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Discovery of In Vivo Active Sphingosine-1-phosphate Transporter (Spns2) Inhibitors

Russell Fritzemeier,
Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24060, United States

Daniel Foster,
Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24060, United States

Ashley Peralta,
Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24060, United States

Michael Payette,
Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24060, United States

Yugesh Kharel,
Department of Pharmacology, University of Virginia, Charlottesville, Virginia 22908, United States

Tao Huang,
Department of Pharmacology, University of Virginia, Charlottesville, Virginia 22908, United States

Kevin R. Lynch,
Department of Pharmacology, University of Virginia, Charlottesville, Virginia 22908, United States

Webster L. Santos
Department of Chemistry and Virginia Tech Center for Drug Discovery, Virginia Tech, Blacksburg, Virginia 24060, United States

Abstract

Sphingosine 1-phosphate (S1P) is a pleiotropic signaling molecule that interacts with five G-protein-coupled receptors (S1P1-5) to regulate cellular signaling pathways. S1P export is facilitated by Mfsd2b and spinster homologue 2 (Spns2). While mouse genetic studies suggest that Spns2 functions to maintain lymph S1P, Spns2 inhibitors are necessary to understand its biology and to learn whether Spns2 is a viable drug target. Herein, we report a structure–activity relationship study that identified the first Spns2 inhibitor **16d** (SLF1081851). In vitro studies in

Corresponding Authors Kevin R. Lynch – Department of Pharmacology, University of Virginia, Charlottesville, Virginia 22908, United States; krl2z@virginia.edu; **Webster L. Santos** – Department of Chemistry and Virginia Tech Center for Drug Discovery, Virginia Tech, Blacksburg, Virginia 24060, United States; santosw@vt.edu.

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Supporting Information

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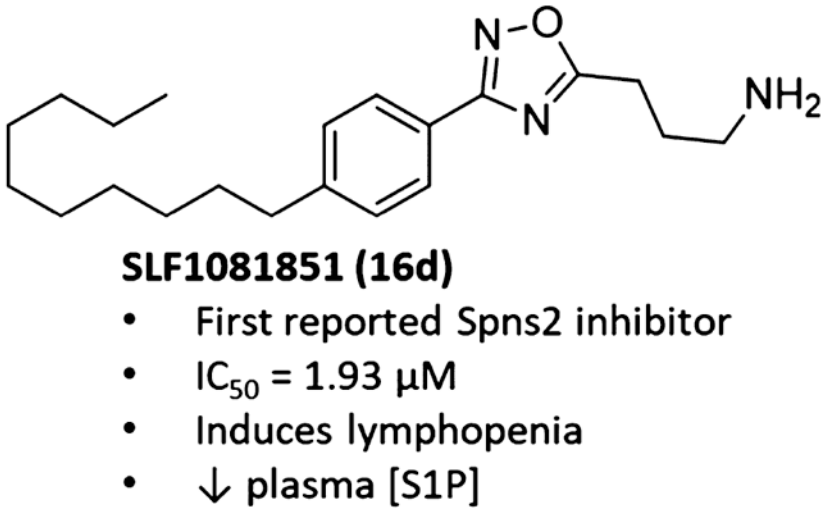
Molecular formula string list (CSV)

Characterizations of compounds and representative HPLC traces (PDF)

The authors declare the following competing financial interest(s): W.L.S. and K.R.L. are among the co-founders of Flux Therapeutics Inc, which was created to commercialize S1P-related discoveries, including Spns2 inhibitors, discovered and characterized in their laboratories.

HeLa cells demonstrated that **16d** inhibited S1P release with an IC_{50} of 1.93 μM. Administration of **16d** to mice and rats drove significant decreases in circulating lymphocyte counts and plasma S1P concentrations, recapitulating the phenotype observed in mice made deficient in Spns2. Thus, **16d** has the potential for development and use as a probe to investigate Spns2 biology and to determine the potential of Spns2 as a drug target.

Graphical Abstract



INTRODUCTION

Sphingosine-1-phosphate (S1P, **2**) is biosynthesized intra-cellularly from sphingosine (**1**) and ATP via sphingosine kinases (SphK) 1 and 2 (Figure 1).[1] Following phosphorylation, S1P can either revert to sphingosine (via S1P phosphatase) or be degraded to 2-hexadecenal (**3**) and phosphoethanolamine (**4**) (via S1P lyase).[1] While this pathway is ubiquitous in eukaryotes, in vertebrates, S1P can also be extruded from S1P transporter-expressing cells where it can serve as a ligand for the cell surface G-protein-coupled receptors (GPCRs) S1P1-5. S1P-derived activation of these GPCRs plays essential roles in organism development,[2] proving critical to processes such as angiogenesis,[3,4] cell survival,[5,6] and cytoskeletal arrangement.[7,8] The diverse array of pathways affected by these receptors have historically made them valuable pharmaceutical targets in medicinal chemistry campaigns.

