33.1, 28.4, 26.3.

7.7.20. 6-(4-Chloro-phenyl)-6-phenyl-hexanal (8c). This compound was prepared from **8b** (250 mg, 0.866 mmol) according to general procedure D. Flash chromatography (3:1 hexanes/EtOAc, $R_f = 0.58$) yielded the product in 73% (181 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.32 (m, 9H), 3.94 (m, 1H), 2.45 (t, $J = 7.1$ Hz, 2H), 2.09 (m, 2H), 1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 202.6, 145.3, 143.8, 129.8, 129.2, 129.1, 128.4, 128.3, 127.1, 126.8, 51.2, 44.2, 35.5, 21.2.

7.7.21. [6-(4-Chloro-phenyl)-6-phenyl-hexyl]-(4-methoxy-benzyl)-amine (8). This compound was prepared from **8c** and 4-methoxybenzylamine according to general procedure A (method 3). Flash chromatography (1:9 MeOH/EtOAc, $R_f = 0.33$) yielded the product in 50% (50 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (m, 9H), 7.07 (m, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 4.80 (s, 1H), 3.80 (t, $J = 7.9$ Hz, 1H), 3.69 (s, 3H), 3.57 (s, 2H), 2.43 (t, $J = 7.4$ Hz, 2H), 1.95 (m, 2H), 1.40 (m, 2H), 1.24 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 159.5, 145.8, 131.3, 129.9, 128.5, 128.4, 127.9, 126.1, 113.9, 54.7, 52.8, 51.6, 50.9, 35.7, 29.1, 28.0, 27.3; [MS] (ESI) m/z 408.1 $[MH]^+$.

7.7.22. 4-(4-Methoxy-benzylamino)-butan-1-ol (9a). This compound was prepared according to general procedure A (method 1). Flash chromatography (30% MeOH/$CHCl_3$) afforded a yellow oil (0.104 g, 39%). ^{1}H NMR ($CDCl_3$): δ 7.21 (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 3.83 (br s, 2H), 3.77 (s, 3H), 3.70 (s, 2H), 3.56 (t, $J = 5.0$ Hz, 2H), 2.66 (t, $J = 5.4$ Hz, 2H), 1.73–1.49 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.34, 131.84, 130.04, 114.43, 63.07, 55.74, 53.70, 49.60, 32.92, 29.06. MS (ESI) m/z 210.1 (M^+).

7.7.23. {4-[(4-Chloro-phenyl)-phenyl-methoxy]-butyl}-(4-methoxy-benzyl)-amine (9). This compound was prepared from **9a** and 4-chlorobenzhydrol according to general procedure C. Flash chromatography (5% MeOH/$CHCl_3$) afforded orange oil (0.168 g, 83%). ^{1}H NMR (acetone-d_6): δ 7.34–7.08 (m, 11H), 6.74 (d, $J = 8.5$ Hz, 2H), 5.31 (s, 1H), 3.65 (s, 3H), 3.56 (s, 2H), 3.33 (t, $J = 6.2$ Hz, 2H), 2.46 (t, $J = 6.9$ Hz, 2H), 1.65–1.41 (m, 4H). ^{13}C NMR (acetone-d_6): δ 158.99, 143.11, 142.63, 133.72, 132.74, 129.44, 128.81, 128.72, 128.64, 127.74, 127.15, 113.82, 82.81, 69.10, 54.96, 53.40, 49.17, 27.94, 27.14. MS (CI) m/z 410.3 (M^+). Anal. Calcd for $C_{25}H_{28}ClNO_2$: C, 73.25; H, 6.88; N, 3.42. Found: C, 73.23; H, 6.84; N, 3.43.

7.7.24. 1-(4-Chloro-phenyl)-1-phenyl-hept-2-yne-1,7-diol (10a). This compound was prepared according to general procedure F. 5-Hexyn-1-ol (500 mg, 5.09 mmol). Flash chromatography (1:1 EtOAc/hexanes, $R_f = 0.39$) yielded the product in 37% (559 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (m, 4H), 7.27 (m, 5H), 3.48 (m, 2H), 2.31 (m, 2H), 1.57 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 146.0, 145.1, 133.6, 128.7, 128.1, 126.5, 88.3, 83.9, 74.3, 62.3, 32.0, 25.4, 19.2; [MS] (ESI) m/z 315.1 $[MH]^+$; 297.2 $[M-OH]^+$.

7.7.25. 7-(4-Chloro-phenyl)-7-phenyl-heptan-1-ol (10b). This compound was prepared from **10a** (559 mg, 1.87 mmol) according to general procedure D. Flash chromatography (3:1 hexanes/EtOAc, $R_f = 0.32$) afforded the product in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (m, 9H), 3.58 (m, 2H), 2.06 (m, 2H), 1.50 (m, 2H), 1.29 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 129.7, 129.0, 128.9, 128.4, 128.3, 63.4, 51.2, 36.1, 33.2. 29.9, 28.4, 26.1; [MS] (APCI) m/z 303.0 $[MH]^+$.

7.7.26. 7-(4-Chloro-phenyl)-7-phenyl-heptanal (10c). This compound was prepared from **10b** (250 mg, 0.826 mmol) according to general procedure D. Flash chromatography (3:1 hexanes/EtOAc, $R_f = 0.57$) yielded the product in 65% (160 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.24 (m, 9H), 3.90 (q, 1H), 2.37 (m, 2H), 2.03 (m, 2H), 1.60 (m, 2H), 1.25 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 203.1, 145.1, 144.2, 132.3, 129.7, 129.2, 129.0, 128.4, 128.3, 51.1, 44.3, 36.0, 35.9, 29.9, 29.6, 28.2, 22.4; [MS] (APCI) m/z 301.0 $[MH]^+$.

