HHS Public Access

Author manuscript

Bioorg Med Chem. Author manuscript; available in PMC 2022 February 22.

Published in final edited form as:

Bioorg Med Chem. 2021 January 15; 30: 115941. doi:10.1016/j.bmc.2020.115941.

Lipophilic tail modifications of 2-(hydroxymethyl)pyrrolidine scaffold reveal dual sphingosine kinase 1 and 2 inhibitors

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Abstract

The sphingosine 1-phosphate (S1P) signaling pathway is an attractive target for pharmacological manipulation due to its involvement in cancer progression and immune cell chemotaxis. The synthesis of S1P is catalyzed by the action of sphingosine kinase 1 or 2 (SphK1 or SphK2) on sphingosine and ATP. While potent and selective inhibitors of SphK1 or SphK2 have been reported, development of potent dual SphK1/SphK2 inhibitors are still needed. Towards this end, we report the structure–activity relationship profiling of 2-(hydroxymethyl)pyrrolidine-based inhibitors with **22d** being the most potent dual SphK1/SphK2 inhibitor (SphK1 K_i = 0.679 μM, SphK2 K_i = 0.951 μM) reported in this series. **22d** inhibited the growth of engineered *Saccharomyces cerevisiae* and decreased S1P levels in histiocytic lymphoma myeloid cell line (U937 cells), demonstrating inhibition of SphK1 and 2 *in vitro*. Molecular modeling studies of **22d** docked inside the Sph binding pocket of both SphK1 and SphK2 indicate essential hydrogen bond between the 2-(hydroxymethyl)pyrrolidine head to interact with aspartic acid and serine residues near the ATP binding pocket, which provide the basis for dual inhibition. In addition, the dodecyl tail adopts a “J-shape” conformation found in crystal structure of sphingosine bound to SphK1. Collectively, these studies provide insight into the intermolecular interactions in the SphK1 and 2 active sites to achieve maximal dual inhibitory activity.

Keywords

Sphingosine kinase; SphK1; Inhibitor; Sphingosine; Sphingosine 1-phosphate; Lipophilic binding pocket; PF-543; Structure-activity relationship

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Declaration of Competing Interest

The authors declare the following competing financial interest(s): W. L.S. and K.R.L. are co-founders of Flux Therapeutics Inc, which was created to commercialize S1P-related discoveries, including SphK inhibitors, discovered and characterized in their laboratories.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2020.115941.

1. Introduction

In humans and other mammals, sphingolipid signaling has emerged as an attractive candidate for pharmacological intervention. Numerous investigations have focused on the role sphingolipids play in maintaining cellular homeostasis, specially via the sphingosine 1-phosphate (S1P) signaling pathway. Examination of the S1P synthetic pathway has revealed it to be a potential mediator of cellular fate (Fig. 1). In particular, ceramide (Cer) and sphingosine (Sph) promote signaling that result in cell arrest and apoptosis whereas surplus S1P encourages proliferation and survival.[1–3] As such, members of the S1P synthetic pathway, particularly S1P, have emerged to be implicated in numerous diseases such as cancer,[4–6] fibrosis,[7,8] and sickle cell disease (SCD).[9,10]

Functionally, S1P can act as both an intra- and extracellular ligand for multiple targets resulting in various cellular responses. Most notably, extracellular S1P has a high affinity for five G-protein coupled receptors (S1P1–5) that when activated lead to a downstream cascade of pro-survival effects.[11–13] Synthetically, the generation of S1P is exclusively due to the ATP-dependent phosphorylation of Sph, mediated by sphingosine kinases (SphK1 and SphK2). The general function of two kinase isoforms is moderately repetitive in that both catalyze the transformation of Sph to S1P. Gene ablation experiments in mice demonstrated that deletion of either isoform was unremarkable, and the animals were viable and fertile. However, elimination of both kinase isoform genes resulted in embryonic death around day E13.5.[14,15] There are some differences observed between SphK1 and SphK2 including subcellular distribution, substrate specificity, and active site topography.[16–19] One salient difference is the consequence of isoform deficiency, whether accomplished by genetic manipulation or inhibitors, with regard to blood S1P concentrations. Interestingly, rodents deficient in SphK1 displayed circulating S1P levels that were reduced by $>50\%$ whereas SphK2 deficient rodents had blood S1P levels increase nearly 3-fold.[20–22] The latter phenomenon is ascribed to be the result of the role SphK2 plays in the clearance of circulating S1P. In short, Sph formed at the hepatocyte membrane is captured by SphK2-mediated phosphorylation and subsequently degraded via S1P lyase. The absence of SphK2 activity thus permits excess Sph to be captured by SphK1-mediated phosphorylation, which is prominent in red blood cells and thereby increasing circulating S1P levels.[23] There are suggestions in the literature that inhibiting SphK activity could be beneficial,[5,16,24,25] thus prompting a search for reliable SphK1-selective, SphK2-selective, and dual SphK1/SphK2 inhibitors. While potent and selective inhibitors of SphK1 and SphK2 have been reported, potent dual SphK1/SphK2 inhibitors are still needed (Fig. 2A). Among these, **1** (PF-543) is the most potent inhibitor of human SphK1 disclosed. Inhibitor **1** was developed by Schnute and coworkers at Pfizer via a lead hopping strategy of two high-throughput screening hits, **7** and **8** (Fig. 2B).[26,27] In short, replacement of the 2-(hydroxymethyl)pyrrolidine head with other hydroxyl pyrrolidine moieties resulted in minimal loss of potency and selectivity for SphK1. Ultimately, it was determined that the 2-(hydroxymethyl)pyrrolidine head of **1** was the most preferred because of its potency *in vitro*. However, despite its impressive *in vitro* properties, the need for a continuously administered dose via an implanted osmotic pump device might be an indicator of a short compound half-life, low metabolic stability, or overall poor pharmacokinetic characteristics *in vivo*. Nonetheless, **1** remains an excellent

tool for probing the effects of human SphK1 inhibition *in vitro* and could serve as a template for the development of potent SphK1/SphK2 dual inhibitors. We herein present the design and synthesis of novel analogues of **1** (PF-543) that retain the 2-(hydroxymethyl)pyrrolidine head while incorporating various lipophilic tail moieties with the interest of transforming SphK1-selective derivatives into potent SphK1/SphK2 dual inhibitors.

2. Results and discussion

2.1. Inhibitor design

Previous work conducted by Schnute and coworkers revealed that replacement of the 2-(hydroxymethyl)pyrrolidine head of **1** resulted in minimal improvements in inhibitor efficacy toward SphK1, with 2-(hydroxymethyl)pyrrolidine being the most preferred.[27] Furthermore, molecular modeling studies conducted with **1** docked in the substrate binding pocket of SphK1 revealed that 2-(hydroxymethyl)pyrrolidine head strongly hydrogen bonds with amino acid Asp178, a vital residue for SphK1 substrate recognition, thus explaining its impressive potency and selectivity for the type 1 kinase isoform.[28] However, alterations to the aryl sulphonyl tail of **1** resulted in differentiating SphK1/SphK2 inhibitor activity.[26,27] Based from these observations, further structural modifications on the scaffold of **1** must retain the 2-(hydroxymethyl) pyrrolidine head to preserve inhibitor SphK1 activity. In this study, various lipophilic substituents (i.e. alkyl, aryl, alkoxy, etc.) were incorporated into the scaffold of **1** in place of the aryl sulphonyl moiety. It was our rational that inclusion of lipophilic moieties that mimic the substrate sphingosine will be tolerated in the enzyme binding pockets of SphK1 and 2. With this approach, we aimed to develop dual SphK1/SphK2 inhibitors.

2.2. Chemistry: Synthesis of 2-(hydroxymethyl)pyrrolidine derivatives

The synthesis of compounds **12a-e**, **18a-i**, **22a-h**, **25a-b**, and **30a-c** are shown in Schemes 1–3. Compound **9** is available for purchase from commercial sources. As shown in Scheme 1, benzaldehyde intermediates **10a-e** were synthesized via a reaction of **9** in the presence of potassium carbonate and various alkyl bromides while refluxed in DMF for 12 h. Subsequently, prolinol intermediates **11a-e** were generated by reductive amination utilizing 2-(hydroxymethyl)pyrrolidine. Lastly, a mixture of free amine intermediates **11a-e** with HCl in methanol was performed to yield the desired alkoxy analogues **12a-e** as HCl salts.

The synthesis of diaryl ether analogues **18a-i** was completed as shown in Scheme 2. Execution of a nucleophilic aromatic substitution reaction of commercially available 4-fluorobenzonitrile with assorted aryl alcohols (**13a-e**) and cesium carbonate was completed to afford benzonitrile intermediates **14a-e**. Next, nitrile reduction was facilitated with DIBAL-H to afford the corresponding benzaldehyde intermediates **15a-e**. Subsequently, **15a-c** were carried forward to a reductive amination reaction to afford free amine intermediates **17a-c**. In contrast, benzaldehyde intermediates **15d** and **15e** were utilized for Suzuki-Miyaura coupling reactions with various aryl boronic acids to yield intermediates **16d-i**. Afterward, compounds **16d-i** were employed for a reductive amination reaction to afford free amine intermediates **17d-i**. Finally, analogues **17a-i** were combined with HCl in methanol to afford the corresponding diaryl ether derivatives **18a-i** as HCl salts.

The synthesis of alkyl analogues **22a-h**, alkenyl analogues **25a-b**, and alkynyl analogues **29a-c**, and **30a-c** is outlined in Scheme 3. Compound **19** is available for purchase from commercial sources. A Suzuki-Miyaura coupling reaction with various substituted borane derivatives was completed to generate benzaldehyde intermediates **20a-g**. The production of 2-(hydroxymethyl)pyrrolidine intermediates **21a-g** was accomplished via reductive amination. Completion of an acylation reaction with free amine **21c** and acetyl chloride was performed to produce acetoxy derivative **21 h**. Lastly, intermediates **21a-h** were added to a mixture of HCl and methanol to produce alkyl derivatives **22a-h** as HCl salts. The synthesis of alkenyl benzaldehyde intermediates **23a-b** was completed via a Heck coupling reaction with **19** and various substituted styrene derivatives. Then, installation of the pyrrolidine head was facilitated via reductive amination to produce **24a** and **24b**. Lastly, intermediates **24a** and **24b** were added to a mixture of HCl and methanol to produce alkenyl analogues **25a** and **25b** as HCl salts. The production of alkynyl benzaldehyde intermediates **26a-c** was accomplished via a Sonogashira coupling reaction with **19** and various substituted phenylacetylene derivatives. Reductive amination of the benzaldehyde was completed to produce pyrrolidine intermediates **27a-c**, which upon catalytic hydrogenation of the internal triple bond generated **28a-c**. Intermediates **27a-c** were also added to a mixture of HCl and methanol to produce alkynyl analogues **30a-c** as HCl salts. Likewise, reduced intermediates **28a-c** were added to a mixture of HCl and methanol to produce alkane analogues **29a-c** as HCl salts.

2.3. Biological evaluation of derivatives

This goal of this investigation was to develop a potent dual SphK1/SphK2 inhibitor whose design was inspired from key structural components of **1** and Sph. A library of analogues that contain an 2-(hydroxymethyl)pyrrolidine head moiety and various lipophilic tail substituents (i.e. alkyl, aryl, alkoxy, etc.) were synthesized and evaluated according to a previously described protocol.[29,30] In short, this assay utilizes recombinant SphK1 or SphK2 and γ-[^{32}P]ATP to screen and rapidly identify inhibitors suitable for further evaluation. All compounds were assayed at 1.0 μM for SphK1 and 0.3 μM for SphK2. Previous inhibitors developed in our group bearing an alkoxy moiety have shown success in inhibiting SphKs but with a guanidine head group.[31,32] Thus, alkylether compounds bearing heptyloxy (**12a**), octyloxy (**12b**), nonyloxy (**12c**), and decyloxy (**12d**) tails were synthesized and assayed against SphK1 and 2 (Table 1). Incorporation of a heptyloxy (**12a**) tail resulted in poor SphK1 and 2 inhibition. Further extension of the alkoxy tail (**12b-d**) displayed an alkyl chain length effect on dual SphK1/SphK2 inhibition, with the nonyloxy (**12c**) variant indicating to be the optimal length and inhibiting SphK1 and SphK2 activity by 84% and 44% respectively. To further explore tolerated changes on this region, we synthesized a 4-trifluoromethylbenzoxy tail (**12e**) based on our previous investigations.[18] However, **12e** displayed weak SphK inhibition. Next, the effect of substitution with a much bulkier aryl substituent (**18a-i**) was explored to probe the size of the ligand docking space as well as potential π-π stacking or hydrophobic interactions with nearby active site residues. Compared to alkoxy derivative **12c**, the inclusion of a phenoxy tail (**18a**) resulted in poor SphK1 and 2 inhibition. Analogues bearing a *tert*-butyl (**18b**) and phenyl groups (**18d**) at the *meta*-position also gave minimal enzyme inhibition. This is thought to be the result

of the acute bond angle caused by the 1,3-disubstitution pattern most likely resulting in steric clash inside the binding pocket. When *tert*-butyl (**18c**) and phenyl (**18e**) moieties were migrated to the *para*-position, both compounds displayed a moderate increase in potency towards both kinase isoforms; however, they were still roughly half as potent as **12c**. The effect of an additional trifluoromethyl group on the terminal phenyl ring was explored with analogues **18f-i**. Of these compounds, only **18 h** displayed significant inhibitory activity (SphK1 = 70%, SphK2 = 52%), indicating that *meta*-CF_3 substitution on the terminal phenyl ring plays an important role for favorable binding. Next, to mimic the lipophilic tail of Sph, analogues with alkyl tails were synthesized in varying lengths (**22a-e**, and **22 h**). Interestingly, elongation of the alkyl tail had a positive impact on SphK1 activity with **22b-22d** having 76% inhibition. **22b** and **22d** had strong inhibitory activity against SphK2. We also introduced a methyl group on the internal phenyl ring (**22e**) but without improvement in activity. We next investigated inserting a phenyl ring onto the alkyl chain with compounds **22f**, **22 g**, and **29a-c**. These analogs showed no improvement in activity. Analogues with rigid tail groups bearing internal double or triple bonds were next evaluated (**25a-b, 30a-c**). These were likewise ineffective inhibitors of SphKs.

Because the initial screen utilized 0.3 μM for SphK2 and 1.0 μM for SphK1 inhibitor concentration, the apparent low activity with SphK2 is expected to increase when extrapolated to 1 μM. To confirm SphK inhibition, select compounds that displayed the greatest dual SphK1 (>70%) and SphK2 (>18%) inhibitory activity were subjected to a cell-based assay that uses the budding yeast *Saccharomyces cerevisiae* as a platform for assessing inhibitors of human SphK1 and 2 (hSphK1 and 2).[33] In short, this assay exploits the observed toxicity of increased concentrations of phosphorylated long chain bases (LCBs), such as S1P, towards *S. cerevisiae*. Rescue of a genetically modified (to enhance phospho-LCB toxicity) yeast cell strain harboring plasmids expressing either hSphK1 or 2 in the presence of select inhibitors can be accomplished in a dose dependent fashion by measuring the growth of yeast culture. As shown in Table 2, top performing compounds **18 h** and **22b-d** were assayed with *S. cerevisiae* and EC_{50} values towards SphK1 and SphK2 were determined. After consideration of metabolic stability, compound **12c** was abandoned because of a structural alert for the formation of iminomethide. With regard to hSphK1 in yeast cells, the dodecyl (**22d**) analogue was the most potent inhibitor with an EC_{50} of 154 nM, followed by decyl (**22b**), undecyl (**22c**), and diaryl ether (**18 h**), respectively, with EC_{50} values ranging from 202 nM to 299 nM. When tested against hSphK2, undecyl analogue **22c** and **22d** had EC50 values within experimental error of 246 ± 21 and 290 ± 21 nM, respectively. Taken altogether, inhibitor **22d** was determined to be the most effective dual SphK1/SphK2 inhibitor tested. Subsequently, an inhibitory constant (K_i) was determined for the compound **22d** for both SphK1 and 2 (Table 2).[21] Dodecyl analogue **22d** displayed good potency (SphK1 K_i = 679 nM, SphK2 K_i = 951 nM) towards both enzyme isoforms with a slight selectivity (1.4-fold) for SphK1.

To further validate the SphK inhibitory activity, compound **22d** was incubated with mammalian U937 cells to determine the effect on S1P synthesis (Fig. 3). U937 cells are a histiocytic lymphoma myeloid cell line that express both SphK1 and SphK2. In this assay, cells were incubated with inhibitor, lysed, and S1P levels were determined by LC-MS/MS.

To our delight, administration of **22d** from 0.1 μM to 1.0 μM resulted in a concentration-dependent reduction of S1P levels, thus indicating dose-dependent SphK inhibition. Taken together, the activity of **22d** in both the yeast assay as well as in U937 cells provide strong support for dual SphK inhibition.

2.4. Molecular modeling of 22d in the active site of hSphK1 and hSphK2

Molecular docking of **22d** into the Sph binding site of SphK1 and SphK2 was performed to provide insight into the intermolecular interactions within the substrate binding pocket (Fig. 4). Compound **22d** fits in the Sph binding pocket of SphK1 that favors strong hydrogen bond formation between the 2-(hydroxymethyl)pyrrolidine moiety: (i) the primary alcohol hydrogen bond (3.0 Å) with Ser168 and (ii) the tertiary nitrogen hydrogen bond (3.6 Å) with Asp178 (Fig. 4A). This is in contrast with the co-crystal structure of PF-573 bound to SphK1[28] where the Asp178 carboxylate moiety to participates in hydrogen bonding with both the primary alcohol and tertiary nitrogen. The change in the positioning between **22d** and PF573 likely results from the rearrangement of the tail groups within the binding pocket. Nonetheless, this data suggests the 2-(hydroxymethyl)pyrrolidine head group within our scaffold is vital for compound binding affinity and its corresponding observed inhibitory activity towards SphK1. As shown in Fig. 4C, docking of **22d** into the homology model of SphK2[18,19] reveals a similar hydrogen bond between the pyrrolidine nitrogen to Asp308 and hydroxyl group to Ser298. We hypothesize that the similar binding pose around this region is the structural basis for the dual inhibitory of **22d**. In addition to the 2-(hydroxymethyl)pyrrolidine head, hydrophobic interaction is observed between **22d** and Ile174 of SphK1 (Fig. 4A). The lack of a large, bulky moiety in the central region of our scaffold contributes to the slight observed SphK1 selectivity given that bulkier substituents have demonstrated to be better tolerated in the hydrophobic core of the Sph binding cavity of SphK2 rather than SphK1. This is due to the presence of the smaller Val304 residue in SphK2 (Ile174 in SphK1) that allows inhibitors bearing larger moieties on this portion of the scaffold to migrate deeper into the binding pocket of SphK2.[18] Indeed, the dodecyl alkyl tail of compound **22d** is posed in a “J-shape” conformation that has been observed in SphK1 structures crystallized with various inhibitors.[34,28] Fig. 4B and D show the Van der Waals radii of **22d** within the SphK1 and SphK2 binding pocket wherein a larger volume for SphK2 accommodates the aliphatic tail.

3. Conclusions

The S1P pathway remains an intriguing target for pharmacological intervention. The biologic role S1P and its generative enzymes SphK1 and SphK2 play in various diseases states have been the subject of intense investigation over the last two decades. While potent and selective inhibitors of SphK1 and SphK2 have been reported, development of potent dual SphK1/SphK2 inhibitors are still needed. Particularly regarding SphK1, many biologically active inhibitors have been developed with the 2-(hydroxymethyl)pyrrolidine-based inhibitor **1** being the most potent (SphK1 K_i = 3.6 nM) to date. Towards that end, we utilized compound **1** as a template and performed a structure–activity relationship profiling of 2-(hydroxymethyl)pyrrolidine-based dual inhibitors of SphK1 and 2 with **22d** being the most effective dual SphK1/SphK2 inhibitor (SphK1 K_i = 679 nM, SphK2 K_i

= 951 nM) reported in this series. Biological assessment of **22d** demonstrated success in reducing measured concentrations of S1P in both *S. cerevisiae* and U937 cell lines. Furthermore, molecular modeling studies suggest that hydrogen bonding of Ser298 and Asp278 with the 2-(hydroxymethyl) pyrrolidine moiety provides the structural basis for dual inhibitory activity at SphK1 and SphK2. Collectively, these studies give insight into the role 2-(hydroxymethyl)pyrrolidine-based inhibitors play inside the SphK1 and SphK2 active sites and provide a foundation for the development of future dual SphK1/SphK2 inhibitors designed to target and manipulate the S1P signaling pathway.

4. Experimental

4.1. Biological assays and molecular modeling

4.1.1. Recombinant hSphK1 and hSphK2 cell lysate assay—The percent inhibition of SphK1 from synthesized compounds was carried forward using a previously described protocol.[30,35] Recombinant human SphK1 (10 μM) and human SphK2 (5 μM) was isolated from a SF9 cell lysate expressing respective plasmid DNAs and incubated with (1.0 μM for SphK1 and 0.3 μM for SphK2) or without compound, sphingosine, and 250 μM γ-[^{32}P] ATP via scintillation counting. SphK activity was determined by the amount of γ-[^{32}P]-S1P as a function of inhibitor concentration. Compounds were assayed in triplicate.

4.1.2. Recombinant yeast assay—The growth of recombinant yeast (*Saccharomyces cerevisiae*) cells encoding either hSphK1 or hSphK2 was performed according to our previously described protocol.[33] Briefly, yeast strain KYA1 harboring plasmid pGAL-HsSPHK1 encoding hSphK1, or plasmid pGAL-HsSPHK2 encoding hSphK2 was selected, maintained and grown in SC-URA media with 2% glucose overnight at 30 °C. Following overnight growth media was diluted 1:100 into SC-URA media supplemented with 2% galactose and various concentrations of test inhibitor. After another incubation period of 24–48 h at 30 °C, cellular growth was quantified by measuring absorbance at 600 nm and EC_{50} values were calculated from the inhibitor concentration-absorbance curve.

4.1.3. U937 cell culture assay—The growth of U937 cells was conducted in RPMI 1640 media supplemented with (L)-glutamate, 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin at 37 °C in an atmosphere containing 5% CO_2. Growth media was replaced with media containing 0.5% FBS 24 h prior to inhibitor introduction. After, cells were treated with compound **22d** for 2 h before being harvested and lipids extracted for LC-MS/MS analysis as described previously.[29]

4.1.4. Molecular modeling—To visualize and rationalize the observed biological efficacy of **22d**, molecular docking was utilized to predict position and ligand–protein interactions of the inhibitor in the sphingosine binding pocket of SphK1 and SphK2. The SphK1 and 2 model, with ATP and Mg^{2+} bound, was generated with Molecular Operating Environment (MOE) and energy minimized as previously described.[32,19] In order to draw, display, and characterize chemical structures, substructures, and reactions for preparation in docking programs, Marvin 17.3.13, 2017 was used (ChemAxon; http://www.chemaxon.com) to create structure files that were cleaned in 3D. AutoDock Tools was used to prepare the

protein and ligand files.[36] In order to perform the docking, AutoDock Vina was utilized to dock the inhibitor to SphK1 or 2, with 9 poses being created for each inhibitor.[37] The grid box was set to 20 X 20 X 28 $Å^3$ with grid spacing of 1.000 Å. To include all known key residues in the sphingosine binding cavity, the grid box was positioned at the approximate center of the ligand-binding cavity based on the position of sphingosine in the crystal structure (PDB ID: 3VZB).[34,32] The lowest energy docked pose for the inhibitor was then used to visualize and rationalize the observed biological efficacy towards SphK1 and SphK2.

4.2. Chemistry

4.2.1. General materials and methods—All solvents were dried using a PureSolv solvent drying system prior to use. All chemical reagents were purchased from commercial sources and used without further purification. Flash column chromatography was performed using a Combiflash Rf purification system with flash grade 40–63 μm silica gel. Where indicated, all reactions utilizing a microwave reactor were conducted with a Discover SP microwave synthesizer (CEM Corporation). ^{1}H NMR spectra were obtained with either a Bruker Advance-II 500 MHz or Agilent 400-MR 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$:7.26 ppm, CD_3OD: 3:31 ppm). ^{13}C NMR spectra were obtained with either a Bruker Advance II 500 MHz or Agilent 400-MR 400 MHz spectrometer with complete proton decoupling. ^{13}C NMR chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.2 ppm, CD_3OD: 49.0 ppm). High-resolution mass spectrometry (HRMS) was performed on an LC-MS time-of-flight mass spectrometer by electrospray ionization (ESI).

4.2.2. General procedure for the synthesis of compounds 10a-e—To a round bottom flask 4-hydroxybenzaldehyde (1.0 equiv.) was added to a solution of DMF, potassium carbonate (5.0 equiv.) and the appropriate alkyl halide (1.2 equiv.) followed by flushing the reaction container with nitrogen gas. The reaction mixture was refluxed at 100 °C for 16 h until TLC indicated the starting material had been fully consumed. Subsequently, the resulting solution was partitioned between EtOAc and LiBr aqueous solution. Using additional EtOAc, the aqueous LiBr solution was washed three times and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated via vacuum. The resulting concentrate was purified by silica gel chromatography.

4.2.2.1. 4-(heptyloxy)benzaldehyde (10a).: Clear oil, yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 7.80 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 4.01 (t, J = 6.6 Hz, 2H), 1.83 –1.73 (m, 2H), 1.48 – 1.39 (m, 2H), 1.39 – 1.23 (m, 6H), 0.90 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 164.4, 132.1, 129.8, 114.8, 68.5, 31.9, 29.2, 29.1, 26.0, 22.7, 14.2. HRMS (ESI +): calcd for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536; found, 221.1548.

4.2.2.2. 4-(octyloxy)benzaldehyde (10b).: Clear oil, yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 7.82 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 1.87 –1.75 (m, 2H), 1.47 (dt, J = 15.2, 6.8 Hz, 2H), 1.40 – 1.21(m, 8H), 0.91 – 0.86(m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 164.4, 132.1, 129.9, 68.6, 31.9, 29.4, 29.4, 29.2, 26.1, 22.8, 14.2. HRMS (ESI +): calcd for $C_{15}H_{23}O_2$ $[M + H]^+$ 235.1693; found: 235.1707.

4.2.2.3. 4-(nonyloxy)benzaldehyde (10c).: Clear oil, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.50 – 1.40 (m, 2H), 1.40 – 1.21 (m, 10*H*), 0.92 – 0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 164.4, 132.1, 129.8, 114.9, 68.6, 32.0, 29.6, 29.5, 29.4, 29.2, 26.1, 22.8, 14.2. HRMS (ESI +): calcd for $C_{16}H_{25}O_2$ $[M + H]^+$ 249.1849; found: 249.1865.

4.2.2.4. 4-(decyloxy)benzaldehyde (10d).: Clear oil, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 1.86 –1.76 (m, 2H), 1.51 – 1.41 (m, 2H), 1.29 (dd, *J* = 14.2, 5.5 Hz, 12H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.0, 164.4, 132.1, 129.9, 114.9, 68.6, 32.0, 29.7, 29.7, 29.5, 29.5, 29.2, 26.1, 22.8, 14.3. HRMS (ESI +): calcd for $C_{17}H_{27}O_2$ $[M + H]^+$ 263.2006; found: 263.2029.

4.2.2.5. 4-((4-(trifluoromethyl)benzyl)oxy)benzaldehyde (10e).: White solid, yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.90 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 5.22 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.8, 163.4, 140.1, 132.2, 130.6, 127.5, 125.9, 125.9, 125.8, 125.8, 115.2, 69.5. HRMS(ESI +): calcd for $C_{30}H_{22}F_6KO_4$ $[2\ M + K]^+$ 599.1054, found: 599.1084.

4.2.3. General procedure for the synthesis of compounds 11a-e, 17a-i, 21a-h, 24a-b, 27a-c—To a round bottom flask containing CH_2Cl_2 the appropriate aldehyde (1.0 equiv.), (*R*)-prolinol (1.3 equiv.) and 100 mg 4.0 Å molecular sieves were added followed by flushing the reaction container with nitrogen gas. The solution was allowed to stir at room temperature for 8 h before the addition of *p*-toluenesulfonic acid monohydrate (0.05 equiv.) and sodium cyanoborohydride (1.3 equiv.). The solution was stirred at room temperature under nitrogen for an additional 12 h. After, the solution was filtered with solids removed and partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated via vacuum. The resulting concentrate was purified by silica gel chromatography and carried forward without characterization. Following silica gel chromatography, the corresponding ester (1.0 equiv.) was added to a round bottom flask containing THF and put under nitrogen gas. Next, the mixture was cooled in an ice bath for 5 min before the addition of lithium aluminum hydride (0.7 equiv.). The mixture was allowed to rise to room temperature and then refluxed for 10 h. Subsequently, the reaction was cooled in ice bath and quenched with 1 mL ethyl acetate and 20 mL saturated sodium hydroxide solution. The mixture was then extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated via vacuum. The concentrate was purified using silica gel column chromatography to yield the desired product.

4.2.3.1. (R)-(1-(4-(heptyloxy)benzyl)pyrrolidin-2-yl)methanol (11a).: White solid, yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.95 – 3.89 (m, 3H), 3.64 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.46 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.39 (d, *J* = 12.9 Hz, 1H), 3.00 (dt, *J* = 9.5, 4.6 Hz, 1H), 2.79 (td, *J* = 6.0, 3.1 Hz, 1H), 2.35 (q, *J* = 8.5 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.86 – 1.79 (m, 1H), 1.79 – 1.66 (m, 4H), 1.49 – 1.39 (m, 2H),

1.38 – 1.24 (m, 6H), 0.93 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.6, 130.2, 130.0, 114.4, 68.0, 64.6, 61.8, 58.0, 54.3, 31.8, 29.1, 27.7, 26.1, 23.4, 22.7, 14.2. HRMS (ESI +): calcd for $C_{19}H_{32}NO_2$ $[M + H]^+$ 306.2428, found: 306.2425.

4.2.3.2. (R)-(1-(4-(octyloxy)benzyl)pyrrolidin-2-yl)methanol (11b).: White solid, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.64 (dd, *J* = 10.7, 3.5 Hz, 1H), 3.41 (dd, *J* = 10.7, 2.2 Hz, 1H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.00 – 2.92 (m, 2H), 2.75 – 2.68 (m, 2H), 2.34 – 2.23 (m, 1H), 1.98 –1.85 (m, 1H), 1.85 – 1.73 (m, 3H), 1.73 – 1.60 (m, 2H), 1.45 (dt, *J* = 15.0, 6.9 Hz, 2H), 1.38 – 1.23 (m, 8H), 0.93 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.4, 131.2, 130.0, 114.4, 68.1, 64.2, 61.8, 58.0, 54.5, 32.0, 29.5, 29.5, 29.4, 28.0, 26.2, 23.6, 22.8. HRMS (ESI +): calcd for $C_{20}H_{34}NO_2$ $[M + H]^+$ 320.2584, found: 320.2589.

4.2.3.3. (R)-(1-(4-(nonyloxy)benzyl)pyrrolidin-2-yl)methanol (11c).: White solid, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.88 (d, *J* = 12.8 Hz, 1H), 3.64 (dd, *J* = 10.7, 3.5 Hz, 1H), 3.42 (dd, *J* = 10.7, 2.2 Hz, 1H), 3.30 (d, *J* = 12.8 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.75 – 2.67 (m, 1H), 2.28 (td, *J* = 9.4, 7.6 Hz, 1H), 1.99 – 1.82 (m, 1H), 1.85 – 1.61 (m, 3H), 1.69 (s, 2H), 1.45 (dt, *J* = 15.0, 7.1 Hz, 2H), 1.39 – 1.21 (m, 10*H*), 0.93 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.4, 131.1, 129.9, 114.4, 68.1, 64.2, 61.9, 58.0, 54.4, 32.0, 29.7, 29.5, 29.4, 29.4, 28.0, 26.2, 23.5, 22.8, 14.2. HRMS (ESI +): calcd for $C_{21}H_{36}NO_2$ $[M + H]^+$ 334.2741, found: 334.2764.

4.2.3.4. (R)-(1-(4-(decyloxy)benzyl)pyrrolidin-2-yl)methanol (11d).: White solid, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.39 (d, *J* = 13.1 Hz, 1H), 4.12 (d, *J* = 13.1 Hz, 1H), 3.92 (t, *J* = 6.6 Hz, 2H), 3.86 – 3.75 (m, 2H), 3.60 (m, 1H), 3.42 (m, 1H), 3.01 (m, 1H), 2.19 – 1.86 (m, 4H), 1.80 – 1.70 (m, 1H), 1.41 (m, 2H), 1.37 – 1.19 (m, 12H), 0.89 – 0.82 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.6, 132.4, 120.9, 115.4, 68.3, 68.0, 60.9, 53.9, 32.0, 29.7, 29.7, 29.5, 29.5, 29.3, 26.6, 26.2, 23.0, 22.8, 14.3. HRMS (ESI +): calcd for $C_{22}H_{38}NO_2$ $[M + H]^+$ 348.2897, found: 348.2902.

4.2.3.5. (R)-(1-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)pyrrolidin-2-yl)methanol (11e).: White solid, yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 2H), 4.34 (d, *J* = 13.1 Hz, 1H), 3.97 (d, *J* = 13.1 Hz, 1H), 3.78 (d, *J* = 4.8 Hz, 2H), 3.45 (dq, *J* = 10.0, 4.9 Hz, 1H), 3.36 (dt, *J* = 11.0, 5.8 Hz, 1H), 2.88 (dt, *J* = 11.0, 7.3 Hz, 1H), 2.19 – 2.04 (m, 1H), 2.06 – 1.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.4, 140.7, 132.1, 127.6, 125.7, 115.6, 69.3, 67.6, 61.1, 58.8, 54.1. HRMS (ESI +): calcd for $C_{20}H_{23}F_3NO_2$ $[M + H]^+$ 366.1675, found: 366.1688.

4.2.3.6. (R)-(1-(4-phenoxybenzyl)pyrrolidin-2-yl)methanol (17a).: Clear oil, yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.13 – 7.07 (m, 1H), 7.01 (dd, *J* = 8.7, 1.1 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.68 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.47 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.40 (d, *J* = 13.0 Hz, 1H), 3.03 (ddd, *J* = 9.5, 5.6, 3.8 Hz, 1H), 2.80 (ddt, *J* = 9.2, 6.1, 3.0 Hz, 1H), 2.35 (td, *J* =

9.2, 7.8 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.89 – 1.80 (m, 1H), 1.78 – 1.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.3, 156.6, 133.4, 130.4, 129.9, 123.4, 119.0, 118.9, 64.7, 61.8, 58.1, 54.5, 27.8, 23.6. HRMS (ESI +): calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1645, found: 284.1656.

4.2.3.7. (R)-(1-(4-(3-(tert-butyl)phenoxy)benzyl)pyrrolidin-2-yl)methanol (17b).: Clear oil, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.5 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 (dd, *J* = 2.4, 1.9 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.81 (dddd, *J* = 8.0, 2.4, 1.0, 0.4 Hz, 1H), 4.04 (d, *J* = 13.0 Hz, 1H), 3.72 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.14 – 3.05 (m, 2H), 2.89 (td, *J* = 5.9, 3.0 Hz, 1H), 2.43 (dt, *J* = 9.5, 8.2 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.91 – 1.86 (m, 1H), 1.82 – 1.75 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.1, 156.8, 153.7, 130.5, 129.3, 120.6, 118.5, 116.7, 115.9, 110.2, 65.0, 61.8, 58.2, 54.4, 34.9, 31.4, 27.7, 23.6. HRMS (ESI +): calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2271, found: 340.2278.

4.2.3.8. (R)-(1-(4-(4-(tert-butyl)phenoxy)benzyl)pyrrolidin-2-yl)methanol (17c).: Clear oil, yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 2.1 Hz, 2H), 7.35 (d, *J* = 2.3 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.30 (d, *J* = 13.0 Hz, 1H), 3.89 (d, *J* = 13.1 Hz, 1H), 3.78 (dd, *J* = 12.1, 3.6 Hz, 1H), 3.72 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.38 – 3.27 (m, 2H), 2.84 – 2.73 (m, 2H), 2.13 – 2.05 (m, 1H), 1.98 – 1.86 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.7, 153.9, 147.0, 131.8, 126.9, 119.1, 118.5, 67.0, 61.2, 58.4, 54.1, 34.5, 31.6, 27.0, 23.2. HRMS (ESI +): calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2271, found: 340.2275.

4.2.3.9. (R)-(1-(4-([1,1′-biphenyl]-3-yloxy)benzyl)pyrrolidin-2-yl)methanol (17d).: Clear oil, yield 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 7.1 Hz, 1H), 7.26 – 7.25 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 7.01 – 6.97 (m, 1H), 4.28 – 4.18 (m, 1H), 3.82 – 3.73 (m, 2H), 3.70 – 3.64 (m, 1H), 3.29 – 3.17 (m, 1H), 2.72 – 2.64 (m, 1H), 2.09 – 2.05 (m, 1H), 1.94 – 1.83 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.9, 157.1, 143.4, 140.4, 131.6, 130.3, 128.9, 127.8, 127.2, 122.7, 118.9, 118.2, 76.8, 61.4, 58.3, 54.3, 29.8, 27.2, 23.2, 14.3. HRMS (ESI +): calcd for $C_{24}H_{26}NO_2$ $[M + H]^+$ 360.1958, found: 360.1963.