7.7.27. 7-(4-Chloro-phenyl)-7-phenyl-heptanoic acid (10d). An aqueous solution of sodium hypochlorite (32 mg, 0.351 mmol) and phosphate monobasic buffer (48 mg, 0.351 mmol) was added to a solution of **10c** (81 mg, 0.270 mmol) in *t*-butanol and 2-methyl-2-butene

(solvent ratio 1:2, respectively). The reaction mixture was allowed to stir at room temperature for 1 h, then an additional equivalent of sodium hypochlorite and monobasic phosphate buffer solution in water was added. After an additional hour the solvent was removed under reduced pressure and the residue was diluted with ether. Next the solution was acidified by the dropwise addition of 10% hydrochloric acid. The organic layer was washed with brine (2×), back extracted with water (2×), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (1:3 EtOAc/hexanes, $R_f = 0.68$) provided the product in 72% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2 (m, 9H), 3.92 (s, 1H), 2.34 (t, $J = 6$ Hz, 2H), 2.08 (m, 2H), 1.64 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 180.4, 145.5, 144.9, 132.9, 129.0, 128.8, 128.5, 128.2, 127.4, 50.5, 35.2, 34.5, 29.8, 25.1, 22.8; [MS] (APCI) *m/z* 282 $[M-Cl]^+$.

7.7.28. 7-(4-Chloro-phenyl)-7-phenyl-heptanoic acid (4-methoxy-phenyl)-amide (10e). To a solution of **10d** (62 mg, 0.196 mmol) in dichloromethane was added diisopropylethylamine (51 mg, 0.391 mmol) followed by PyBOP (102 mg, 0.196 mmol). The reaction mixture was allowed to stir for 10 min at room temperature before a solution of 4-anisidine (24 mg, 0.196 mmol) in dichloromethane was added. The reaction was then stirred for 30 min and then diluted with CH_2Cl_2, extracted with a saturated solution of sodium bicarbonate in water (3×), then 10% HCl (3×), and then washed with brine (2×). The organic layer was then concentrated under reduced pressure. Flash chromatography (1:1 EtOAc/hexanes, $R_f = 0.73$) yielded the product in 76% yield (62 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, $J = 8.9$ Hz, 2H), 7.25 (m, 9H), 6.84 (d, $J = 8.9$ Hz, 2H), 3.78 (s, 3H), 2.26 (t, $J = 7.4$ Hz, 2H), 2.03 (m, 2H), 1.66 (p, $J = 7.1$, 7.5 Hz, 2H), 1.29 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 171.7, 156.9, 145.1, 144.2, 131.6, 129.7, 129.0, 128.9, 128.4, 128.3, 127.3, 122.3, 114.6, 56.0, 51.2, 37.9, 36.0, 35.9, 29.7, 28.2, 26.0; [MS] (APCI) *m/z* 422.2 $[MH]^+$.

7.7.29. [7-(4-Chloro-phenyl)-7-phenyl-heptyl]-(4-methoxy-phenyl)-amine (10). $LiAlH_4$ (17 mg, 0.441 mmol) was added to THF. Reaction mixture was allowed to stir until a homogenous slurry was formed. Reaction was then cooled to 0 °C and a solution of **10e** (62 mg, 0.147 mmol) in tetrahydrofuran (THF) was added dropwise to reaction mixture. Reaction was allowed to warm to room temperature and to stir overnight. Next, reaction was quenched with sodium hydroxide (1.5 mL, 3 M solution). Mixture was filtered to remove any aluminum salts. Solid was washed with methanol to remove any residual organics, and methanol was removed under reduced pressure. The product was purified by flash chromatography (1:3 EtOAc/hexanes, $R_f = 0.61$). Yield: 30 mg, 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 9H), 6.80 (d, $J = 8.9$ Hz, 2H), 6.58 (d, $J = 8.9$ Hz, 2H), 3.88 (t, $J = 8.9$ Hz, 1H), 3.76 (s, 3H), 3.04 (t, $J = 6.9$ Hz, 2H), 2.06 (q, $J = 7.7$, 7.3 Hz, 2H), 1.57 (m, 2H), 1.34 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 152.5, 145.8, 143.3, 130.4, 129.7, 129.0, 128.9, 128.6, 128.4, 126.6, 115.4, 114.6, 56.4, 51.9, 45.5, 36.2, 30.1, 30.0, 28.5, 27.5; [MS] (ESI) *m/z* 408.3 $[M-H_2O]^+$.

7.7.30. 3-(4-Methoxyphenyl)-*N*-[2-(1,1,2,2-tetramethyl-1-silapropoxy)ethyl]propanamide (11a). TBDMS protected ethanol amine (389 mg, 2.2 mmol) was added to a solution of 3-(4-methoxyphenyl)propionic acid (400 mg, 2.2 mmol) in CH_2Cl_2 and TEA (289 mg, 2.2 mmol). Reaction mixture was cooled to 0 °C and DCC (458 mg, 2.2 mmol) was added at this temperature. Reaction mixture was warmed to room temperature and allowed to stir for 5 h. The solution was then filtered to remove DCU, and solvent was removed under reduced pressure. EtOAc was then added to crude product and mixture was cooled to 4 °C. Then, mixture was filtered at this temperature to remove any residual DCU. Product was purified by flash chromatography (1:3 EtOAc/hexanes, $R_f = 0.16$). Yield: 314 mg (42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, $J = 8.9$ Hz, 2H), 6.81 (d, $J = 8.9$ Hz, 2H), 3.77 (s, 3H), 3.62 (t, $J = 5.4$ Hz, 2H), 3.34 (q, $J = 5.4$ Hz, 2H), 2.90 (t, $J = 7.3$ Hz, 2H), 2.44 (t, $J = 7.3$ Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 172.5, 158.5, 133.4, 129.7, 114.4, 62.4, 55.7, 42.1, 39.3, 31.3, 26.4, 18.8, −4.9; MS (APCI) *m/z* 338.1 $[MH]^+$.