4.2.3.10. (R)-(1-(4-([1,1′-biphenyl]-4-yloxy)benzyl)pyrrolidin-2-yl)methanol (17e).: Clear oil, yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 4H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.06 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.68 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.54 – 3.44 (m, 2H), 3.07 (dt, *J* = 9.6, 4.4 Hz, 1H), 2.85 (td, *J* = 6.0, 3.0 Hz, 1H), 2.39 (q, *J* = 8.4 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.89 – 1.81 (m, 1H), 1.81 – 1.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 159.1, 145.4, 142.4, 133.6, 132.3, 130.9, 129.8, 129.2, 124.7, 120.9, 120.2, 63.4, 60.3, 56.3, 31.8, 29.2, 25.2, 16.3. HRMS (ESI +): calcd for $C_{24}H_{26}NO_2$ $[M + H]^+$ 360.1958, found: 360.1967.

4.2.3.11. (R)-(1-(4-((3′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (17f).: Clear oil, yield 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 2.1

Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 3H), 4.21 (d, *J* = 13.1 Hz, 1H), 3.77 – 3.70 (m, 2H), 3.65 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.21 (td, *J* = 6.6, 2.8 Hz, 1H), 3.15 (q, *J* = 5.0 Hz, 1H), 2.66 – 2.60 (m, 1H), 2.06 – 2.01 (m, 1H), 1.91 – 1.83 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.3, 157.3, 141.7, 141.2, 131.6, 131.3, 131.3, 131.0, 130.8, 130.4, 129.6, 129.3, 127.3, 125.2, 124.3, 124.3, 124.3, 124.3, 123.9, 123.9, 123.9, 123.8, 123.0, 122.5, 120.8, 118.8, 118.6, 118.0, 66.1, 61.4, 58.2, 54.1, 27.1, 23.2. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$: 428.1832, found: 428.1840.

4.2.3.12. (R)-(1-(4-((4′ -(trifluoromethyl)-[1,1′ -biphenyl]-3-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (17 g).: Clear oil, yield 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 – 7.63 (m, 4H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.32 (m, 3H), 7.25 (t, *J* = 2.1 Hz, 1H), 7.06 – 7.00 (m, 3H), 4.15 – 4.09 (m, 1H), 3.72 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.63 – 3.55 (m, 2H), 3.16 (ddd, *J* = 10.4, 6.7, 3.7 Hz, 1H), 3.00 (ddt, *J* = 9.5, 6.5, 3.6 Hz, 1H), 2.55 –2.46 (m, 1H), 2.03 – 1.97 (m, 1H), 1.92 – 1.77 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.5, 156.8, 143.9, 143.9, 141.7, 131.0, 130.4, 130.0, 129.8, 129.5, 129.3, 127.4, 125.8, 125.8, 125.7, 125.7, 125.3, 123.1, 122.4, 121.0, 118.9, 118.5, 117.8, 77.3, 65.6, 61.1, 58.2, 54.2, 27.3, 23.41. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$: 428.1832, found: 428.1844.

4.2.3.13. (R)-(1-(4-((3′ -(trifluoromethyl)-[1,1′ -biphenyl]-4-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (17 h).: Clear oil, yield 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.61 – 7.51 (m, 4H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.26 (d, *J* = 13.0 Hz, 1H), 3.82 – 3.75 (m, 2H), 3.69 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.30 – 3.21 (m, 2H), 2.74 – 2.67 (m, 1H), 2.11 – 2.03 (m, 1H), 1.95 – 1.83 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 156.8, 141.2, 135.2, 131.5, 131.3, 131.0, 130.8, 130.2, 129.3, 129.0, 128.7, 127.4, 125.2, 123.8, 123.8, 123.8, 123.7, 123.7, 123.7, 123.6, 123.6, 123.1, 120.9, 66.5, 61.3, 58.3, 54.1, 27.1, 23.1. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$: 428.1832, found: 428.1839.

4.2.3.14. (R)-(1-(4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (17i).: Clear oil, yield 44%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 – 7.64 (m, 4H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.07 (d, *J* = 13.0 Hz, 1H), 3.71 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.57 – 3.51 (m, 2H), 3.13 (dd, *J* = 6.8, 3.6 Hz, 1H), 2.93 (dt, *J* = 8.0, 4.3 Hz, 1H), 2.46 (q, *J* = 8.8 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.88 (dt, *J* = 12.4, 6.5 Hz, 1H), 1.84 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 156.4, 144.0, 144.0, 134.8, 130.7, 129.5, 129.2, 129.0, 128.7, 128.7, 127.5, 127.1, 125.8, 125.8, 125.7, 125.7, 125.4, 123.2, 121.0, 119.1, 119.1, 65.3, 61.6, 58.2, 54.3, 27.5, 23.5. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$: 428.1832, found:428.1834.

4.2.3.15. (R)-(1-(4-nonylbenzyl)pyrrolidin-2-yl)methanol (21a).: Clear oil, yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.96 (d, *J* = 12.9 Hz, 1H), 3.67 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.46 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.39 (d, *J* = 12.9 Hz, 1H), 3.05 – 2.98 (m, 1H), 2.78 (ddt, *J* = 9.1, 6.1, 3.0 Hz, 1H), 2.61 – 2.55 (m, 2H), 2.34 (td, *J* = 9.1, 7.9 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.88 – 1.77 (m, 1H), 1.76 – 1.66 (m,

2H), 1.65 – 1.54 (m, 2H), 1.36 – 1.22 (m, 12H), 0.91 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.1, 135.8, 128.9, 128.5, 64.6, 61.8, 58.4, 54.5, 35.7, 32.0, 31.6, 29.7, 29.6, 29.5, 29.4, 27.8, 23.5, 22.8, 14.2. HRMS (ESI +): calcd for $C_{21}H_{36}NO$ $[M + H]^+$ 318.2791, found: 318.2802.

4.2.3.16. (R)-(1-(4-decylbenzyl)pyrrolidin-2-yl)methanol (21b).: Clear oil, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.18 (d, *J* = 13.1 Hz, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.76 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.66 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.34 – 3.27 (m, 1H), 3.26 – 3.20 (m, 1H), 2.69 (dd, *J* = 8.1, 3.7 Hz, 1H), 2.60 – 2.54 (m, 2H), 2.03 – 1.89 (m, 3H), 1.88 – 1.79 (m, 1H), 1.56 (q, *J* = 7.2 Hz, 2H), 1.32 – 1.20 (m, 14H), 0.88 – 0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 143.9, 130.3, 129.0, 126.1, 67.0, 61.2, 58.6, 54.0, 35.7, 32.0, 31.4, 29.8, 29.7, 29.7, 29.7, 29.6, 29.4, 27.0, 23.5, 22.8, 14.2. HRMS (ESI +): calcd for $C_{22}H_{38}NO$ $[M + H]^+$ 332.2948, found: 332.2955.

4.2.3.17. (R)-(1-(4-undecylbenzyl)pyrrolidin-2-yl)methanol (21c).: Clear oil, yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 3.92 (d, *J* = 12.9 Hz, 1H), 3.65 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.42 (dd, *J* = 10.7, 2.1 Hz, 1H), 3.32 (d, *J* = 12.9 Hz, 1H), 2.98 (dq, *J* = 9.3, 5.6, 4.4 Hz, 1H), 2.77 – 2.67 (m, 1H), 2.62 – 2.53 (m, 2H), 2.29 (td, *J* = 9.3, 7.6 Hz, 1H), 1.93 (dq, *J* = 12.6, 8.8 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.69 (td, *J* = 8.9, 5.7 Hz, 2H), 1.59 (dt, *J* = 15.0, 6.2 Hz, 2H), 1.34 – 1.19 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.9, 136.6, 128.8, 128.5, 64.3, 61.8, 58.3, 54.6, 35.8, 32.1, 31.7, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 28.0, 23.6, 22.8, 14.3. HRMS (ESI +): calcd for $C_{23}H_{40}NO$ $[M + H]^+$ 346.3104, found: 346.3132.

4.2.3.18. (R)-(1-(4-dodecylbenzyl)pyrrolidin-2-yl)methanol (21d).: Clear oil, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.07 (d, *J* = 13.0 Hz, 1H), 3.74 – 3.66 (m, 1H), 3.55 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.12 (dt, *J* = 10.0, 4.9 Hz, 1H), 2.97 (m, 1H), 2.63 – 2.55 (m, 2H), 2.50 (m, 1H), 2.06 – 1.92 (m, 2H), 1.92 – 1.74 (m, 2H), 1.59 (m, 2H), 1.37 – 1.18 (m, 18H), 0.91 – 0.81 (m, 3H). HRMS (ESI +): calcd. for $C_{24}H_{42}NO$ $[M + H]^+$ 360.3261, found: 360.3266.

4.2.3.19. (R)-(1-(4-dodecyl-2-methylbenzyl)pyrrolidin-2-yl)methanol (21e).: Clear oil, yield 33%. ^{1}H NMR (400 MHz, CDCl3) δ: 7.38 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 4.45 (d, *J* = 13.0 Hz, 1H), 4.15 (d, *J* = 13.1 Hz, 1H), 3.88 – 3.74 (m, 2H), 3.66 – 3.58 (m, 1H), 3.43 (ddd, *J* = 11.7, 6.8, 4.9 Hz, 1H), 3.02 (ddd, *J* = 11.3, 8.3, 7.2 Hz, 1H), 2.93 – 2.82 (m, 4H), 2.31 (s, 3H), 2.21 – 2.12 (m, 1H), 2.09 – 1.89 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.2, 138.2, 135.6, 130.9, 129.6, 129.2, 128.4, 127.2, 68.2, 60.9, 58.9, 54.1, 37.8, 37.2, 26.6, 23.0, 21.2. HRMS (ESI +): calcd for $C_{25}H_{44}NO$ $[M + H]^+$ 374.3417, found: 374.3412.

4.2.3.20. (R)-(1-(4-(4-methylphenethyl)benzyl)pyrrolidin-2-yl)methanol (21f).: Clear oil, yield 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.04 (m, 4H), 4.05 (d, *J* = 13.0 Hz, 1H), 3.70 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.65 – 3.51 (m, 2H), 3.17 (s, 1H), 2.99 (s, 1H), 2.92 – 2.83 (m, 4H), 2.54 – 2.46 (m, 1H), 2.32 (s, 3H), 2.02 – 1.73 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.5, 135.4, 129.6,

129.5, 129.0, 128.7, 128.3, 65.7, 61.4, 58.5, 54.2, 37.7, 37.4, 27.3, 23.5, 21.0. HRMS (ESI +): calcd for $C_{21}H_{28}NO$ $[M + H]^+$ 310.2165, found: 310.2170.

4.2.3.21. (R)-(1-(4-(4-methoxyphenethyl)benzyl)pyrrolidin-2-yl)methanol (21g).: Clear oil, yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 16.3 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.09 (d, *J* = 13.0 Hz, 1H), 3.83 (s, 3H), 3.73 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.67 – 3.55 (m, 2H), 3.17 (d, *J* = 6.4 Hz, 1H), 3.00 (s, 1H), 2.52 (q, *J* = 8.4 Hz, 9H), 2.04 – 1.74 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.5, 130.1, 130.0, 128.8, 127.9, 126.6, 126.1, 114.3, 65.8, 61.6, 58.7, 55.5, 54.4, 32.1, 29.8, 27.5, 23.6. HRMS (ESI +): calcd for $C_{21}H_{28}NO_2$ $[M + H]^+$ 326.2115, found: 326.2119.

4.2.3.22. (R,E)-(1-(4-(4-(tert-butyl)styryl)-2-methylbenzyl)pyrrolidin-2-yl)methanol (24a).: Clear oil, yield 42%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 2H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.64 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.46 – 3.34 (m, 2H), 3.03 – 2.94 (m, 1H), 2.76 (s, 1H), 2.54 (t, *J* = 8.9, 6.7 Hz, 2H), 2.34 (s, 3H), 2.33 – 2.27 (m, 1H), 2.01 – 1.89 (m, 1H), 1.89 – 1.79 (m, 1H), 1.76 – 1.64 (m, 2H), 1.58 (p, *J* = 10.6, 4.8 Hz, 2H), 1.37 – 1.20 (m, 19H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.7, 136.4, 130.8, 130.4, 130.0, 126.0, 65.5, 62.0, 56.5, 54.7, 35.7, 32.1, 31.7, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 27.8, 23.8, 22.9, 19.5, 14.3, 14.2. HRMS (ESI +): calcd for $C_{25}H_{34}NO$ $[M + H]^+$ 364.2635, found: 364.2622.

4.2.3.23. (R,E)-(1-(4-(3-(trifluoromethyl)styryl)benzyl)pyrrolidin-2-yl) methanol (24b).: Clear oil, yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.54 – 7.43 (m, 4H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.13 (q, *J* = 16.4 Hz, 2H), 3.98 (d, *J* = 13.1 Hz, 1H), 3.68 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.46 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.80 – 2.72 (m, 1H), 2.71 (s, 1H), 2.37 – 2.26 (m, 1H), 2.01 – 1.90 (m, 1H), 1.90 – 1.80 (m, 1H), 1.77 – 1.66 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) *δ* 140.1, 139.6, 132.4, 132.0, 131.2, 131.0, 131.0, 131.0, 131.0, 130.6, 130.6, 129.8, 128.6, 125.4, 125.4, 125.3, 125.3, 124.4, 124.3, 124.3, 124.3, 70.0, 60.7, 59.3, 55.6, 27.3, 23.2. HRMS (ESI +): calcd for $C_{21}H_{23}F_3NO$ $[M + H]^+$ 362.1726, found: 362.1712.

4.2.3.24. (R)-(1-(4-((4-propylphenyl)ethynyl)benzyl)pyrrolidin-2-yl) methanol (27a).: Clear oil, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.45 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.00 – 2.94 (m, 1H), 2.77 – 2.70 (m, 1H), 2.62 – 2.57 (m, 2H), 2.32 – 2.24 (m, 1H), 1.99 – 1.89 (m, 1H), 1.85 (dt, *J* = 13.0, 6.4 Hz, 1H), 1.75 – 1.68 (m, 2H), 1.64 (dt, *J* = 14.8, 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.2, 139.5, 131.7, 131.6, 128.8, 128.6, 122.4, 120.6, 89.6, 88.8, 64.5, 62.0, 58.5, 54.6, 38.1, 27.9, 24.5, 23.6, 13.9. HRMS (ESI +): calcd for $C_{23}H_{28}NO$ $[M + H]^+$ 334.2165, found: 334.2142.

4.2.3.25. (R)-(1-(4-((4-butylphenyl)ethynyl)benzyl)pyrrolidin-2-yl)methanol (27b).: Clear oil, yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.45 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.37 (d, *J*

= 13.2 Hz, 1H), 2.98 (dt, *J* = 9.3, 4.4 Hz, 1H), 2.74 (ddt, *J* = 9.1, 5.9, 2.9 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.34 – 2.23 (m, 1H), 1.95 (dt, *J* = 12.6, 8.7 Hz, 1H), 1.84 (td, *J* = 13.0, 12.6, 7.1 Hz, 1H), 1.71 (tt, *J* = 8.6, 3.8 Hz, 2H), 1.66 – 1.54 (m, 2H), 1.36 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.5, 139.4, 131.7, 131.6, 128.8, 128.6, 122.3, 120.5, 89.6, 88.7, 64.5, 61.9, 58.5, 54.6, 35.7, 33.5, 27.8, 23.6, 22.4, 14.1. HRMS (ESI +): calcd for $C_{24}H_{30}NO$ $[M + H]^+$ 348.2322, found: 348.2342.

4.2.3.26. (R)-(1-(4-((4-pentylphenyl)ethynyl)benzyl)pyrrolidin-2-yl) methanol (27c).: Clear oil, yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.45 (dd, *J* = 10.8, 2.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.80 – 2.69 (m, 1H), 2.66 – 2.57 (m, 2H), 2.35 – 2.23 (m, 1H), 2.02 – 1.78 (m, 2H), 1.77 – 1.66 (m, 2H), 1.62 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.33 (td, *J* = 7.8, 6.5, 4.5 Hz, 4H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.5, 139.5, 131.7, 131.6, 128.8, 128.6, 122.3, 120.5, 89.6, 88.7, 64.5, 61.9, 58.5, 54.6, 36.0, 31.6, 31.1, 27.9, 23.6, 22.7, 14.2. HRMS (ESI +): calcd for $C_{25}H_{32}NO$ $[M + H]^+$ 362.2478, found: 362.2456.

4.2.4. General procedure for the synthesis of compounds 12a-e, 18a-i, 22a-h, 25a-b, 29a-c, 30a-c—

To a round bottom flask containing methanol (0.2 M), the appropriate tertiary amine analogue (1.0 equiv.) was added and stirred. Next, the mixture was bubbled with HCl gas for 1 min and then stirred for 5 – 10 min. The reaction progress was monitored by TLC. Lastly, the organic mixture was concentrated via vacuum and triturated with diethyl ether to afford the corresponding analogue as an HCl salt.

4.2.4.1. (R)-(1-(4-(heptyloxy)benzyl)pyrrolidin-2-yl)methanol (12a).: White solid, yield 95%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.48 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.58 (d, *J* = 13.0 Hz, 1H), 4.24 (d, *J* = 13.0 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.79 – 3.68 (m, 3H), 3.42 – 3.36 (m, 1H), 3.30 – 3.23 (m, 1H), 2.30 – 2.20 (m, 1H), 2.14 – 2.05 (m, 1H), 1.83 – 1.74 (m, 2H), 1.53 – 1.44 (m, 2H), 1.39 – 1.31 (m, 6H), 0.95 – 0.89 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 161.8, 133.4, 123.3, 116.0, 69.5, 69.1, 60.8, 59.0, 55.2, 32.9, 30.3, 30.1, 27.3, 27.1, 23.6, 23.1, 14.4. HRMS (ESI +): calcd for $C_{19}H_{32}NO_2$ $[M + H]^+$ 306.2428, found: 306.2438.

4.2.4.2. (R)-(1-(4-(octyloxy)benzyl)pyrrolidin-2-yl)methanol (12b).: White solid, yield 97%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.37 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.49 (d, *J* = 13.0 Hz, 1H), 4.13 (d, *J* = 13.0 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.72 – 3.57 (m, 3H), 3.34 – 3.26 (m, 1H), 3.21 – 3.14 (m, 1H), 2.17 (ddt, *J* = 10.5, 6.3, 3.4 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.93 – 1.83 (m, 2H), 1.77 – 1.69 (m, 2H), 1.41 (t, *J* = 7.7 Hz, 2H), 1.31 – 1.23 (m, 8H), 0.87 – 0.81 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 161.9, 133.3, 123.3, 116.1, 69.4, 69.1, 60.8, 59.1, 55.3, 33.0, 30.4, 30.4, 30.3, 27.3, 27.1, 23.7, 23.1, 14.4. HRMS (ESI +): calcd for $C_{20}H_{34}NO_2$ $[M + H]^+$ 320.2584, found: 320.2582.

4.2.4.3. (R)-(1-(4-(nonyloxy)benzyl)pyrrolidin-2-yl)methanol (12c).: White solid, yield 97%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.42 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.54 (d, *J* = 12.9 Hz, 1H), 4.18 (d, *J* = 13.0 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.80 – 3.70

(m, 1H), 3.71 – 3.61 (m, 2H), 3.41 – 3.33 (m, 1H), 3.27 – 3.20 (m, 1H), 2.29 – 2.16 (m, 1H), 2.14 – 2.02 (m, 1H), 1.99 – 1.85 (m, 2H), 1.77 (dt, *J* = 14.6, 6.5 Hz, 2H), 1.53 – 1.41 (m, 2H), 1.40 – 1.24 (m, 10*H*), 0.94 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 146.3, 131.9, 130.3, 129.0, 69.8, 60.8, 59.4, 55.5, 36.6, 33.0, 32.5, 30.7, 30.6, 30.4, 30.3, 27.3, 23.7, 23.1, 14.4. HRMS (ESI +): calcd for $C_{21}H_{36}NO_2$ $[M + H]^+$ 334.2741, found: 334.2762.

4.2.4.4. (R)-(1-(4-(decyloxy)benzyl)pyrrolidin-2-yl)methanol (12d).: White solid, yield 91%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.44 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.55 (d, *J* = 13.0 Hz, 1H), 4.20 (d, *J* = 13.0 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.78 – 3.66 (m, 3H), 3.40 – 3.35 (m, 1H), 3.27 – 3.21 (m, 1H), 2.28 – 2.19 (m, 1H), 2.12 – 2.04 (m, 1H), 1.97 – 1.87 (m, 2H), 1.82 – 1.72 (m, 2H), 1.47 (p, *J* = 6.9 Hz, 2H), 1.40 – 1.25 (m, 12H), 0.92 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 161.9, 133.4, 123.3, 116.1, 69.5, 69.2, 60.8, 59.1, 55.3, 33.1, 30.7, 30.7, 30.5, 30.5, 30.3, 27.3, 27.1, 23.7, 23.1, 14.4. HRMS (ESI +): calcd for $C_{22}H_{38}NO_2$ $[M + H]^+$ 348.2897, found: 348.2917.

4.2.4.5. (R)-(1-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)pyrrolidin-2-yl)methanol (12e).: White solid, yield 90%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.53 (s, 2H), 6.91 (s, 2H), 4.26 (m, 4H), 3.89 (d, *J* = 19.7 Hz, 2H), 3.60 (s, 3H), 3.00 (s, 1H), 2.07 (s, 3H), 1.76 (s, 2H), 1.34 (m, 10*H*), 0.85 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 160.6, 133.1, 120.6, 115.2, 68.8, 68.3, 61.0, 59.1, 53.8, 50.8, 32.0, 29.6, 29.5, 29.3, 29.2, 26.6, 26.1, 23.7, 22.8, 14.2. HRMS (ESI +): calcd for $C_{20}H_{23}F_3NO_2$ $[M + H]^+$ 366.1675, found: 366.1680.

4.2.4.6. (R)-(1-(4-phenoxybenzyl)pyrrolidin-2-yl)methanol (18a).: White solid, yield 90%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.56 – 7.51 (m, 2H), 7.42 – 7.36 (m, 2H), 7.20 – 7.14 (m, 1H), 7.06 – 7.01 (m, 4H), 4.62 (d, *J* = 13.0 Hz, 1H), 4.26 (d, *J* = 13.0 Hz, 1H), 3.84 – 3.72 (m, 3H), 3.48 – 3.40 (m, 1H), 3.29 – 3.24 (m, 1H), 2.28 – 2.19 (m, 1H), 2.15 – 2.07 (m, 1H), 2.04 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 160.5, 157.6, 133.8, 131.1, 126.1, 125.3, 120.6, 119.6, 69.7, 67.0, 58.9, 55.4, 27.3, 23.1. HRMS (ESI +): calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1645, found: 284.1656.

4.2.4.7. (R)-(1-(4-(3-(tert-butyl)phenoxy)benzyl)pyrrolidin-2-yl)methanol (18b).: White solid, yield 92%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.54 – 7.49 (m, 2H), 7.31 (td, *J* = 7.9, 0.4 Hz, 1H), 7.23 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1H), 7.07 (ddd, *J* = 2.4, 1.9, 0.4 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.81 (ddd, *J* = 8.0, 2.4, 1.1 Hz, 1H), 4.61 (d, *J* = 13.0 Hz, 1H), 4.25 (d, *J* = 13.0 Hz, 1H), 3.80 – 3.68 (m, 3H), 3.40 (ddd, *J* = 11.4, 7.5, 4.8 Hz, 1H), 3.29 – 3.23 (m, 1H), 2.28 – 2.20 (m, 1H), 2.13 – 2.07 (m, 1H), 1.99 – 1.89 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ: 160.8, 157.2, 155.0, 133.7, 130.6, 125.8, 122.4, 119.3, 118.0, 117.7, 69.7, 60.8, 58.9, 55.4, 35.6, 31.6, 27.3, 23.1. HRMS (ESI +): calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2271, found: 340.2278.

4.2.4.8. (R)-(1-(4-(4-(tert-butyl)phenoxy)benzyl)pyrrolidin-2-yl)methanol (18c).: White solid, yield 94%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.72 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.47 – 7.35 (m, 4H), 4.70 (d, *J* = 12.9 Hz, 1H), 4.32 (d, *J* = 12.9 Hz, 1H), 3.83 – 3.72 (m, 3H), 3.43 (ddd, *J* = 11.6, 6.9, 4.2 Hz, 1H), 3.31 (dt, *J* = 3.4, 1.7 Hz, 2H), 2.27 (dtd, *J* = 14.3, 8.3, 7.4, 4.3 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.02 – 1.89 (m, 2H), 1.38

(s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ: 153.1, 144.8, 141.1, 132.5, 129.8, 128.9, 126.0, 125.1, 69.9, 60.8, 59.2, 55.5, 35.7, 31.8, 27.3, 23.1. HRMS (ESI +): calcd for $C_{22}H_{30}NO_2$ $[M + H]^+$ 340.2271, found: 340.2275.

4.2.4.9. (R)-(1-(4-([1,1′-biphenyl]-3-yloxy)benzyl)pyrrolidin-2-yl)methanol (18d).: White solid, 97%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.58 – 7.52 (m, 4H), 7.49 – 7.39 (m, 4H), 7.36 – 7.31 (m, 1H), 7.26 (ddd, *J* = 2.3, 1.6, 0.5 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.01 (ddd, *J* = 7.5, 2.4, 1.6 Hz, 1H), 4.62 (d, *J* = 12.9 Hz, 1H), 4.25 (d, *J* = 13.0 Hz, 1H), 3.81 – 3.68 (m, 3H), 3.44 – 3.37 (m, 1H), 3.29 – 3.22 (m, 1H), 2.28 – 2.21 (m, 1H), 2.14 – 2.07 (m, 1H), 1.99 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 159.1, 156.8, 143.4, 140.1, 132.4, 130.1, 128.6, 127.4, 126.6, 124.9, 122.5, 118.4, 117.9, 117.7, 68.4, 59.4, 57.5, 54.0, 25.9, 21.8. HRMS (ESI +): calcd for $C_{24}H_{26}NO_2$ $[M + H]^+$ 360.1958, found: 360.1963.

4.2.4.10. (R)-(1-(4-([1,1′ -biphenyl]-4-yloxy)benzyl)pyrrolidin-2-yl)methanol (18e).: White solid, yield 90%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.66 – 7.63 (m, 2H), 7.62 – 7.58 (m, 2H), 7.57 – 7.53 (m, 2H), 7.45 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 7.13 – 7.08 (m, 4H), 4.63 (d, *J* = 13.0 Hz, 1H), 4.27 (d, *J* = 13.0 Hz, 1H), 3.82 – 3.69 (m, 3H), 3.45 – 3.40 (m, 1H), 3.30 – 3.24 (m, 1H), 2.31 – 2.21 (m, 1H), 2.18 – 2.07 (m, 1H), 2.01 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 160.4, 157.1, 141.5, 138.6, 133.8, 129.9, 129.6, 128.3, 127.8, 126.2, 120.9, 119.7, 69.7, 60.8, 58.9, 55.4, 27.3, 23.1. HRMS (ESI +): calcd for $C_{24}H_{26}NO_2$ $[M + H]$+ 360.1958, found: 360.1968.

4.2.4.11. (R)-(1-(4-((3′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (18f).: White solid, yield 98%. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.84 – 7.76 (m, 2H), 7.61 (t, *J* = 5.2 Hz, 2H), 7.55 – 7.52 (m, 2H), 7.50 – 7.45 (m, 1H), 7.44 – 7.41 (m, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.10 – 7.06 (m, 2H), 7.05 – 7.02 (m, 1H), 4.60 (d, *J* = 13.0 Hz, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.71 – 3.66 (m, 2H), 3.37 (ddd, *J* = 11.6, 7.3, 4.5 Hz, 1H), 3.27 – 3.22 (m, 2H), 2.25 – 2.18 (m, 1H), 2.07 (qd, *J* = 8.0, 3.1 Hz, 1H), 1.98 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 188.4, 186.6, 171.2, 170.7, 162.1, 160.5, 160.3, 160.0, 160.0, 159.0, 154.8, 154.7, 153.6, 152.7, 152.1, 148.2, 148.1, 147.3, 98.0, 89.0, 87.0, 83.6, 55.5, 51.3. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$ 428.1832, found: 428.1840.

4.2.4.12. (R)-(1-(4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (18 g).: White solid, yield 95%. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.81 (d, *J* = 8.0 Hz, 2H), 7.73 (dd, *J* = 8.4, 4.5 Hz, 4H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.17 – 7.11 (m, 4H), 4.63 (d, *J* = 13.0 Hz, 1H), 4.26 (d, *J* = 13.0 Hz, 1H), 3.81 – 3.77 (m, 1H), 3.74 – 3.68 (m, 1H), 3.41 (td, *J* = 7.2, 3.7 Hz, 1H), 3.30 – 3.25 (m, 2H), 2.25 (dddd, *J* = 12.9, 8.7, 6.2, 3.1 Hz, 1H), 2.15 – 2.09 (m, 1H), 2.00 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 160.1, 158.1, 145.3, 136.7, 133.8, 130.0, 128.3, 126.8, 126.8, 126.8, 126.8, 126.5, 124.7, 120.9, 120.1, 69.8, 60.7, 58.9, 55.4, 27.3, 23.1. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$ 428.1832, found: 428.1837.

4.2.4.13. (R)-(1-(4-((3′ -(trifluoromethyl)-[1,1′ -biphenyl]-4-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (18 h).: White solid, yield 97%. ^{1}H NMR (500 MHz,

CD3OD) δ: δ 7.79 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.61 – 7.51 (m, 4H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.26 (d, *J* = 13.0 Hz, 1H), 3.82 – 3.75 (m, 2H), 3.69 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.30 – 3.21 (m, 2H), 2.74 – 2.67 (m, 1H), 2.11 – 2.03 (m, 1H), 1.95 – 1.83 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 157.4, 156.8, 141.2, 135.2, 131.5, 131.3, 131.0, 130.8, 130.2, 129.3, 129.0, 128.7, 127.4, 125.2, 123.8, 123.8, 123.8, 123.7, 123.7, 123.7, 123.6, 123.6, 123.1, 120.9, 66.5, 61.3, 58.3, 54.1, 27.1, 23.1. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$ 428.1832, found: 428.1839.

4.2.4.14. (R)-(1-(4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)oxy) benzyl)pyrrolidin-2-yl)methanol (18i).: White solid, yield 91%. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.80 (s, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 4.5 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.07 (dd, *J* = 13.8, 8.4 Hz, 4H), 4.59 (d, *J* = 13.0 Hz, 1H), 4.23 (d, *J* = 13.0 Hz, 1H), 3.77 – 3.71 (m, 1H), 3.70 – 3.65 (m, 1H), 3.39 – 3.33 (m, 1H), 3.26 – 3.20 (m, 2H), 2.24 – 2.17 (m, 1H), 2.09 – 2.02 (m, 1H), 1.95 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 162.6, 160.5, 145.2, 139.2, 136.5, 135.2, 134.9, 134.6, 134.4, 134.1, 133.4, 132.4, 131.5, 129.3, 127.4, 127.4, 127.4, 127.3, 127.2, 126.9, 126.9, 126.9, 125.0, 123.5, 122.6, 72.4, 63.4, 61.4, 58.0, 29.9, 25.7. HRMS (ESI +): calcd for $C_{25}H_{25}F_3NO_2$ $[M + H]^+$ 428.1832, found: 428.1834.

4.2.4.15. (R)-(1-(4-nonylbenzyl)pyrrolidin-2-yl)methanol (22a).: White solid, yield 92%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.45 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.27 (m, 2H), 4.60 (d, *J* = 12.9 Hz, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 3.80 – 3.67 (m, 3H), 3.41 – 3.29 (m, 1H), 3.30 – 3.22 (m, 1H), 2.68 – 2.62 (m, 2H), 2.24 (qd, *J* = 6.0, 2.9 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.98 – 1.86 (m, 2H), 1.66 – 1.58 (m, 2H), 1.37 – 1.25 (m, 12H), 0.93 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 144.9, 130.5, 128.9, 127.6, 68.4, 59.4, 57.9, 54.1, 35.2, 31.6, 31.1, 29.3, 29.2, 29.0, 28.9, 22.3, 21.7, 13.0. HRMS (ESI +): calcd for $C_{21}H_{36}NO$ $[M + H]^+$ 318.2791, found: 318.2802.

4.2.4.16. (R)-(1-(4-decylbenzyl)pyrrolidin-2-yl)methanol (22b).: White solid, yield 90%. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.02 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 13.1 Hz, 1H), 4.49 (d, *J* = 13.4 Hz, 1H), 4.40 (dd, *J* = 12.3, 3.1 Hz, 1H), 4.30 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.90 – 3.84 (m, 1H), 3.33 (dd, *J* = 8.1, 3.7 Hz, 2H), 3.24 – 3.18 (m, 2H), 2.67 – 2.53 (m, 3H), 2.52 – 2.43 (m, 1H), 2.20 (q, *J* = 7.2 Hz, 2H), 1.96 – 1.84 (m, 16H), 1.52 – 1.47 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 145.9, 132.3, 131.0, 128.1, 69.0, 63.2, 60.6, 56.0, 37.7, 34.0, 33.4, 31.8, 31.7, 31.7, 31.7, 31.6, 31.4, 29.0, 25.5, 24.8, 16.2. HRMS (ESI +): calcd for $C_{22}H_{38}NO$ $[M + H]^+$ 332.2948, found: 332.2955.

4.2.4.17. (R)-(1-(4-undecylbenzyl)pyrrolidin-2-yl)methanol (22c).: White solid, yield 91%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.27 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.70 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.55 – 3.49 (m, 2H), 3.11 (ddd, *J* = 9.9, 6.6, 3.4 Hz, 1H), 2.92 (td, *J* = 6.0, 3.0 Hz, 1H), 2.60 – 2.57 (m, 2H), 2.49 – 2.40 (m, 1H), 2.00 – 1.91 (m, 1H), 1.90 – 1.84 (m, 1H), 1.83 – 1.72 (m, 2H), 1.59 (p, *J* = 7.2 Hz, 2H), 1.35 – 1.22 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 142.8, 134.1, 129.4, 128.7, 65.4, 61.6, 58.5, 54.3, 35.8, 32.0, 31.6, 29.8, 29.8, 29.7, 29.6, 29.5,

27.6, 23.6, 22.8, 14.3. HRMS (ESI +): calcd for $C_{23}H_{40}NO$ $[M + H]^+$ 346.3104, found: 346.3132.

4.2.4.18. (R)-(1-(4-dodecylbenzyl)pyrrolidin-2-yl)methanol (22d).: White solid, yield 89%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.43 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 4.59 (d, *J* = 12.7 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.71 – 3.64 (m, 2H), 3.40 – 3.35 (m, 1H), 3.27 – 3.21 (m, 1H), 2.69 – 2.61 (m, 2H), 2.27 – 2.18 (m, 1H), 2.15 – 2.03 (m, 1H), 2.00 – 1.84 (m, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.35 – 1.23 (m, 18H), 0.92 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 146.4, 131.9, 130.4, 129.0, 69.8, 60.7, 59.4, 55.5, 36.6, 33.1, 32.6, 30.8, 30.8, 30.7, 30.7, 30.6, 30.5, 30.3, 27.3, 23.7, 23.1, 14.4. HRMS (ESI +): calcd for $C_{24}H_{42}NO$ $[M + H]^+$ 360.3261, found: 360.3266.

4.2.4.19. (R)-(1-(4-dodecyl-2-methylbenzyl)pyrrolidin-2-yl)methanol (22e).: White solid, yield 98%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.36 (d, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.11 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.77 (d, *J* = 13.2 Hz, 1H), 4.15 (d, *J* = 13.2 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.76 – 3.69 (m, 2H), 3.41 – 3.33 (m, 1H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.47 (s, 3H), 2.34 – 2.21 (m, 1H), 2.18 – 2.06 (m, 1H), 2.00 – 1.86 (m, 2H), 1.65 – 1.56 (m, 2H), 1.37 – 1.23 (m, 19H), 0.90 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 146.5, 139.5, 132.8, 132.5, 127.8, 127.6, 70.5, 60.4, 57.0, 55.6, 36.5, 33.1, 32.5, 30.8, 30.7, 30.7, 30.7, 30.6, 30.5, 30.3, 27.0, 23.7, 23.0, 19.5, 14.4. HRMS (ESI +): calcd for $C_{25}H_{44}NO$ $[M + H]^+$ 374.3417, found: 374.3427.

4.2.4.20. (R)-(1-(4-(4-methylphenethyl)benzyl)pyrrolidin-2-yl)methanol (22f).: White solid, yield 93%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.40 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.03 – 6.96 (m, 4H), 4.56 (d, *J* = 12.9 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 3.74 – 3.63 (m, 3H), 3.37 – 3.32 (m, 1H), 3.26 – 3.19 (m, 1H), 2.94 – 2.81 (m, 4H), 2.24 (s, 3H), 2.20 (d, *J* = 3.2 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.97 – 1.85 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 143.9, 138.0, 135.0, 130.4, 129.2, 128.5, 128.0, 127.8, 68.4, 59.4, 58.0, 54.1, 37.3, 36.8, 25.9, 21.8, 19.7. HRMS (ESI +): calcd for $C_{21}H_{28}NO$ $[M + H]^+$ 310.2165, found: 310.2176.