7.7.31. *N*-(2-Hydroxyethyl)-3-(4-methoxyphenyl)propanamide (11b). This compound was prepared from **11a** (314 mg, 0.93 mmol) according to general procedure G. Purification was not needed and product was yielded in quantitative amounts. Yield: 217 mg (100%). $R_f = 0.47$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J = 8.8$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 3.74 (s, 3H), 3.61 (t, $J = 4.6$ Hz, 2H), 3.32 (q, $J = 5.4$ Hz, 2H), 3.17 (m, 1H), 2.86 (t, $J = 7.3$ Hz, 2H), 2.45 (t, $J = 7.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 174.0, 158.5, 133.4, 129.8, 114.4, 62.3, 55.8, 43.0, 39.0, 31.4; MS (APCI) *m/z* 224.1 $[MH]^+$.

7.7.32. 2-[3-(4-Methoxy-phenyl)-propylamino]-ethanol (11c). This compound was prepared from **11b** according to General Procedure B. The product was purified by flash chromatography (1:4 MeOH/EtOAc, $R_f = 0.11$). Yield: 80 mg (39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.5$ Hz, 2H); 3.78 (s, 3H), 3.67 (t, 2H), 2.80 (t, 2H), 2.70 (t, 2H), 2.60 (t, 2H), 1.83 (p, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 134.0, 129.7, 114.4, 60.4, 55.8, 51.3, 49.1, 32.9, 31.4; MS (APCI) *m/z* 210.3 $[MH]^+$.

7.7.33. {2-[(4-Chlorophenyl)phenylmethoxy]ethyl}[3-(4-methoxyphenyl)propyl]amine (11). This compound was prepared from **11c** according to general procedure C. The product was semi-purified by flash chromatography using 10% MeOH in EtOAc. Product was totally purified with a Uniplate 1000 μm alumina prep plate using 25% EtOAc in hexanes ($R_f = 0.40$). Yield: 27 mg (17%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.16–7.28 (m, 9H), 7.01 (d, 2H), 6.73 (d, 2H), 5.32 (s, 1H), 3.67 (s, 3H), 3.48 (t, $J = 5.3$ Hz, 2H), 2.72 (t, $J = 5.3$ Hz, 2H), 2.49–2.50 (m, 4H), 1.71 (p, $J = 7.5$ Hz, 2H). ^{13}C NMR

($CDCl_3$, 300 MHz) ppm: 158.4, 142.3, 141.7, 134.1, 133.2, 129.3, 128.6, 128.5, 127.8, 127.1, 113.9, 83.5, 67.9, 54.7, 48.8, 32.6, 31.3; MS (ESI) *m/z* 410.2 $[MH]^+$.

7.7.34. 1-(4-Benzyloxy-1-phenyl-but-1-enyl)-4-chlorobenzene (12a). To a solution of (3-benzyloxypropyl)triphenylphosphonium bromide (680 mg, 1.38 mmol) in anhydrous THF under a nitrogen atmosphere was added potassium *t*-butoxide (171 mg, 1.52 mmol). The solution was heated to 70 °C for 3 h and then cooled to an ambient temperature. 4-Chlorobenzophenone (300 mg, 1.38 mmol) was added to the reaction mixture and the solution was then reheated to 70 °C for 6 h. After cooling to room temperature the reaction was quenched by pouring into water (200 mL). The product was extracted into EtOAc (3 × 60 mL). The organic layer was washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography yielded the product (1.388 g, 98%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.7 (m, 4H), 7.4 (m, 5H), 7.3 (m, 5H), 4.4 (s, 3H), 3.5 (t, 2H), 2.3 (m, 2H), 1.9 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 138.8, 134.2, 132.9, 132.2, 131.3, 131.2, 129.2, 129.1, 128.9 128.1, 73.3, 70.6, 70.5, 27.5, 26.5, 22.6; MS (APCI) *m/z* 351.1 $[MH_3]^+$.

7.7.35. 4-(4-Chloro-phenyl)-4-phenyl-butan-1-ol (12b). This compound was prepared from **12a** (484 mg, 1.39 mmol) according to general procedure E. Flash chromatography (10% MeOH/EtOAc, R_f = 0.5) afforded the product (318 mg, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.34 (m, 5H), 4.8 (s, 1H), 3.58 (t, J = 5.8 Hz, 2H), 2.34 (m, 2H), 1.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 133.5, 132.3, 131.2, 131.1, 129.2, 129.1, 62.6, 62.4, 27.5, 26.5, 25.4; MS (APCI) *m/z* 261.2 $[MH]^+$.

To a solution of **12b** (179 mg, 0.767 mmol) in CH_2Cl_2 was added the Dess–Martin periodinate (325 mg, 0.767 mmol). The reaction was allowed to stir for 1 h. It was then quenched with sodium metabisulfate and extracted with dichloromethane (3 × 20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography yielded the product (179 mg, 90%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.7 (m, 4H), 7.4 (m, 5H), 2.85 (m, 2H), 2.5 (m, 2H).