4.2.4.21. (R)-(1-(4-(4-methoxyphenethyl)benzyl)pyrrolidin-2-yl)methanol (22 g).: White solid, yield 94%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.24 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.98 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 3H), 3.67 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.50 – 3.42 (m, 2H), 3.05 (ddd, *J* = 9.7, 5.8, 4.0 Hz, 1H), 2.89 – 2.82 (m, 5H), 2.42 – 2.34 (m, 1H), 1.98 – 1.92 (m, 1H), 1.90 – 1.83 (m, 1H), 1.78 – 1.71 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 158.0, 141.3, 135.6, 133.9, 129.5, 129.2, 128.7, 113.9, 64.9, 61.7, 58.5, 55.4, 54.5, 38.0, 37.1, 27.8, 23.6. HRMS (ESI +): calcd for $C_{21}H_{28}NO_2$ $[M + H]^+$ 326.2115, found: 326.2135.

4.2.4.22. (R)-(1-(4-undecylbenzyl)pyrrolidin-2-yl)methyl acetate (22 h).: White solid, 90%. ^{1}H NMR (400 MHz, CD_3OD) *δ* 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.57 (d, *J* = 12.9 Hz, 1H), 4.36 – 4.31 (m, 2H), 4.20 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.98 – 3.93 (m, 1H), 3.49 (ddd, *J* = 12.0, 7.3, 5.3 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.66 (dd, *J* = 8.5, 6.8 Hz, 2H), 2.41 – 2.31 (m, 1H), 2.19 – 2.12 (m, 1H), 2.08 (s, 3H), 2.05 – 1.91 (m, 2H), 1.67 – 1.59 (m, 2H), 1.31 (d, *J* = 17.3 Hz, 16H), 0.92 – 0.87 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ:

171.8, 146.5, 132.0, 130.5, 128.8, 67.2, 63.1, 59.6, 56.0, 36.6, 33.1, 32.5, 30.8, 30.7, 30.7, 30.6, 30.5, 30.3, 27.6, 23.7, 23.1, 20.6, 14.5. HRMS (ESI +): calcd for $C_{25}H_{42}NO_2$ [M + H]$^+$ 388.3210, found: 388.3240.

4.2.4.23. (R,E)-(1-(4-(4-(tert-butyl)styryl)-2-methylbenzyl)pyrrolidin-2-yl)methanol (25a).: White solid, yield 94%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.54 – 7.47 (m, 3H), 7.47 – 7.43 (m, 1H), 7.44 – 7.38 (m, 2H), 7.18 (q, *J* = 16.3 Hz, 3H), 4.20 (d, *J* = 13.2 Hz, 1H), 4.00 – 3.91 (m, 1H), 3.81 – 3.70 (m, 2H), 2.53 (s, 3H), 2.36 – 2.24 (m, 2H), 2.21 – 2.09 (m, 2H), 2.03 – 1.89 (m, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ: 152.3, 141.0, 140.0, 135.6, 133.2, 131.2, 130.3, 129.1, 127.7, 127.5, 126.7, 125.4, 70.5, 60.4, 56.9, 55.7, 35.5, 31.7, 27.0, 23.0, 19.5. HRMS (ESI +): calcd for $C_{25}H_{33}NO$ [M + H]$^+$ 363.2562, found: 363.2564.

4.2.4.24. (R,E)-(1-(4-(3-(trifluoromethyl)styryl)benzyl)pyrrolidin-2-yl) methanol (25b).: White solid, yield 94%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.86 (s, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.36 (s, 2H), 4.67 (d, *J* = 12.9 Hz, 1H), 4.29 (d, *J* = 13.0 Hz, 1H), 3.86 – 3.68 (m, 3H), 3.46 – 3.37 (m, 1H), 3.30 – 3.22 (m, 1H), 2.33 – 2.20 (m, 1H), 2.19 – 2.06 (m, 1H), 2.05 – 1.87 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ: 140.1, 139.6, 132.4, 132.0, 131.2, 131.0, 131.0, 131.0, 131.0, 130.6, 130.6, 129.8, 128.6, 125.4, 125.4, 125.3, 125.3, 124.4, 124.3, 124.3, 124.3, 70.0, 60.7, 59.3, 55.6, 27.3, 23.2. HRMS (ESI +): calcd for $C_{21}H_{22}F_3NO$ [M + H]$^+$ 361.1653, found: 361.1663.

4.2.4.25. (R)-(1-(4-(4-propylphenethyl)benzyl)pyrrolidin-2-yl)methanol (29a).: White solid, yield 90%. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.41 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.04 (s, 4H), 4.58 (d, *J* = 12.8 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 3.69 (dt, *J* = 13.4, 7.2 Hz, 2H), 3.36 (ddd, *J* = 6.7, 4.8, 2.4 Hz, 1H), 3.24 (dt, *J* = 11.4, 7.9 Hz, 1H), 2.98 – 2.85 (m, 4H), 2.55 – 2.50 (m, 2H), 2.26 – 2.19 (m, 1H), 2.12 – 2.05 (m, 1H), 1.93 (dq, *J* = 12.9, 6.9, 6.2 Hz, 2H), 1.65 – 1.55 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ: 145.4, 141.3, 139.7, 131.8, 130.6, 129.4, 129.4, 127.7, 69.7, 60.7, 59.4, 55.5, 38.7, 38.6, 38.3, 27.3, 25.8, 23.1, 14.1. HRMS (ESI +): calcd for $C_{23}H_{32}NO$ [M + H]$^+$ 338.2478, found: 338.2498.

4.2.4.26. (R)-(1-(4-(4-butylphenethyl)benzyl)pyrrolidin-2-yl)methanol (29b).: White solid, yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 4H), 4.06 (d, *J* = 13.0 Hz, 1H), 3.74 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.13 (dd, *J* = 9.7, 5.5 Hz, 1H), 2.99 – 2.87 (m, 4H), 2.68 – 2.59 (m, 2H), 2.51 – 2.40 (m, 1H), 2.06 – 1.85 (m, 2H), 1.87 – 1.74 (m, 2H), 1.66 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.42 – 1.34 (m, 2H), 1.00 – 0.91 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 140.9, 139.3, 132.5, 129.5, 128.9, 128.8, 128.7, 65.2, 62.0, 58.8, 54.7, 38.1, 37.9, 36.0, 31.7, 28.0, 23.9, 23.0, 14.5. HRMS (ESI +): calcd for $C_{24}H_{34}NO$ [M + H]$^+$ 352.2635, found: 352.2638.

4.2.4.27. (R)-(1-(4-(4-pentylphenethyl)benzyl)pyrrolidin-2-yl)methanol (29c).: White solid, yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.15 (s, 4H), 4.05 (d, *J* = 12.8 Hz, 1H), 3.73 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.12 (dd, *J* = 9.7, 5.6 Hz, 1H), 2.98 – 2.86 (m, 4H), 2.67 – 2.58 (m, 2H),

2.50 – 2.39 (m, 1H), 2.05 – 1.84 (m, 2H), 1.86 – 1.73 (m, 2H), 1.65 (dt, *J* = 15.0, 7.6 Hz, 2H), 1.41 – 1.33 (m, 2H), 0.99 – 0.90 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 141.9, 141.1, 139.5, 132.7, 129.7, 129.1, 129.0, 128.9, 65.4, 62.2, 59.0, 54.9, 38.3, 38.1, 36.2, 32.2, 31.9, 28.2, 24.1, 23.2, 14.7. HRMS (ESI +): calcd for $C_{25}H_{36}NO$ $[M + H]^+$ 366.2791, found: 366.2814.

4.2.4.28. (R)-(1-(4-((4-propylphenyl)ethynyl)benzyl)pyrrolidin-2-yl) methanol (30a).: Yellow solid, yield 98%. ^{1}H NMR (400 MHz, CD_3CD) δ: 7.62 – 7.59 (m, 2H), 7.57 – 7.54 (m, 2H), 7.44 – 7.41 (m, 2H), 7.23 – 7.18 (m, 2H), 4.70 – 4.63 (m, 1H), 4.29 (d, *J* = 13.0 Hz, 1H), 3.82 – 3.69 (m, 3H), 3.43 – 3.36 (m, 1H), 3.28 – 3.24 (m, 1H), 2.61 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.29 – 2.23 (m, 1H), 2.16 – 2.09 (m, 1H), 2.01 – 1.88 (m, 2H), 1.71 – 1.59 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3CD) δ: 143.6, 131.7, 131.2, 130.7, 130.1, 128.4, 125.2, 119.9, 90.7, 87.1, 68.7, 59.4, 57.8, 54.2, 37.5, 25.9, 24.1, 21.8, 12.7. HRMS (ESI +): calcd for $C_{23}H_{27}NO$ $[M + H]^+$ 333.2093, found: 333.2103.

4.2.4.29. (R)-(1-(4-((4-butylphenyl)ethynyl)benzyl)pyrrolidin-2-yl)methanol (30b).: Yellow solid, yield 93%. ^{1}H NMR (400 MHz, CD_3CD) δ: 7.63 – 7.59 (m, 2H), 7.56 – 7.52 (m, 2H), 7.44 – 7.40 (m, 2H), 7.23 – 7.19 (m, 2H), 4.66 (d, *J* = 12.9 Hz, 1H), 4.27 (d, *J* = 12.9 Hz, 1H), 3.82 – 3.68 (m, 3H), 3.42 – 3.35 (m, 1H), 3.29 – 3.23 (m, 1H), 2.66 – 2.61 (m, 2H), 2.29 – 2.22 (m, 1H), 2.17 – 2.09 (m, 1H), 2.00 – 1.90 (m, 2H), 1.65 – 1.57 (m, 2H), 1.41 – 1.31 (m, 2H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, CD_3CD) δ: 145.3, 133.1, 132.6, 132.1, 131.5, 129.7, 126.7, 121.2, 92.2, 88.4, 70.1, 60.7, 59.2, 55.6, 36.5, 34.7, 27.2, 23.3, 23.1, 14.2. HRMS (ESI +): calcd for $C_{24}H_{29}NO$ $[M + H]^+$ 347.2249, found: 347.2269.

4.2.4.30. (R)-(1-(4-((4-pentylphenyl)ethynyl)benzyl)pyrrolidin-2-yl) methanol (30c).: Yellow solid, yield 99%. ^{1}H NMR (400 MHz, CD_3CD) δ: 7.63 – 7.59 (m, 2H), 7.57 – 7.53 (m, 2H), 7.44 – 7.40 (m, 2H), 7.22 – 7.17 (m, 2H), 4.66 (d, *J* = 12.9 Hz, 1H), 4.28 (d, *J* = 13.0 Hz, 1H), 3.84 – 3.68 (m, 3H), 3.40 (ddd, *J* = 11.5, 7.3, 4.5 Hz, 1H), 3.29 – 3.23 (m, 1H), 2.65 – 2.60 (m, 2H), 2.29 – 2.22 (m, 1H), 2.16 – 2.08 (m, 1H), 2.00 – 1.87 (m, 2H), 1.67 – 1.58 (m, 2H), 1.39 – 1.30 (m, 4H), 0.93 – 0.88 (m, 3H). ^{13}C NMR (101 MHz, CD_3CD) δ: 145.3, 133.1, 132.6, 132.1, 131.5, 129.7, 126.7, 121.2, 92.1, 88.5, 70.1, 60.7, 59.2, 55.6, 36.8, 32.5, 32.1, 27.2, 23.5, 23.1, 14.4. HRMS (ESI +): calcd for $C_{25}H_{31}NO$ $[M + H]^+$ 361.2406, found: 361.2408.

4.2.5. General procedure for the synthesis of compounds 14a-e—To a round bottom flask containing DMF the appropriate phenol analogue (1.5 equiv.), sodium bicarbonate (5.0 equiv.) and 4-fluorobenzonitrile (1.0 equiv.) were added and refluxed under nitrogen gas for 12 h. After, the resulting solution was partitioned between EtOAc and LiBr aqueous solution. Using additional EtOAc, the aqueous LiBr solution was washed three times and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated via vacuum. The resulting concentrate was purified by silica gel chromatography.

4.2.5.1. 4-phenoxybenzonitrile (14a).: White solid, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 9.0 Hz, 2H), 7.40 (dd, *J* = 8.5, 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.06 (dd, *J* = 8.6, 1.1 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ: 161.6, 154.7, 134.1, 130.2, 125.1, 120.4, 118.8, 117.9, 105.7. HRMS (ESI +): calcd for $C_{13}H_{10}NO$ $[M + H]^+$ 196.0757, found: 196.0744.

4.2.5.2. 4-(3-(tert-butyl)phenoxy)benzonitrile (14b).: White solid, yield 70%. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 9.0 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.09 (t, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.84 (ddd, *J* = 7.9, 2.4, 1.1 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.0, 154.6, 154.3, 134.2, 129.8, 122.3, 119.0, 117.8, 117.8, 117.4, 105.6, 35.0, 31.4. HRMS (ESI +): calcd for $C_{17}H_{18}NO$ $[M + H]^+$ 252.1383, found: 252.1363.

4.2.5.3. 4-(4-(tert-butyl)phenoxy)benzonitrile (14c).: White solid, yield 73%. ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.58 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 2.3 Hz, 2H), 6.98 (d, *J* = 2.2 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 162.0, 152.3, 148.2, 134.1, 127.1, 120.0, 119.0, 117.7, 105.5, 34.5, 31.5. HRMS (ESI +): calcd for $C_{17}H_{18}NO$: $[M + H]^+$ 252.1383, found: 252.1366.

4.2.5.4. 4-(3-bromophenoxy)benzonitrile (14d).: White solid, yield 79%. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.9 Hz, 2H), 7.35 (ddd, *J* = 8.0, 1.8, 1.1 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.04 – 6.98(m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.9, 155.8, 134.4, 131.4, 128.2, 123.6, 118.9, 118.7, 118.5, 106.7. HRMS (ESI +): calcd for $C_{13}H_9BrNO$ $[M + H]^+$ 273.9862, found: 273.9860.

4.2.5.5. 4-(4-iodophenoxy)benzonitrile (14e).: White solid, yield 82%. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 5.9 Hz, 2H), 7.60 (dd, *J* = 5.0, 2.3 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.0, 155.0, 139.4, 134.4, 122.5, 118.7, 118.3, 106.5. HRMS (ESI +): calcd for $C_{13}H_9INO$ $[M + H]^+$ 321.9723, found: 321.9751.

4.2.6. General procedure for the synthesis of compounds 15a-e—To a round bottom flask containing THF, the appropriate aryl nitrile analogue (1.0 equiv.) was added followed by the addition of nitrogen gas. Next, the solution was cooled to − 70 °C before the addition of a DIBAL-H (1.1 equiv.) solution (1.0 M in THF). After, the mixture was stirred at − 40 °C for 5 h under nitrogen until TLC indicated the starting material had been fully consumed. Subsequently, the reaction vessel was placed in an ice bath and quenched with 1 mL ethyl acetate and 20 mL HCl (1.0 M). After, the resulting solution was partitioned between EtOAc and brine. Using additional EtOAc, the aqueous brine solution was washed three times and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated via vacuum. The resulting concentrate was purified by silica gel chromatography.

4.2.6.1. 4-phenoxybenzaldehyde (15a).: White solid, yield 82%. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.92 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.3, 155.2, 132.1, 131.4, 130.3, 125.1, 120.5, 117.7. HRMS (ESI +) $[M + H]^+$ calcd for $C_{13}H_{11}O_2$: 199.0754, found: 199.0753.

4.2.6.2. 4-(3-(tert-butyl)phenoxy)benzaldehyde (15b).: White solid, yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.14 – 7.10 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.91 – 6.83 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.6, 154.9, 154.1, 132.1, 131.2, 129.7, 122.1, 117.8, 117.5, 117.4, 31.4. HRMS (ESI +) $[M + H]^+$ calcd for $C_{17}H_{19}O_2$: 255.1380, found: 255.1369.

4.2.6.3. 4-(4-(tert-butyl)phenoxy)benzaldehyde (15c).: White solid, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.7, 152.7, 148.1, 132.1, 131.2, 127.1, 120.1, 117.5, 34.6, 31.6. HRMS (ESI +) $[M + H]^+$ calcd for $C_{17}H_{19}O_2$: 255.1380, found: 255.1372.

4.2.6.4. 4-(3-bromophenoxy)benzaldehyde (15d).: White solid, yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.21 (dd, *J* = 3.6, 1.5 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.01 – 6.97 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.8, 162.4, 156.2, 132.2, 132.0, 131.3, 128.1, 123.6, 123.3, 119.0, 118.2. HRMS (ESI +) calcd for $C_{13}H_{10}BrO_2$ $[M + H]^+$ 276.9859, found: 276.9860.

4.2.6.5. 4-(4-iodophenoxy)benzaldehyde (15e).: White solid, yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.93 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.8, 162.6, 155.4, 139.3, 132.1, 131.8, 122.5, 118.0, 88.3. HRMS (ESI +): calcd for $C_{13}H_{10}IO_2$ $[M + H]^+$ 324.9720, found: 324.9701.

4.2.7. General procedure for the synthesis of compounds 16d-i—To a microwave reaction tube, the appropriate aryl halide (1.0 equiv.) and aryl boronic acid (1.3 equiv.) were dissolved in THF. Next, the resulting solution was purged with argon gas for 5 min followed by the addition of sodium hydroxide (aq.) (3.0 equiv.) to form a THF/H_2O = 5:1 mixture. After, the mixture was further purged with argon gas for 5 min before the addition of $Pd(dppf)Cl_2$ (0.1 equiv.). The resulting mixture was then heated in a microwave reactor at 100 °C for 10 min. After, the solid was removed via filtration and the resulting solution was partitioned between ethyl acetate and water. The organic layer was washed with a saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated via vacuum. The resulting mixture was then purified by silica gel chromatography to yield the desired product.

4.2.7.1. 4-([1,1′-biphenyl]-3-yloxy)benzaldehyde (16d).: Off-white solid, yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.93 (t, *J* = 0.4 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.51 – 7.41 (m, 4H), 7.39 – 7.34 (m, 1H), 7.33 (ddd, *J* = 2.3, 1.4, 0.7 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (dt, *J* = 6.8, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.3, 155.7, 143.7, 140.2, 132.1, 131.5, 130.6, 129.0, 128.0, 127.2, 123.8, 119.2, 117.8. HRMS (ESI +): calcd for $C_{19}H_{15}O_2$ $[M + H]^+$ 275.1067, found: 275.1077.

4.2.7.2. 4-([1,1′-biphenyl]-4-yloxy)benzaldehyde (16e).: White solid, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.60 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.3, 154.7, 140.3, 138.2, 132.1, 131.5, 129.0, 128.9, 127.5, 127.1, 120.8, 117.8. HRMS (ESI +): calcd for $C_{19}H_{15}O_2$ $[M + H]^+$ 275.1067, found: 275.1057.

4.2.7.3. 4-((3′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)oxy)benzaldehyde (16f).: Off-white solid, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.82 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.51 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.46 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.12 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.1, 155.9, 142.2, 141.0, 132.2, 131.9 (q, $^{2}J_{CF3}$ = 33.6 Hz), 130.9, 130.5, 130.5, 129.5, 124.6 (q, $^{3}J_{CF3}$ = 3.8 Hz), 124.0 (q, $^{4}J_{CF}$ = 3.9 Hz), 123.8, 122.6, 121.2 (q, $^{1}J_{CF3}$ = 277.1 Hz), 120.0, 119.3, 117.8. HRMS (ESI +): calcd for $C_{20}H_{14}F_3O_2$ $[M + H]^+$ 343.0940, found: 343.0943.

4.2.7.4. 4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)oxy)benzaldehyde (16 g).: Off-white solid, yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.74 – 7.63 (m, 4H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.36 – 7.30 (m, 1H), 7.15 – 7.09 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.8, 163.0, 155.9, 143.6, 142.2, 132.1, 131.7, 130.9, 127.5, 126.0, 123.8, 120.0, 119.3, 117.9. HRMS (ESI +): calcd for $C_{20}H_{14}F_3O_2$ $[M + H]^+$ 343.0940, found: 343.0949.

4.2.7.5. 4-((3′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)oxy)benzaldehyde (16 h).: Off-white solid, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.95 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.83 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.68 – 7.53 (m, 4H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.9, 163.0, 155.4, 141.1, 136.6, 132.1, 131.7, 130.4, 129.5, 129.1, 124.2, 120.9, 118.0. HRMS (ESI +): calcd for $C_{20}H_{14}F_3O_2$ $[M + H]^+$ 343.0940, found: 343.0946.

4.2.7.6. 4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)oxy)benzaldehyde (16i).: Off-white solid, yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.95 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 2.3 Hz, 4H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.8, 162.9, 155.6, 143.8, 136.5, 132.1, 131.7, 129.1, 127.4, 125.9, 120.8, 118.1. HRMS (ESI +): calcd for $C_{20}H_{14}F_3O_2$ $[M + H]^+$ 343.0940, found: 343.0935.

4.2.8. General procedure for the synthesis of compounds 20a-g—To a microwave reaction tube containing THF (0.2 M), the appropriate alkene (1.3 equiv.) and 9-BBN (1.6 equiv.) were dissolved followed by addition of argon gas. Next, the resulting mixture was heated in a microwave reactor at 100 °C for 10 min. After heating, the solution was again purged with argon for 5 min followed by the addition of sodium hydroxide (aq.) (3.0 equiv.) to form a THF/H_2O = 5:1 mixture. Once more, the mixture was further purged with argon for 5 min followed by the addition of 4-iodobenzaldehyde (1.0 equiv.) then $Pd(dppf)Cl_2$ (0.1 equiv.). The resulting mixture was heated in a microwave reactor at 100 °C for 10 min. After, the solid was removed via filtration and solution was partitioned between

ethyl acetate and water. The resulting organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated via vacuum. The resulting mixture was then purified by silica gel chromatography to yield the desired product.

4.2.8.1. 4-nonylbenzaldehyde (20a).: Tan oil, yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.72 – 2.64 (m, 2H), 1.64 (p, *J* = 7.5 Hz, 2H), 1.36 – 1.22 (m, 12H), 0.97 – 0.81 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 150.7, 134.5, 130.0, 129.2, 36.4, 32.0, 31.2, 29.7, 29.6, 29.4, 29.4, 22.8, 14.3. HRMS (ESI +): calcd for $C_{16}H_{25}O$ $[M + H]^+$ 233.1900, found: 233.1905.

4.2.8.2. 4-decylbenzaldehyde (20b).: Tan oil, yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.95 – 2.43 (m, 2H), 1.63 (m, 2H), 1.28 (d, *J* = 20.3 Hz, 14H), 1.15 – 0.61 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 150.7, 134.5, 130.0, 129.2, 36.4, 32.0, 31.2, 29.7, 29.7, 29.6, 29.5, 29.4, 22.8, 14.3. HRMS (ESI +): calcd for $C_{17}H_{27}O$ $[M + H]^+$247.2056, found: 247.2059.

4.2.8.3. 4-undecylbenzaldehyde (20c).: Tan oil, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.00 – 2.46 (m, 2H), 1.64 (p, *J* = 7.4 Hz, 2H), 1.45 – 1.05 (m, 16H), 1.15 – 0.56 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 150.7, 134.5, 130.0, 129.2, 36.4, 32.1, 31.2, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 22.8, 14.3. HRMS (ESI +): calcd for $C_{18}H_{29}O$ $[M + H]^+$ 261.2213, found: 261.2214.

4.2.8.4. 4-dodecylbenzaldehyde (20d).: Brown oil, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.72 – 2.64 (m, 2H), 1.64 (dt, *J* = 15.0, 7.4 Hz, 2H), 1.37 – 1.21 (m, 18H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 150.7, 134.5, 130.0, 129.2, 36.4, 32.1, 31.2, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 22.8, 14.3. HRMS (ESI +): calcd for $C_{19}H_{31}O$ $[M + H]^+$ 275.2369, found: 275.2371.

4.2.8.5. 4-dodecyl-2-methylbenzaldehyde (20e).: Clear oil, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.91 (ddd, *J* = 8.7, 6.5, 2.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 149.4, 138.0, 135.8, 134.7, 130.0, 129.3, 128.4, 38.3, 37.1, 21.2. HRMS (ESI +): calcd for $C_{20}H_{33}O$ $[M + H]^+$ 289.2526, found: 289.2545.

4.2.8.6. 4-(4-methylphenethyl)benzaldehyde (20f).: Yellow oil, yield 58%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.98 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.91 (ddd, *J* = 8.7, 6.5, 2.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 192.2, 149.4, 138.0, 135.8, 134.7, 130.0, 129.3, 128.4, 38.3, 37.1, 21.2. HRMS (ESI +): calcd for $C_{16}H_{17}O$ $[M + H]^+$ 225.1274, found: 225.1285.

4.2.8.7. 4-(4-methoxyphenethyl)benzaldehyde (20 g).: Tan oil, yield 52%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.97 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* =

8.8 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 2.97 (ddd, J = 9.0, 6.7, 2.0 Hz, 2H), 2.89 (ddd, J = 8.5, 6.6, 2.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 158.1, 149.3, 134.7, 133.1, 130.0, 129.5, 129.4, 114.0. HRMS (ESI +): calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1223, found: 241.1233.

4.2.9. General procedure for the synthesis of compound 21 h—To a round bottom flask containing CH_2Cl_2 (0.2 M), compound **21c** (1 equiv.) was dissolved and then cooled in an ice bath for 5 min. After, pyridine (3.0 equiv.) was added slowly followed by acetic anhydride (2.0 equiv.). The mixture was allowed to slowly rise to room temperature and stirred overnight. After, the resulting solution was partitioned between EtOAc and brine. Using additional EtOAc, the aqueous brine solution was washed three times and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated via vacuum. The resulting concentrate was purified by silica gel chromatography to yield the final product.

4.2.9.1. (R)-(1-(4-undecylbenzyl)pyrrolidin-2-yl)methyl acetate (21 h).: Tan oil, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 4.11 (dd, J = 11.0, 5.2 Hz, 1H), 4.05 – 4.00 (m, 2H), 3.38 (d, J = 12.9 Hz, 1H), 2.93 (ddd, J = 9.4, 6.9, 3.0 Hz, 1H), 2.80 (dq, J = 8.5, 5.7 Hz, 1H), 2.61 – 2.54 (m, 2H), 2.31 – 2.18 (m, 1H), 2.06 (s, 3H), 1.98 – 1.88 (m, 1H), 1.76 – 1.55 (m, 5H), 1.26 (m, 16H), 0.87 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 141.7, 136.7, 67.3, 61.9, 59.3, 54.5, 35.8, 32.1, 31.7, 29.8, 29.8, 29.7, 29.7, 29.5, 28.6, 23.0, 22.8, 21.2, 14.3. HRMS (ESI +): calcd for $C_{25}H_{42}NO_2$ $[M + H]^+$ 388.3210, found: 388.3204.

4.2.10. General procedure for the synthesis of compounds 23a-b—Aryl halide (1 equiv.), aryl alkene (1.3 equiv.) and potassium carbonate (3 equiv.) were added into microwave reaction tube containing DMF. The mixture was purged with argon for 5 min before the addition of $Pd(PPh)_3Cl_2$ (0.1 equiv.) and was heated to 140 °C for 2 h in the microwave. The reaction was extracted with ethyl acetate and saturated LiBr solution. The combined organic layers were washed with brine and dried over sodium sulfate. After filtration and concentration via reduced pressure, the resulting oil residue was purified on a silica column with hexane and ethyl acetate as the eluent to yield pure product. The residue was purified using silica gel column chromatography (5% ethyl acetate/hexanes) to yield the product.

4.2.10.1. (E)-4-(4-(tert-butyl)styryl)-2-methylbenzaldehyde (23a).: White solid, yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.21 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.09 – 7.04 (m, 1H), 2.65 (s, 3H), 2.63 – 2.60 (m, 2H), 1.66 – 1.58 (m, 2H), 1.35 – 1.22 (m, 18H), 0.88 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.6, 149.7, 140.8, 132.6, 132.3, 132.1, 126.6, 36.2, 36.0, 32.1, 31.2, 31.2, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.5, 22.8, 19.8, 14.3. HRMS (ESI +): calcd for $C_{20}H_{23}O$ $[M + H]^+$ 279.1743, found: 279.1733.

4.2.10.2. (E)-4-(3-(trifluoromethyl)styryl)benzaldehyde (23b).: White solid, yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 7.94 – 7.86 (m, 2H), 7.79 (s, 1H), 7.73 – 7.69 (m, 1H), 7.70 – 7.66 (m, 2H), 7.59 – 7.48 (m, 2H), 7.24 (q, J = 16.4 Hz, 2H). ^{13}C NMR (101

MHz, $CDCl_3$) δ: 191.5, 142.6, 137.3, 135.7, 131.1, 130.5, 130.3, 129.9, 129.9, 129.9, 129.9, 129.3, 129.2, 127.1, 124.9, 124.9, 124.8, 124.8, 123.5, 123.4, 123.4, 123.4, 110.0. HRMS (ESI +): calcd for $C_{16}H_{12}F_3O$ $[M + H]^+$ 277.0835, found: 277.0846.

4.2.11. General procedure for the synthesis of compounds 26a-c—To a microwave reaction tube containing THF (0.2 M), the appropriate 4-iodobenzaldehyde derivative (1.0 equiv.), phenylacetylene derivative (1.3 equiv.) and triethylamine (3.0 equiv.) were added and then purged with argon gas for 5 min. After, $Pd(PPh)_3Cl_2$ (0.1 equiv.) was added and the solution was further purged with argon gas for an additional 5 min before the addition of CuI (0.05 equiv.). The mixture was heated to 50 °C for 30 min in the microwave. The resulting mixture was heated in a microwave reactor at 50 °C for 30 min. After, the resulting mixture was concentrated via vacuum and then purified by silica gel chromatography to yield the desired product.

4.2.11.1. 4-((4-propylphenyl)ethynyl)benzaldehyde (26a).: Yellow oil, yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.73 – 1.58 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.6, 144.2, 135.4, 132.2, 131.9, 130.1, 129.7, 128.8, 119.8, 94.0, 88.1, 38.2, 24.5, 13.9. HRMS (ESI +): calcd for $C_{18}H_{17}O$ $[M + H]^+$ 249.1274, found: 249.1267.

4.2.11.2. 4-((4-butylphenyl)ethynyl)benzaldehyde (26b).: Yellow oil, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 10.01 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 2.66 – 2.60 (m, 2H), 1.66 – 1.55 (m, 2H), 1.36 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 191.5, 144.4, 135.4, 132.1, 131.8, 130.0, 129.7, 128.7, 119.7, 94.0, 88.1, 35.8, 33.5, 22.4, 14.1. HRMS (ESI +): calcd for $C_{19}H_{19}O$ $[M + H]^+$ 263.1430, found: 263.1426.

4.2.11.3. 4-((4-pentylphenyl)ethynyl)benzaldehyde (26c).: Yellow oil, yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.01 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.67 – 2.58 (m, 2H), 1.62 (p, *J* = 7.6 Hz, 2H), 1.40 – 1.25 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.6, 144.4, 135.4, 132.1, 131.8, 130.0, 129.7, 128.7, 119.7, 94.0, 88.1, 36.1, 31.6, 31.0, 22.7, 14.2. HRMS (ESI +): calcd for $C_{20}H_{21}O$ $[M + H]^+$ 277.1587, found: 277.1590.

4.2.12. General procedure for the synthesis of compounds 28a-c—To a round bottom flask containing methanol (0.2 M), the appropriate alkyne derivative (1.0 equiv.) was added followed by addition of 10% Pd/C (0.1 equiv.) and then put under an argon gas atmosphere. After, while stirring at room temperature, the solution was subjected to a vacuum followed by a subsequent purge of hydrogen gas. This process of vacuum followed by hydrogen gas purge was repeated twice more. Next, while under a hydrogen gas atmosphere, the mixture was stirred for 2 h. Subsequently, the hydrogen gas atmosphere was replaced by argon gas. Afterward, the solid was removed via filtration upon celite and the solvent was removed via vacuum. The resulting concentrate was then purified by silica gel chromatography to yield the final product.

4.2.12.1. (R)-(1-(4-(4-propylphenethyl)benzyl)pyrrolidin-2-yl)methanol (28a).: Clear oil, yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 4H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.66 (dd, *J* = 10.7, 3.5 Hz, 1H), 3.43 (dd, *J* = 10.7, 2.1 Hz, 1H), 3.35 (d, *J* = 12.9 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.90 (s, 4H), 2.79 – 2.68 (m, 1H), 2.62 – 2.50 (m, 1H), 2.33 – 2.27 (m, 1H), 2.02 – 1.77 (m, 2H), 1.76 – 1.57 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.9, 140.4, 139.1, 136.9, 128.8, 128.5, 128.5, 128.4, 64.3, 61.9, 58.3, 54.6, 37.8, 37.8, 37.7, 28.0, 24.8, 23.6, 14.0. HRMS (ESI +): calcd for $C_{23}H_{32}NO$ $[M + H]^+$ 338.2478, found: 338.2480.

4.2.12.2. (R)-(1-(4-(4-butylphenethyl)benzyl)pyrrolidin-2-yl)methanol (28b).: Clear oil, yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 4H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.67 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.53 – 3.42 (m, 2H), 3.06 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.92 – 2.80 (m, 4H), 2.61 – 2.53 (m, 2H), 2.45 – 2.33 (m, 1H), 2.00 – 1.78 (m, 2H), 1.80 – 1.68 (m, 2H), 1.60 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.35 – 1.28 (m, 2H), 0.93 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ:140.4, 139.7, 138.0, 131.2, 128.3, 127.7, 127.5, 127.4, 64.0, 60.8, 57.5, 53.4, 36.8, 36.6, 34.7, 30.4, 26.7, 22.6, 21.7, 13.2. HRMS (ESI +): calcd for $C_{24}H_{34}NO$ $[M + H]^+$ 352.2635, found: 352.3633.

4.2.12.3. (R)-(1-(4-(4-pentylphenethyl)benzyl)pyrrolidin-2-yl)methanol (28c).: Clear oil, yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.10 (s, 4H), 4.00 (d, *J* = 13.0 Hz, 1H), 3.68 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.53 – 3.43 (m, 2H), 3.07 (dd, *J* = 9.7, 5.5 Hz, 1H), 2.93 – 2.81 (m, 5H), 2.62 – 2.53 (m, 2H), 2.45 – 2.34 (m, 1H), 2.00 – 1.79 (m, 2H), 1.81 – 1.68 (m, 2H), 1.60 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.36 – 1.28 (m, 4H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.4, 140.7, 139.0, 132.2, 129.3, 128.7, 128.5, 128.4, 65.0, 61.8, 58.5, 54.4, 37.8, 37.6, 35.7, 31.7, 31.4, 27.7, 23.6, 22.7, 14.2, 7.3. HRMS (ESI +): calcd for $C_{25}H_{36}NO$ $[M + H]^+$ 366.2791, found: 366.2792.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH (R01 GM104366 and R01 GM121075).

Abbreviations:

S1P	Sphingosine 1-phosphate
Sph	Sphingosine
SphK	Sphingosine kinase
HCTU	O-(1*H*-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

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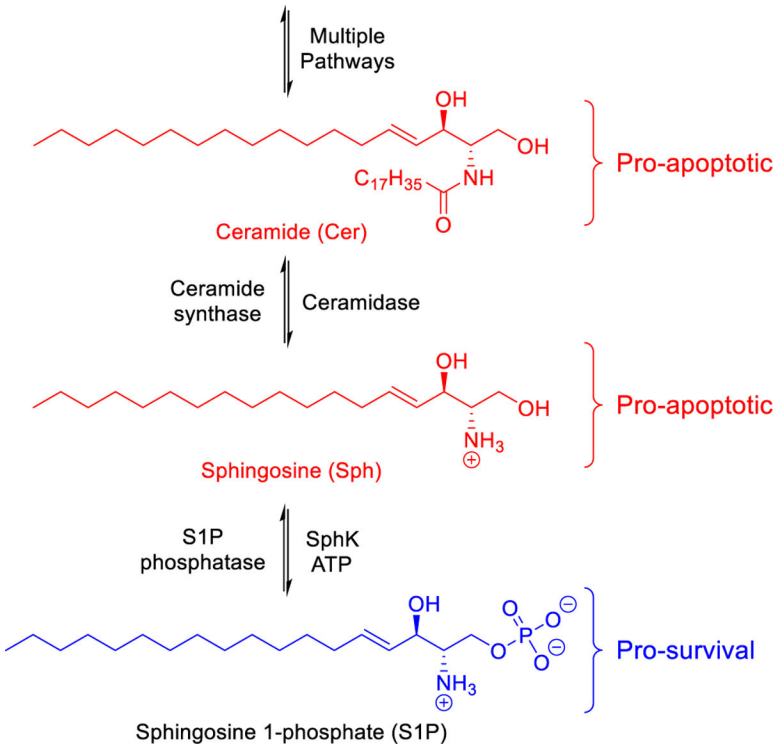


Fig. 1.
The S1P synthetic pathway and its role in cellular fate.