7.7.36. 3-(4-Methoxy-phenyl)-propylamine (12c). $LiAlH_4$ (262 mg, 6.91 mmol) was added to THF. Reaction mixture was allowed to stir until a homogenous slurry was formed. Aluminum chloride (921 mg, 6.91 mmol) was then added to the slurry. Reaction was then cooled to 0 °C and a solution of 4-methoxycinnamon nitrile (1 g, 6.28 mmol) in tetrahydrofuran was added dropwise to the reaction mixture. Reaction was allowed to warm to room temperature and to stir overnight. Next, reaction was quenched with sodium hydroxide. The mixture was filtered to remove any aluminum salts. Solid was washed with methanol to remove any residual organics, and methanol was removed under reduced pressure. The product was purified by flash chromatography (40% MeOH/CHlL$_3$, R_f = 0.71). Yield: 760 mg (37%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.4 (m, 1H), 6.16 (m, 1H), 3.76 (s, 3H), 3.41 (d, J = 5.8 Hz, 2H), 1.56 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 158.4, 134.4, 129.4, 113.9, 54.8, 41.2, 35.1, 32.4; MS (ESI) *m/z* 147.2 $[MH-NH_3]^+$.

To a solution of **12c** (198 mg, 1.21 mmol) in ethanol under nitrogen was added a catalytic amount of 10% palladium hydroxide on carbon. The reaction mixture was then placed under a hydrogen atmosphere for 18 h. The reaction was then filtered through Celite to remove palladium and then concentrated under reduced pressure. Residue was diluted with $CHCl_3$ and extracted with 10% HCl. The aqueous solution was back extracted with $CHCl_3$, then basified using solid NaOH to a pH of 13. Aqueous layer was then extracted with $CHCl_3$. Organic layer was dried using anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. No further purification was needed. Product was a pale yellow oil (200 mg 100%). R_f = 0.12. ^1H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.72 (s, 3H), 2.66 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 7.7 Hz, 2H), 1.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 158.2, 134.7, 129.7, 129.4, 114.2, 55.7, 42.2, 36.2, 32.8; MS (APCI) *m/z* 166.1 $[MH]^+$.

7.7.37. [4-(4-Chloro-phenyl)-4-phenyl-butyl]-[3-(4-methoxy-phenyl)-propyl]-amine (12). This compound was prepared from **12b** (104 mg, 0.404 mmol) and **12c** (200 mg, 1.21 mmol) according to general procedure A (method 3). Flash chromatography (10% MeOH in $CHCl_3$, R_f = 0.16) yielded the product. ^{13}C NMR ($CDCl_3$, 300 MHz) ppm: 158.3, 133.8, 133.3, 132.5, 132.0, 131.3, 131.2, 129.8, 129.4, 129.2, 114.3, 55.7, 50.1, 49.9, 49.0, 32.8, 30.8, 28.4, 27.4, 21.4; MS (APCI) *m/z* 408.2 $[MH]^+$.

7.7.38. 4-(4-Methoxy-phenyl)-butyraldehyde (13a). To a solution of 1-[4-methoxyphenyl]-4-butanol (300 mg, 1.66 mmol) in CH_2Cl_2 was added Dess–Martin periodinate (706 mg, 1.66 mmol). The reaction was allowed to stir for 1 h. It was then quenched with sodium metabisulfate and extracted with dichloromethane (3 × 20), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography yielded the product (257 mg, 87%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.76 (s, 3H), 2.58 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 1.90 (p, J = 7.5 Hz, 2H).

7.7.39. 3-(4-Chloro-phenyl)-3-phenyl-acrylonitrile (13b). To 4-chlorobenzophenone (3.307 g, 15.3 mmol) at 100 °C was added (triphenylphosphoranylidene)acetonitrile (4.6 g, 15.3 mmol) and the reaction was allowed to stir for 60 h. The reaction was then quenched by adding

directly to 100 mL of water. The mixture was then extracted with EtOAc, the organic layer was extracted with brine dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (10% EtOAc/hexanes, $R_f = 0.35$) yielded the desired product (1.416 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 10H), 5.72 (d, $J = 6.9$ Hz, 1H); [MS] (APCI) m/z 240.3 $[MH]^+$.

7.7.40. 3-(4-Chloro-phenyl)-3-phenyl-allylamine (13c). $LiAlH_4$ (87 mg, 2.29 mmol) was added to THF. Reaction mixture was allowed to stir until a homogenous slurry was formed. Aluminum chloride (306 mg, 2.29 mmol) was then added to the slurry. Reaction was then cooled to 0 °C and a solution of **13b** (500 mg, 2.09 mmol) in tetrahydrofuran was added dropwise to reaction mixture. Reaction was allowed to warm to room temperature, and to stir overnight. Next, the reaction was quenched with sodium hydroxide. The mixture was filtered to remove any aluminum salts. Solid was washed with methanol to remove any residual organics, and methanol was removed under reduced pressure. The product was purified by flash chromatography (10% MeOH in $CHCl_3$, $R_f = 0.32$). Yield: 189 mg (37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.21 (m, 9H), 6.17 (q, $J = 6.6$ Hz, 1H), 3.51 (m, 2H).