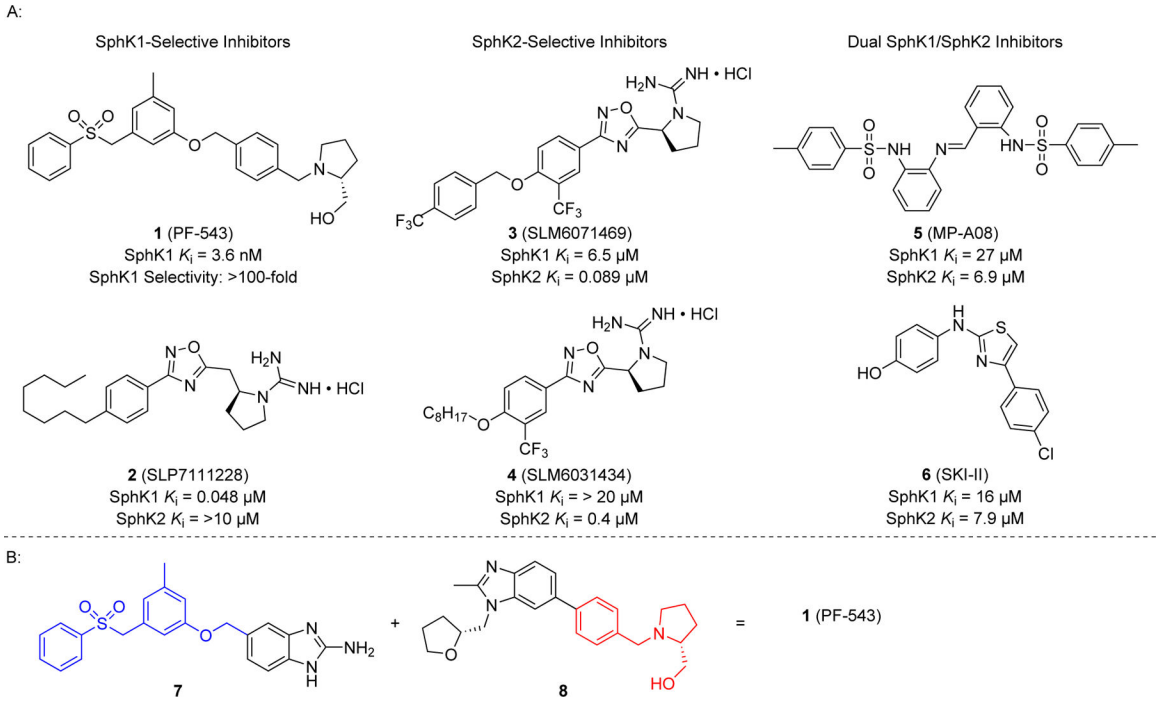


Fig. 2.

Structures of (A) select SphK inhibitors and (B) lead hopping combination of hit compounds **7** and **8** to generate **1** (PF-543).

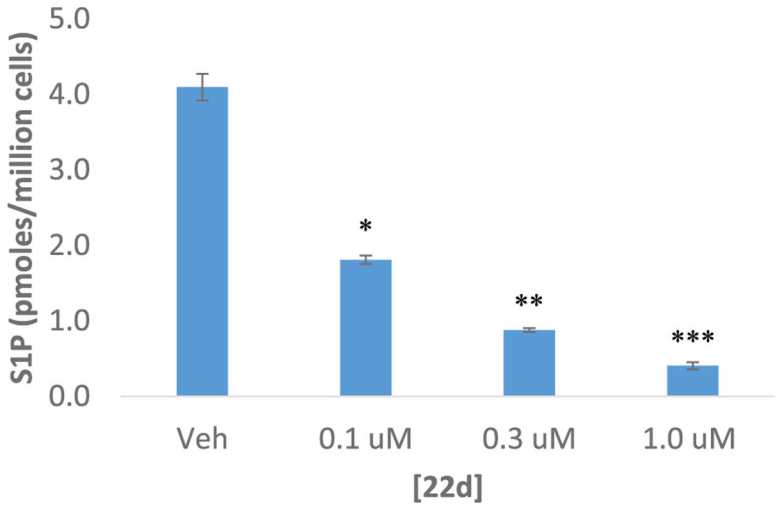


Fig. 3.

The effect of **22d** on S1P concentrations in U937 cells. After a 2.0 h incubation, U937 cells were harvested by centrifugation and lysed, and levels of S1P were measured using LC-MS/MS. Amounts associated with cells are expressed as the number of picomoles per 10^6 cells. The experiment was performed in duplicate. The level of significance is indicated for each experiment (*P < 0.05, **P < 0.005, ***P < 0.001) using an unpaired *t*-test (compared to control).

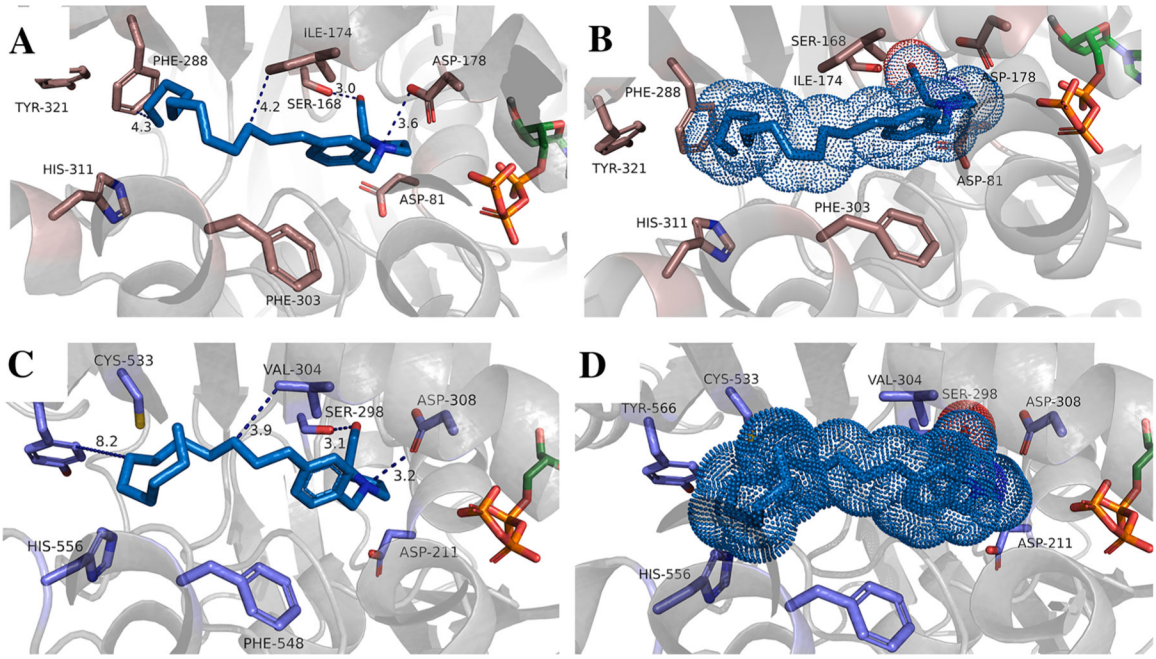
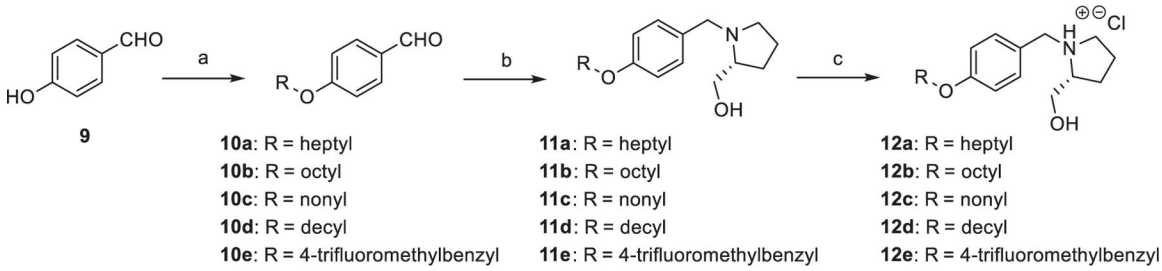


Fig. 4.

Docking of inhibitor **22d** into hSphK1 (A, B) and hSphK2 (C, D). Key residues in the binding pocket are represented by grey sticks and are labeled. ATP is shown in orange and colored by element. The SphK1 and SphK2 protein structures are depicted in grey cartoon. Distances between interacting atoms are shown as dashed lines. Inhibitors are shown as stick and colored by element. Panels B and D illustrate the inhibitor as Van der Waals radii in dots to represent volume occupancy of the inhibitor.



9

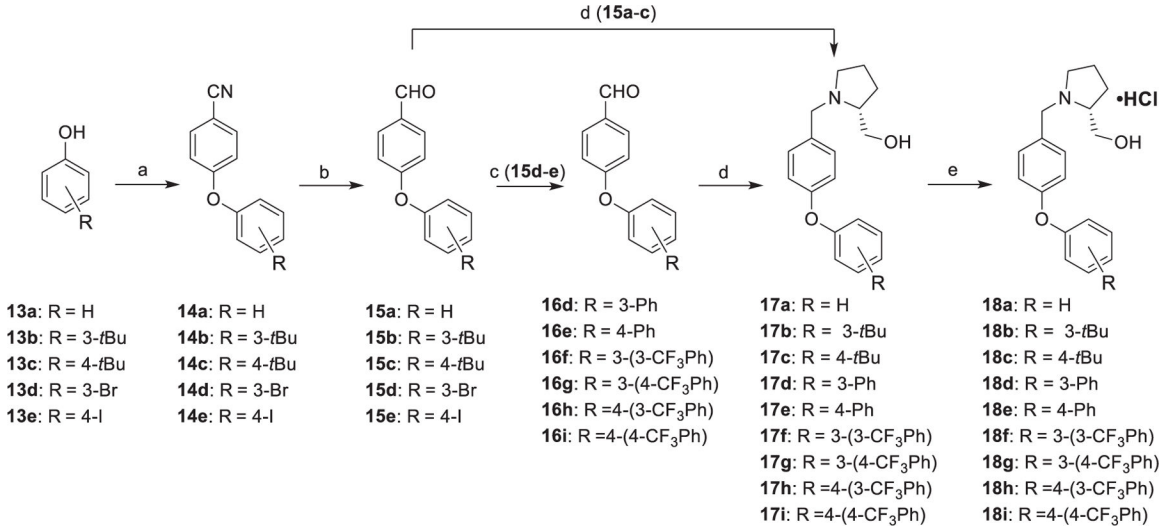
10a: R = heptyl
10b: R = octyl
10c: R = nonyl
10d: R = decyl
10e: R = 4-trifluoromethylbenzyl

11a: R = heptyl
11b: R = octyl
11c: R = nonyl
11d: R = decyl
11e: R = 4-trifluoromethylbenzyl

12a: R = heptyl
12b: R = octyl
12c: R = nonyl
12d: R = decyl
12e: R = 4-trifluoromethylbenzyl

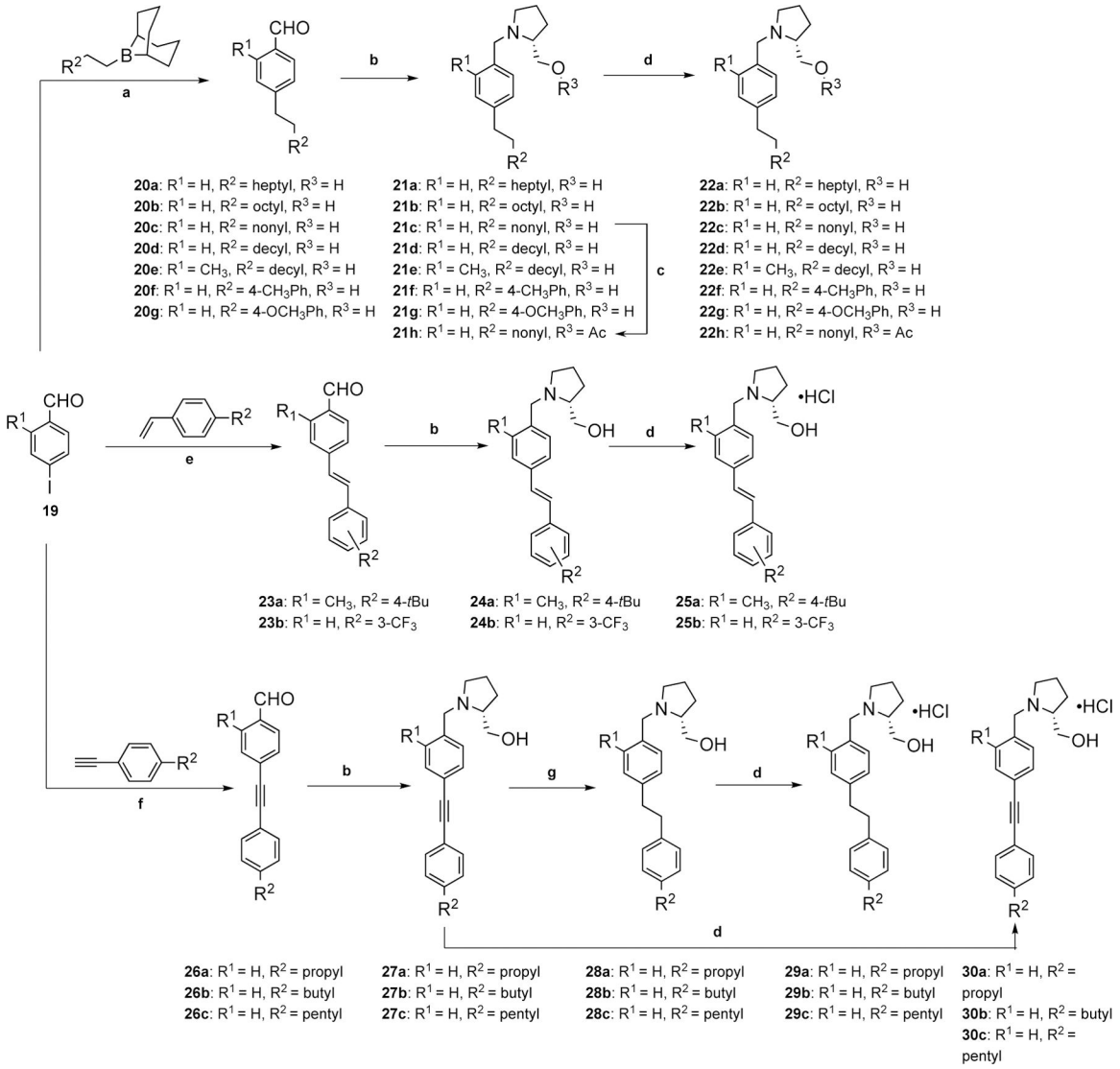
Scheme 1.

Synthesis of analogues **12a**-**f**. Reagents and conditions: (a) Alkyl bromide derivative, K_2CO_3, DMF, reflux, 12 h; (b) (*R*)-Prolinol, $TsOH{\cdot}H_2O$, $NaCNBH_3$, molecular sieves, CH_2Cl_2, rt, 12 h; (c) HCl (g), MeOH, rt, 10 min.



Scheme 2.

Synthesis of analogues **18a-i**. Reagent and conditions: (a) 4-fluorobenzonitrile, Cs_2CO_3, DMF, reflux, 12 h; (b) DIBAL-H, CH_2Cl_2, − 70 °C to rt, 4 h; (c) Arylboronic acid derivative, Pd(dppf)Cl_2, NaOH, THF/H_2O, 100 °C, 30 min, microwave; (d) (*R*)-Prolinol, $NaCNBH_3$, $TsOH·H_2O$, MeOH, rt, 12 h; (e) HCl (g), MeOH, rt, 10 min.

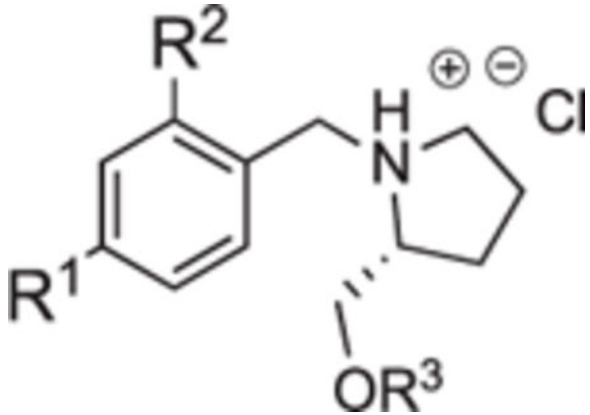


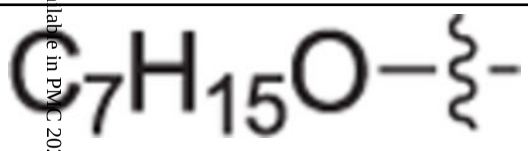
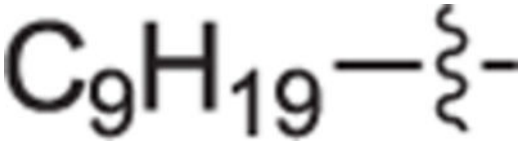
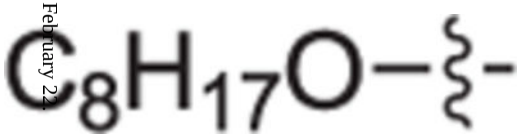
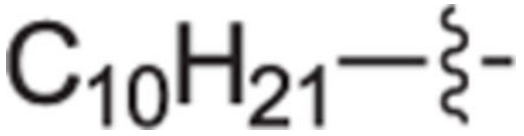
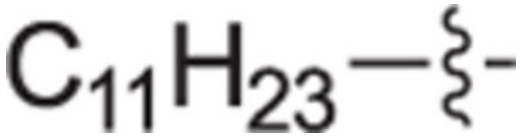
Scheme 3.

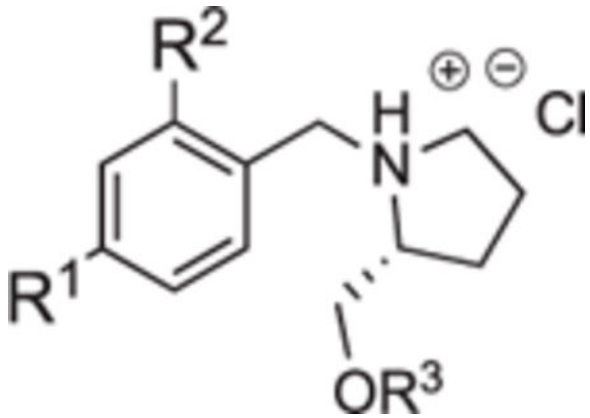
Synthesis of analogues **22a-h**, **25a-b**, **29a-c**, and **30a-c**. Reagent and conditions: (a) (i) Alkene derivative, 9-BBN, THF, 100 °C, 30 min, microwave; (ii) Benzaldehyde derivative, $Pd(dppf)Cl_2$, NaOH, THF/H_2O, 100 °C, 30 min, microwave; (b) (*R*)-Prolinol, $NaCNBH_3$, $TsOH{\cdot}H_2O$, MeOH, rt, 12 h; (c) Acetyl chloride, pyridine, rt, 16 h; (d) HCl (g), MeOH, rt, 10 min; (e) Styrene derivative, $Pd(PPh_3)_2Cl_2$, K_2CO_3, DMF, reflux, 16 h; (f) Phenylacetylene derivative, $Pd(PPh_3)_2Cl_2$, CuI, TEA, THF, 50 °C, 1 h, microwave; (g) H_2 (g), 10% Pd/C, rt, 1 h.

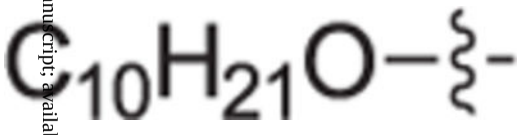
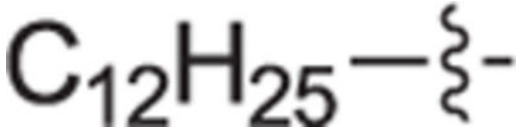
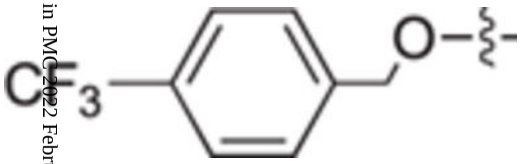
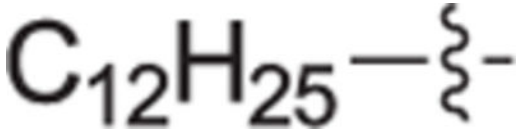
Table 1

Activity of sphingosine kinase inhibitors.[a]



Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
12a		H	H	5 ± 2	0 ± 4	**22a**		H	H	62 ± 4	44 ± 3
12b		H	H	36 ± 1	1 ± 2	**22b**		H	H	76 ± 2	54 ± 1
12c		H	H	84 ± 2	44 ± 3	**22c**		H	H	76 ± 3	18 ± 7



Cmpd	R^1	R^2	R^3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R^1	R^2	R^3	% SphK1 Inhibition	% SphK2 Inhibition
12d		H	H	62 ± 6	11 ± 1	**22d**		H	H	78 ± 2	37 ± 5
12e		H	H	14 ± 4	0 ± 7	**22e**		CH_3	H	67 ± 2	38 ± 3

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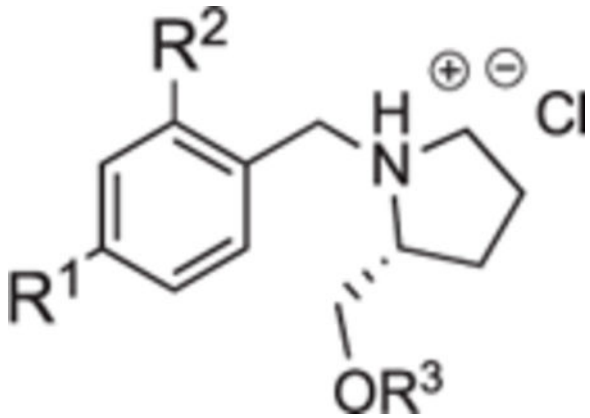
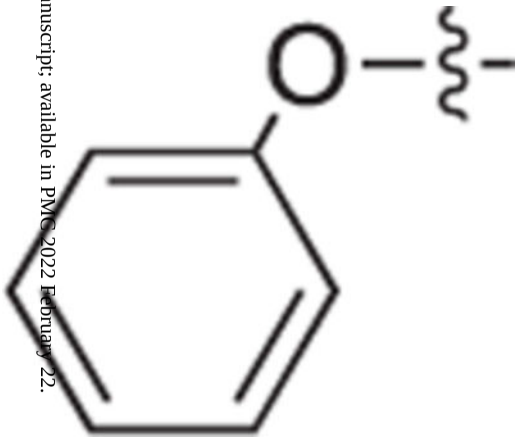
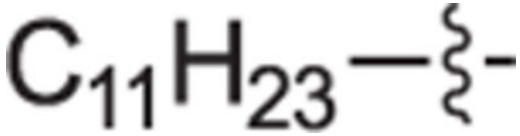


Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
18a		H	H	4 ± 7	13 ± 4	**22h**		H	Ac	47 ± 6	26 ± 6

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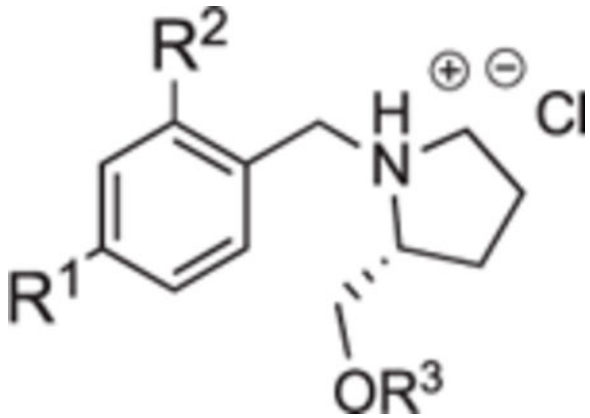
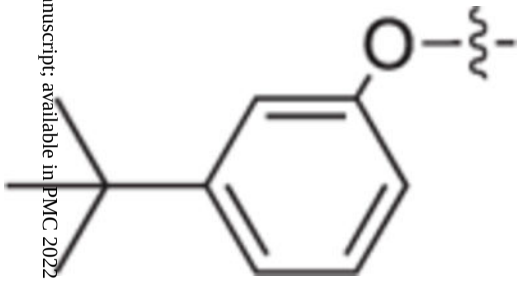
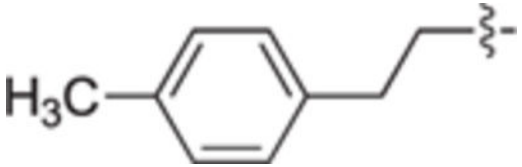
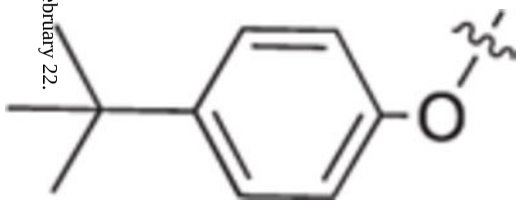
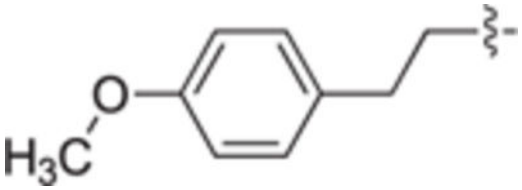


Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
18b		H	H	0 ± 4	11 ± 5	**22f**		H	H	4 ± 4	3 ± 5
18c		H	H	42 ± 4	22 ± 1	**22g**		H	H	8 ± 7	2 ± 2

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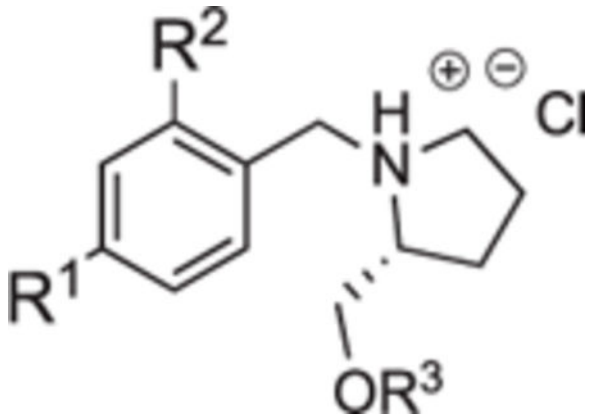
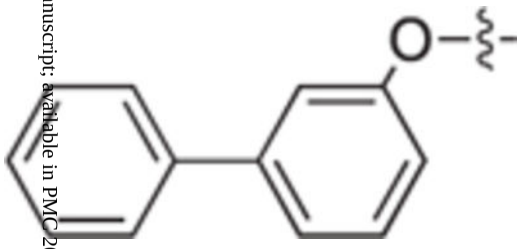
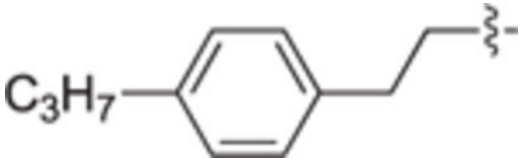
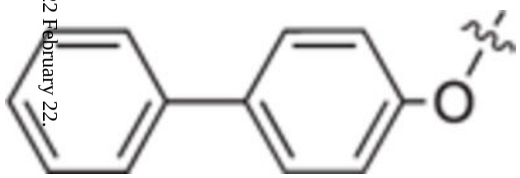
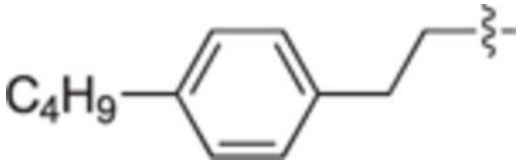


Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
18d		H	H	7 ± 5	0 ± 1	**29a**		H	H	29 ± 8	3 ± 4
18e		H	H	35 ± 3	9 ± 6	**29b**		H	H	31 ± 4	0 ± 3

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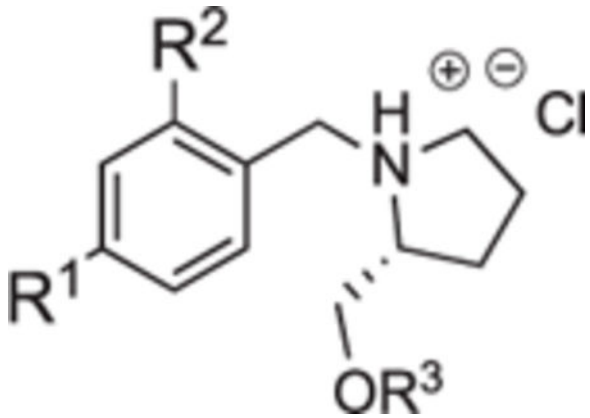
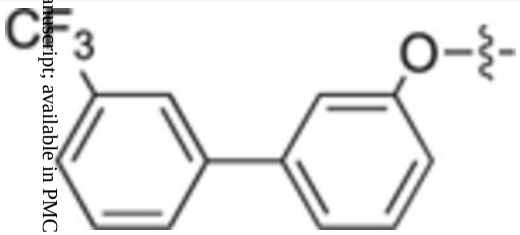
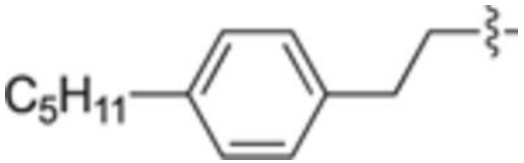
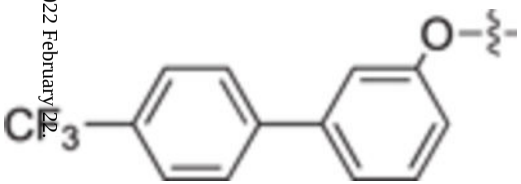
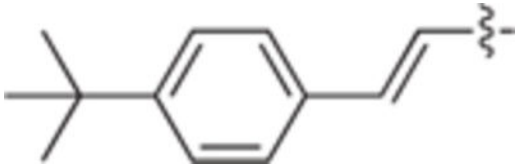


Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
18f		H	H	19 ± 8	11 ± 2	**29c**		H	H	36 ± 3	15 ± 5
18g		H	H	12 ± 1	1 ± 1	**25a**		CH_3	H	23 ± 3	0 ± 1

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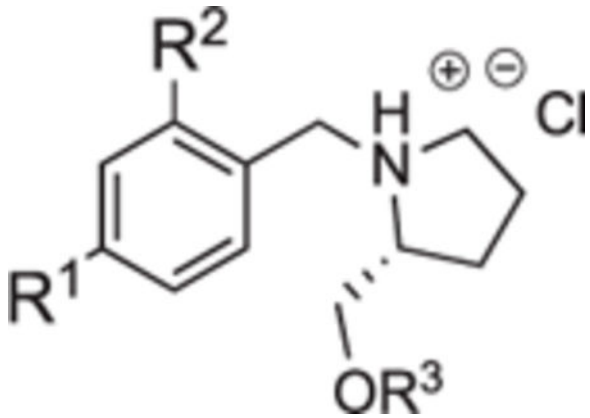
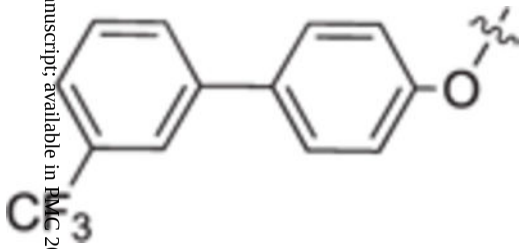
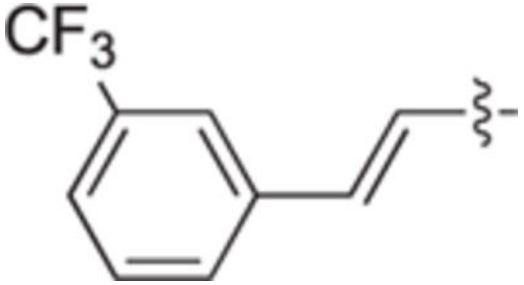
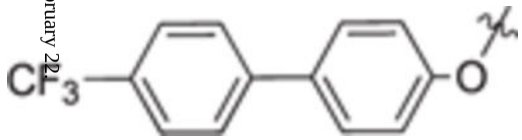
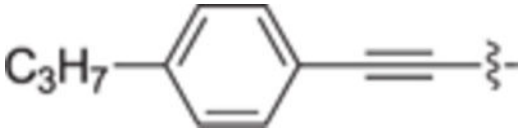
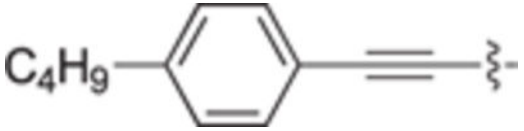
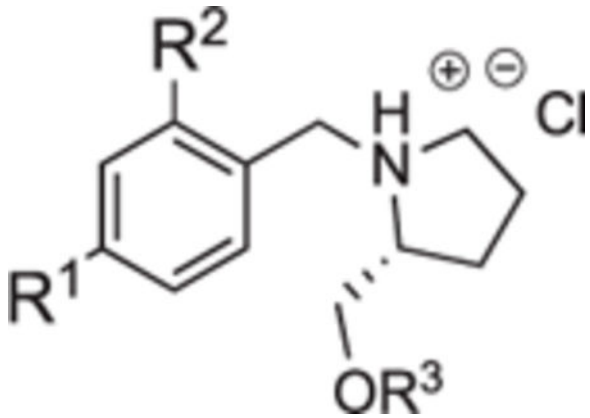
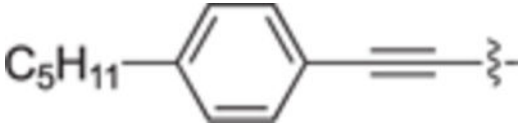


Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
18h		H	H	70 ± 5	52 ± 2	**25b**		H	H	45 ± 1	13 ± 5
18i		H	H	7 ± 7	0 ± 5	**30a**		H	H	16 ± 1	0 ± 4
						30b		H	H	53 ± 4	25 ± 1

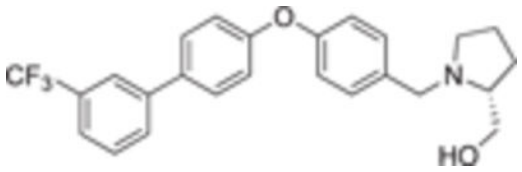
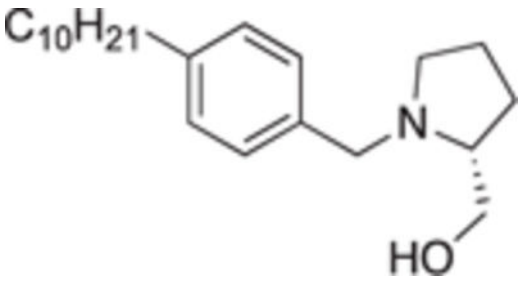
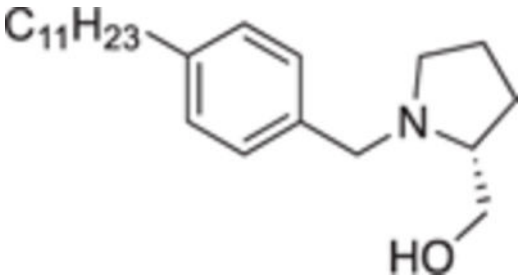


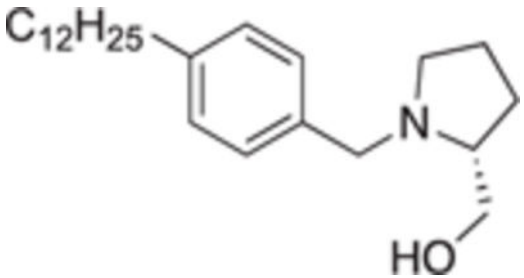
Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition	Cmpd	R1	R2	R3	% SphK1 Inhibition	% SphK2 Inhibition
						30c		H	H	49 ± 1	19 ± 2

[a] SphK inhibition is presented as % of control (no inhibitor added). Recombinant human SphK1 and SphK2 were isolated from cell lysates. Enzyme activity was measured for SphK1 and SphK2 with 10 μM and 5 μM sphingosine respectively, and 250 μM γ-[^{32}P] ATP. Compounds were assayed at 1.0 μM for SphK1 and 0.3 μM for SphK2 in triplicate.

Table 2

EC_{50} Values of Select Inhibitors[a] and K_i of **22d**[b].

Cmpd	Structure	hSphK1 EC_{50} (nM)	hSphK2 EC_{50} (nM)	hSphK1 K_I (nM)	hSphK2 K_I (nM)
18h		299 ± 19	488 ± 36	–	–
22b		202 ± 31	401 ± 50	–	–
22c		276 ± 22	246 ± 21	–	–

Cmpd	Structure	hSphK1 EC_{50} (nM)	hSphK2 EC_{50} (nM)	hSphK1 K_I (nM)	hSphK2 K_I (nM)
22d		154 ± 11	290 ± 30	679 ± 12	951 ± 32

[a] EC_{50} values of various compounds were calculated from the growth curves of yeast strain KYA1 encoding either hSphK1 or hSphK2 in the presence of inhibitor over 24 h. By way of comparison, the EC_{50} at hSphK1 for **1** (PF-543) in this assay is 5700 nM[23]. For detailed assay conditions, see the experimental section.

[b] Inhibitory constants for recombinant enzymes were obtained by kinetic analysis of S1P production using variable concentration of sphingosine and a fixed concentration of ATP in the presence or absence of compounds.