7.7.41. [3-(4-Chloro-phenyl)-3-phenyl-allyl]-[4-(4-methoxy-phenyl)-butyl]-amine (13d). This compound was prepared from **13a** (100 mg, 5.54 mmol) and **13c** (405 mg, 1.66 mmol) according to general procedure A (method 3). Flash chromatography (10% MeOH in $CHCl_3$, $R_f = 0.26$) yielded the product in 18% (41 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (m, 11H), 6.82 (d, $J = 7.5$ Hz, 2H), 6.18 (q, $J = 5.4$ Hz, 1H), 3.31 (dd, $J = 2.9$, 3.9 Hz, 2H), 2.57 (m, 4H), 1.57 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 158.2, 139.6, 134.9, 133.7, 133.7, 131.7, 130.2, 129.8, 129.2, 128.9, 128.8, 128.0, 114.2, 55.8, 49.8, 49.7, 48.9, 35.3; MS (APCI) m/z 406.1 $[MH]^+$, 408.3 $[MH_3]^+$.

7.7.42. [3-(4-Chloro-phenyl)-3-phenyl-propyl]-[4-(4-methoxy-phenyl)-butyl]-amine (13). To a solution of **13d** (60 mg, 0.148 mmol) in ethanol under nitrogen was added a catalytic amount of 10% palladium hydroxide on carbon. The reaction mixture was then placed under a hydrogen atmosphere for 18 h. The reaction was then filtered through Celite to remove palladium and then concentrated under reduced pressure. Flash chromatography (10% MeOH/$CHCl_3$) afforded the product in 53% yield (32 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (m, 9H), 7.01 (d, $J = 8.3$ Hz, 2H), 6.80 (d, $J = 8.5$ Hz, 2H), 4.03 (t, $J = 7.9$ Hz, 1H), 3.77 (s, 3H), 2.75 (m, 2H), 2.44 (t, $J = 7.6$ Hz, 2H), 1.50 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 158.4, 143.8, 134.2, 129.7, 129.2, 128.7, 128.2, 127.1, 127.0, 126.4, 114.3, 55.8, 49.2, 48.3, 47.1, 34.8, 32.5, 29.3, 26.5; MS (APCI) m/z 374.4 $[MH-Cl]^+$.

7.7.43. 5-(4-Methoxy-phenyl)-5-oxo-pentanoic acid (14a). To a solution of anisol (solvent) and gluteric anhydride (2.5 g, 21.9 mmol) under neat conditions was added aluminum chloride (6.427 g, 48.2 mmol). The reaction mixture was stirred at 0 °C for 3 h and then was carefully quenched by the dropwise addition of water. Reaction mixture was then extracted with sodium bicarbonate (3×20 mL). Aqueous layer was then acidified with concentrated HCl and extracted with EtOAc. Organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Product was yielded in 50% (2.44 g, 50% yield); [MS] (APCI) m/z 223.0 $[MH]^+$, 205/0 $[MH-OH]^+$.

7.7.44. 5-(4-Methoxy-phenyl)-pentanoic acid (14b). To a solution of **14a** (300 mg, 1.35 mmol) in 3:1 ethanol/acetic acid was added 10% palladium on carbon and the reaction was placed under a hydrogen atmosphere. The reaction was allowed to stir for 4 h and then it was filtered through a Celite plug to remove all palladium. Next it was concentrated under reduced pressure to produce a white grainular solid (yield 266 mg, 95%) $R_f = 0.77$. ^{1}H NMR (300 MHz, CD_3OD): δ 7.0 (d, 2H), 6.7 (d, 2H), 3.7 (s, 3H), 2.5 (m, 2H), 2.2 (m, 2H), 1.55 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 176.7, 158.3, 134.5, 129.3, 113.8, 54.7, 34.7, 33.9, 31.4, 24.7; [MS] (APCI) m/z 191.0 $[MH-OH]^+$.

7.7.45. 5-(4-Methoxy-phenyl)-pentanoic acid methoxy-methyl-amide (14c). To a solution of **14b** (1 g, 4.80 mmol) in dichloromethane was added diisopropylethylamine (1.862 g, 14.4 mmol) followed by PyBOP (2.498 g, 4.80 mmol). The reaction mixture was allowed to stir for 10 min at room temperature before a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (468 mg, 4.80 mmol) in dichloromethane was added. The reaction was then stirred overnight. It was then diluted with CH_2Cl_2, extracted with a saturated aqueous solution of sodium bicarbonate (3×20 mL), 10% HCl (3×20 mL) then washed with brine (2×20 mL). The organic layer was then concentrated under reduced pressure. Flash chromatography (1:1 EtOAc/hexanes, $R_f = 0.72$) yielded the product in 78% yield (940 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1 (d, 2H), 6.8 (d, 2H), 3.76 (s, 3H), 3.65 (s, 3H), 3.15 (s, 3H), 2.56 (t, 2H), 2.43 (m, 2H), 1.65 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 175.8, 158.2, 134.9, 129.8, 114.2, 61.7, 55.7, 35.3, 32.7, 32.2, 31.9, 24.8.

7.7.46. 5-(4-Methoxy-phenyl)-pentanal (14d). To a solution of **14c** (400 mg, 1.59 mmol) in THF at −78 °C was added powdered lithium aluminum hydride (72 mg, 1.91 mmol). Stirring was continued for 30 min and then the reaction was poured into a 5% ethanolic HCl solution at 0 °C. Mixture was extracted with EtOAc and then back extracted with brine. Organic layer is then dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography (10% EtOAc/hexane, $R_f = 0.5$) yielded the product in 53% (161 mg).

7.7.47. 2-Amino-1-(4-chloro-phenyl)-1-phenyl-ethanol (14e). To a solution of 4-chlorobenzophenone (1 g, 4.62 mmol) in a minimal amount of CH_2Cl_2 was added trimethylsilylcyanide (1.007 g, 10.2 mmol) dropwise. Reaction mixture was stirred for 30 min and then cooled to 0 °C and a catalytic amount of both 18-crown-6 and

potassium cyanide were added to the reaction mixture. Reaction mixture was allowed to slowly warm to room temperature over 2 h time, and it was allowed to stir overnight. Next the CH_2Cl_2 was evaporated under reduced pressure, and the resulting residue was diluted in THF (3 mL). The reaction mixture was cooled to 0 °C and 10% HCl was added. Then the mixture was warmed to room temperature and stirred for 2 h. Then the mixture was combined with water and extracted with EtOAc. The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Product was carried on to the next reaction without further purification.

$LiAlH_4$ (210 mg, 5.54 mmol) was added to THF. Reaction mixture was allowed to stir until a homogenous slurry was formed. Reaction was then cooled to 0 °C and a solution of the nitrile in tetrahydrofuran was added dropwise to the reaction mixture. Reaction was allowed to warm to room temperature and to stir overnight. Next, reaction was quenched with sodium hydroxide. Mixture was filtered to remove any aluminum salts. Solid was washed with methanol to remove any residual organics, and methanol was removed under reduced pressure. The product was purified by flash chromatography (10% MeOH in EtOAc, $R_f = 0.43$) (169 mg, 15%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 9H), 3.4 (q, 2H), 2.5 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 145.4, 144.5, 133.4, 128.9, 128.2, 127.7, 126.6, 77.2, 51.3; [MS] (ESI) *m/z* 230.2 $[M-H_2O]^+$.

7.7.48. [2-(4-Chloro-phenyl)-2-phenyl-ethyl]-[5-(4-methoxy-phenyl)-pentyl]-amine (14). This compound was prepared from **14d** (161 mg, 0.837 mmol) and **14e** (601 mg, 2.51 mmol) according to general procedure A (method 3). Flash chromatography (EtOAc, $R_f = 0.72$) yielded the product in 64% (226 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 4H), 7.35 (m, 5H), 7.12 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 3.81 (s, 3H), 3.30 (q, $J = 11.9$, 12.9 Hz, 2H), 2.65 (t, $J = 7.0$ Hz, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.61 (m, 2H), 1.48 (m, 2H), 1.35 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 158.3, 145.9, 145.1, 135.1, 133.3, 129.8, 128.9, 128.1, 127.6, 126.5, 126.3, 114.3, 76.3, 59.1, 55.8, 50.3, 35.4, 32.0, 30.5, 27.2; [MS] (APCI) *m/z* 424.1 $[MH]^+$, 406.3 $[MH-H_2O]^+$.

To a solution of the product of the prior reaction (107 mg, 0.452 mmol) in ethanol under nitrogen was added a catalytic amount of 10% palladium on carbon and formic acid. The reaction mixture was then placed under a hydrogen atmosphere for 18 h. Reaction was then filtered through Celite to remove palladium and then concentrated under reduced pressure. Flash chromatography (10% MeOH/EtOAc, $R_f = 0.43$) afforded the product in 80% yield (82 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 4H), 7.34 (m, 5H), 7.08, (d, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 4.13 (m, 1H), 3.80 (s, 3H), 3.40 (s, 2H), 2.65 (t, $J = 7.2$ Hz, 2H), 2.54 (t, $J = 7.6$ Hz, 2H), 1.55 (m, 4H), 1.28 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 158.2, 145.9, 135.0, 129.8, 128.8, 127.6, 126.5, 126.2, 114.2, 76.5, 58.7, 55.7, 50.1, 35.4, 31.9, 29.6, 27.0.

7.7.49. 6-(4-Methoxy-phenyl)-hex-5-yn-1-ol (15a). A solution of iodoanisole (500 mg, 2.14 mmol), diisopropyl ethyl amine (1.104 g, 8.55 mmol), and 5-hexyn-1-ol (231 mg, 2.35 mmol) with catalytic amounts of triphenylphosphine and copper iodide in tetrahydrofuran (30 mL) was degassed with nitrogen for 1 h before a catalytic amount of palladium bis(dibenzylideneacetone) was added to the reaction mixture. The flask was then sealed with parafilm and the reaction was stirred for 12 h before it was diluted with ethyl acetate and extracted with ammonium chloride (3×20 mL) and then brine (2×20 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. Flash chromatography afforded the product in 100 percent yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.7$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 3.77 (s, 3H), 3.68 (t, $J = 6.0$ Hz, 2H), 2.42 (t, $J = 6.6$ Hz, 2H), 1.69 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 159.5, 133.4, 116.6, 114.3, 88.8, 81.2, 62.9, 55.7, 32.4, 25.6, 19.7; MS (APCI) *m/z* 205.1 $[MH]^+$.

7.7.50. 6-(4-Methoxy-phenyl)-hexan-1-ol (15b). This compound was prepared from **15a** (437 mg, 2.14 mmol) according to general procedure E. Flash chromatography afforded the product in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, $J = 7.9$ Hz, 2H), 6.83 (d, $J = 7.9$ Hz, 2H), 3.79 (s, 3H), 3.62 (t, $J = 6.2$ Hz, 2H), 2.56 (t, $J = 7.1$ Hz, 2H), 1.85 (s, 1H), 1.57 (m, 4H), 1.37 (m, 4H). ^{13}C (300 MHz, $CDCl_3$) ppm: 158.1, 135.4, 129.7, 114.2, 63.4, 55.8, 35.4, 33.2, 33.1, 29.5, 26.1.

7.7.51. 6-(4-Methoxy-phenyl)-hexanal (15c). This compound was prepared from **15b** (455 mg, 2.18 mmol) according to general procedure D. Flash chromatography yielded the product in 84%. $R_f = 0.2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.09 (d, $J = 8.1$ Hz, 2H), 6.82 (d, $J = 8.9$ Hz, 2H), 3.79 (s, 3H), 2.56 (t, $J = 7.4$ Hz, 2H), 2.42 (t, $J = 6.9$ Hz, 2H), 1.63 (m, 4H), 1.45 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) ppm: 203.2, 158.2, 135.0, 129.7, 114.2, 55.7, 44.3, 35.3, 31.9, 29.2, 22.4.

7.7.52. [(4-Chloro-phenyl)-phenyl-methyl]-[6-(4-methoxy-phenyl)-hexyl]-amine (15). To a solution of **15c** (200 mg, 0.97 mmol), 4-chlorobenzhydrylamine hydrochloride (739 mg, 2.91 mmol), and triethylamine (392 mg, 3.88 mmol) in dichloromethane was added titanium tetrachloride (92 mg, 0.485 mmol) via syringe. The reaction was stirred for 18 h and then carefully quenched with a solution of methanolic sodium cyanoborohydride (244 mg, 3.88 mmol) and stirred for an additional 15 min. The reaction was then made basic to a pH of 13 with 3 N sodium hydroxide, extracted with ethyl acetate (3×20 mL), dried using magnesium sulfate, and concentrated under reduced pressure. Flash chromatography yielded the product in 75% (298 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 9H), 7.11 (d, $J = 7.9$ Hz, 2H), 6.84 (d, $J = 8.1$ Hz, 2H), 4.80 (s, 1H), 3.80 (s, 3H), 2.56 (t, $J = 7.0$ Hz, 4H), 1.51 (m, 4H), 1.34 (m, 4H). ^{13}C (300 MHz, $CDCl_3$) ppm: 158.2, 144.5, 143.4, 135.4, 133.1, 129.8, 129.2, 129.1, 127.7,

114.2, 67.5, 55.7, 48.7, 35.3, 32.2, 30.7, 29.7, 27.7; [MS] (ESI) *m*/*z* 408.1 $[MH]^+$.

7.7.53. [2-(Aminomethyl)phenyl]methan-1-ol (16a). To 7.6 mL of THF was added $LiAlH_4$ (0.434 g, 11.4 mmol), which was allowed to stir until the dark gray color persisted. The slurry was cooled to 0 °C, and 2-cyanobenzaldehyde (0.500 g, 3.81 mmol), dissolved in a minimum volume of THF, was added dropwise via syringe. After 12 h, 10% HCl was added dropwise to quench. Enough 10% HCl was added to obtain a pH of 2–3. Then the mixture was partitioned between ether and an aqueous layer. Using 3 N NaOH, the acidic aqueous layer was made basic (pH 9). The basic aqueous layer was extracted four times with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a dark brown oil (0.433 g, 83%). ^1H NMR ($CDCl_3$): δ 7.38–7.16 (m, 4H), 4.63 (s, 2H), 3.97 (s, 2H), 3.90–3.64 (br s, 3H). ^{13}C NMR ($CDCl_3$): δ 141.97, 140.51, 130.63, 130.22, 128.78, 128.56, 65.09, 45.92. MS (CI) *m*/*z* 138.0 (M^+).

7.7.54. [2-({[(4-Methoxyphenyl)methyl]amino}methyl)phenyl]methan-1-ol (16b). This compound was prepared from **16a** according to general procedure A (method 3). Flash chromatography (2.5% MeOH/chloroform) afforded a dark orange oil (0.062 g, 66%). ^1H NMR ($CDCl_3$): δ 7.40–7.17 (m, 6H), 6.86 (d, J = 8.9 Hz, 2H), 4.63 (s, 2H), 4.09 (br s, 2H), 3.90 (s, 3H), 3.79 (s, 2H), 3.76 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 159.48, 142.35, 138.30, 131.09, 131.00, 130.61, 130.17, 128.98, 128.40, 114.53, 65.34, 55.78, 53.11, 52.92. MS (CI) *m*/*z* 258.2 (M^+).

7.7.55. [(2-{[(4-Chlorophenyl)phenylmethoxy]methyl}phenyl)methyl][(4-methoxyphenyl)methyl]amine (16). This compound was prepared from **16b** and 4-chlorobenzhydrol according to general procedure C. Flash chromatography (75% ethyl acetate/hexanes) afforded dark orange oil (0.073 g, 66%). ^1H NMR (acetone-d_6): δ 7.36–7.01 (m, 15H), 6.73 (d, J = 8.9 Hz, 2H), 5.41 (s, 1H), 4.52 (s, 2H), 3.66 (s, 3H), 3.63 (s, 2H), 3.53 (s, 2H). ^{13}C NMR (acetone-d_6): δ 159.05, 142.65, 142.18, 139.73, 137.11, 133.29, 132.90, 129.60, 129.52, 129.29, 128.90, 128.83, 128.74, 127.96, 127.91, 127.27, 127.11, 113.87, 82.53, 68.90, 54.96, 53.02, 50.62. MS (CI) *m*/*z* 458.5 (M^+). Anal. Calcd for $C_{29}H_{28}ClNO_2$: C, 76.05; H, 6.16; N, 3.06. Found: C, 75.90; H, 6.16; N, 3.05.

7.7.56. 2-[(1,1,2,2-Tetramethyl-1-silapropoxy)methyl]phenylamine (17a). To 20 mL of DMF was added *t*-butyldimethylsilyl chloride (0.581 g, 3.86 mmol), imidazole (0.276 g, 4.06 mmol), and 2-aminobenzyl alcohol (0.500 g, 4.06 mmol). This reaction was allowed to stir 12 h. Then the reaction was diluted with ethyl acetate and extracted with saturated LiBr and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (10% ether/hexanes, R_f = 0.25) afforded a pale yellow liquid (0.748 g, 78%). ^1H NMR ($CDCl_3$): δ 7.18–6.98 (m, 2H), 6.78–6.62 (m, 2H), 4.71 (s, 2H), 4.34–4.05 (br s, 2H), 0.92 (s, 9H), 0.091 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 146.69, 129.21, 128.95, 125.73, 118.35, 116.22, 65.44, 26.39, 18.77, −4.74. MS (ESI) *m*/*z* 237.9 (M^+).

7.7.57. 2-(4-Methoxyphenyl)-*N*-{2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]phenyl}acetamide (17b). To a solution of 4-methoxyphenylacetic acid (0.255 g, 1.54 mmol) in CH_2Cl_2 (15 mL) was added DiEA (0.32 mL, 1.84 mmol) and PyBOP (0.80 g, 1.54 mmol). This mixture was allowed to stir for 15 min before **17a** (0.365, 1.54 mmol) was added. After 1 h, the reaction was diluted with ethyl acetate and extracted with saturated solutions of NH_4Cl and $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (50% ether/hexanes, R_f = 0.3) to afford a pale yellow oil (0.46 g, 78%). ^1H NMR ($CDCl_3$): δ 8.67–8.52 (br s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.34–7.23 (m, 3H), 7.13–6.97 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.57 (s, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 0.86 (s, 9H), 0.016 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.15, 159.37, 137.98, 130.82, 130.02, 129.11, 128.42, 127.32, 124.35, 122.60, 114.87, 65.33, 55.74, 44.86, 26.35, 18.71, −4.70. MS (CI) *m*/*z* 386.1 (M^+).

7.7.58. *N*-[2-(Hydroxymethyl)phenyl]-2-(4-methoxyphenyl)acetamide (17c). This compound was prepared from **17b** (0.46 g, 1.19 mmol) according to general procedure G. The crude solid was recrystallized in methanol/hexanes (≈95:5). The desired product (R_f = 0.30 in 50% ethyl acetate/hexanes) was obtained (0.323 g, 100%) as a white solid. ^1H NMR ($CDCl_3$): δ 8.51–8.35 (br s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.36–7.23 (m, 3H), 7.18–7.00 (m, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.47 (d, J = 5.0 Hz, 2H), 3.81 (s, 3H), 3.68 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 170.80, 159.53, 137.76, 131.24, 130.17, 129.59, 129.37, 127.15, 124.92, 122.93, 114.97, 64.63, 55.85, 44.66. MS (ESI) *m*/*z* 272.0 (M^+).

7.7.59. (2-{[2-(4-Methoxyphenyl)ethyl]amino}phenyl)-methan-1-ol (17d). This compound was prepared from **17c** according to general procedure B, with the addition of $AlCl_3$ (0.5 equiv). However, this reaction was conducted at 0.1 M in THF with respect to **17c**, due to its low solubility in THF, and the reaction was refluxed for 53 h. Flash chromatography (20% ethyl acetate/hexanes, R_f = 0.15) afforded an orange oil (0.116 g, 38%). ^1H NMR ($CDCl_3$): δ 7.28–7.10 (m, 3H), 7.06 (dd, J = 7.3, 1.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.76–6.60 (m, 2H), 4.59 (s, 2H), 3.80 (s, 3H), 3.39 (t, J = 6.9 Hz, 2H), 2.91 (t, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 158.73, 147.89, 131.99, 130.25, 130.16, 129.61, 124.90, 116.97, 114.49, 111.21, 65.23, 55.79, 45.59, 35.17. MS (ESI) *m*/*z* 258.1 (M^+).

7.7.60. (2-{[(4-Chlorophenyl)phenylmethoxy]methyl}phenyl)[2-(4-methoxyphenyl)ethyl]amine (17). Molecular sieves (4 Å) were added to 2 mL of DMF before NaH (60% dispersion in mineral oil, 7.8 mg, 0.194 mmol) was added. After 10 min, this mixture was cooled to 0 °C, and **17d** (50 mg, 0.194 mmol), dissolved in a minimum amount of DMF, was added slowly via syringe. The reaction was allowed to stir for 30 min. Then, 4-chloro-bromobenzhydrol dissolved in a minimum amount of DMF, was added slowly via syringe. The reaction was allowed to stir overnight and then it was diluted with ethyl acetate and filtered to remove the

molecular sieves and NaBr. The organic layer was extracted with saturated solutions of LiBr and brine. Then the organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purification on a Analtech 1000 μm silica prep plate (10% ether/hexanes, $R_f = 0.30$) afforded a yellow oil (16.1 mg, 18%). ^{1}H NMR (acetone-d_6): δ 7.33–6.93 (m, 12H), 6.89 (dd, $J = 7.3$, 1.2 Hz, 1H), 6.72 (d, $J = 8.9$ Hz, 2H), 6.63–6.43 (m, 2H), 5.37 (s, 1H), 4.35 (s, 2H), 3.63 (s, 3H), 3.26–3.14 (m, 2H), 2.65 (t, $J = 7.1$ Hz, 2H). ^{13}C NMR (acetone-d_6): δ 158.74, 148.02, 142.34, 141.86, 132.95, 131.93, 130.25, 130.00, 129.81, 128.95, 128.87, 128.75, 127.99, 127.36, 121.92, 116.30, 114.22, 110.66, 81.40, 69.95, 54.94, 45.20, 34.86. MS (CI) *m/z* 458.7 (M^+).

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