The recognition that the immunomodulatory drug fingolimod (**5**) is a sphingosine analogue that is converted to an S1P receptor agonist [fingolimod-phosphate (**6**)] led to the discovery that S1P gradients are required for normal lymphocyte recirculation (Figure 2).[9] During clinical trials, it was revealed that fingolimod was effective in reducing relapses in multiple sclerosis patients.[10,11] Analysis of blood samples revealed that fingolimod drove reductions in circulating lymphocyte counts (lymphopenia), demonstrating the efficacy of fingolimod as an immunosuppressant and establishing precedence for targeting the S1P pathway.[12,13] To date, three additional S1P1/5 receptor agonists [siponimod (**7**), ozanimod (**8**), and ponesimod (**9**)] have received marketing approval in the US for multiple sclerosis

indications[14,15] and, in some cases, ulcerative colitis.[16] All four of these drugs have on-target liabilities including pronounced immunosuppression and first-dose bradycardia.[17]

An alternative to S1P receptor modulation is inhibiting S1P release, which lies upstream of receptor activation. Two proteins, Spns2 and Mfsd2b, have been validated as S1P transporters. Both transport proteins are members of the major facilitator superfamily (MFS) and extrude S1P in an ATP-independent fashion.[18,19] Genetic studies in mice revealed that Mfsd2b, which is expressed only in the erythroid lineage, is required for red blood cell release of S1P into plasma,[19-21] while Spns2 is more widely expressed.[22] Genetic studies in mice indicate that lymph S1P is primarily generated by Spns2- expressing endothelial cells lining the lymphatic vessels.[23-26] While endothelial cells also line blood vessels, S1P transport by Mfsd2b is predominately responsible for maintaining plasma S1P concentrations.[19-21] Maintenance of adequate lymph S1P is thought to be essential to promote lymphocyte egress from secondary lymphatic tissue into efferent lymph.[23,24,27,28] Inhibition of Spns2 might be a pharmaceutically viable method to direct highly localized reductions in fluid S1P concentrations.[23,24] As such, our laboratories concentrated on developing chemical tools for inhibiting Spns2.

Mice made deficient in Spns2 by genetic manipulation have decreased circulating lymphocyte counts and increased cellular localization to lymphatic tissue.[23,24,27,28] Indeed, knockout of the *Spns2* gene in mice has been shown to be protective against experimental autoimmune encephalomyelitis (EAE), which is the standard model of multiple sclerosis.[29,30] Selective Spns2 inhibitors with in vivo activity are required to learn whether such molecules can mimic the efficacy of S1P receptor modulators without the undesirable effects. Herein, we describe the discovery, synthesis, and evaluation of the first reported Spns2 inhibitors, as well as preliminary in vivo data.

RESULTS AND DISCUSSION

Inhibitor Design and Development.

To discover Spns2 inhibitors, we screened an in-house library of sphingosine kinase (SphK)[31-39] inhibitors using a yeast (*Saccharomyces cerevisiae*) assay adapted from a previously reported SphK assay.[40] Although the yeast-based assay ultimately proved problematic for screening (nonspecific cytotoxicity of test compounds), we were able to use the assay to identify one hit (**11**, Figure 3), which is a guanidine-containing oxadiazole derivative.[35] Fortunately, as **11** is derived from a β-amino acid and not an α-amino acid (as found in our SphK inhibitors), it displayed minimal activity against either SphK isoform.[31] Thus, **11** provided a chemical scaffold for use as a starting point for Spns2 inhibitor development.

For analogue design, **11** was divided into three distinct regions for chemical modification (Figure 3). Analogous to S1P, **11** contains a positively charged, polar head group moiety, a conformationally restricted 1,2,4-oxadiazole linker, and a hydrophobic alkyl tail. Given that the head group in S1P contains charged ammonium and phosphate groups, we envisioned that inhibitory activity should be particularly sensitive to modifications in these regions. As such, the medicinal chemistry campaign was initially focused on the polar head group and

the oxadiazole linker. Once these regions were optimized, we then probed the tail portion of the pharmacophore.

Guanidines, which are strongly basic and hydrophilic, have historically been challenging to incorporate into orally bioavailable drugs as they often fail to be absorbed through the gastrointestinal tract. Thus, we focused on ammonium derivatives of **11**. Initial modifications to the structure of **11** centered on replacing *β*-guanidine with different cyclic or linear amino acid derivatives in accordance with Scheme 1. Synthesis of these derivatives began with a hydroboration of 1-decene (**12**), followed by a one-pot Suzuki–Miyaura cross-coupling reaction with 4-iodobenzonitrile to provide **13** in 92% yield. Reaction of **13** with hydroxylamine hydrochloride and triethylamine (TEA) in refluxing ethanol afforded the common intermediate amidoxime **14**. Subsequent HCTU-mediated coupling of **14** with the corresponding Boc-protected amino acids and Hünig's base at 100 °C provided the 1,2,4-oxadiazoles **15a**–**w** in moderate-to-good yield. Acetylation of **15w** yielded the corresponding protected analogue **15x**. Treatment with hydrogen chlorine in dioxane removed the Boc group and generated compounds **16a**–**x** as hydrochloride salts.

Diamines were synthesized as described in Scheme 2 using the common amidoxime intermediate **14**. HCTU-mediated condensation with 2-*N*-Fmoc terminal *N*-Boc-protected amino acids afforded the oxadiazole structures **17a**–**d**, which were deprotected using morpholine to yield the monoprotected compounds **18a**–**d**. Subsequent treatment with hydrochloric acid afforded **19a**–**d**. Compound **18d** was acetylated using acetyl chloride to yield **20** in excellent yield, which upon treatment with hydrochloric acid produced the ammonium salt **21**.

Modifications to the ammonium head of **16d** and **16w** were accomplished according to Scheme 3. The primary amine salts **16d** and **16w** were treated with dibromoalkanes in the presence potassium carbonate under microwave irradiation to generate the cyclic tertiary amines **22a**–**f**. Secondary amine derivatives were achieved through a two-step one-pot reductive amination reaction. Thus, the corresponding primary ammonium salts were dissolved in methanol and treated with acetaldehyde or paraformaldehyde and acetic acid. The generated iminium intermediate was reduced with sodium cyanoborohydride and quenched with dilute hydrochloric acid, yielding products **23a**–**b**.

A highly varying approach was undertaken with the linker region of **11** and focused on substituting the 1,2,4-oxadiazole ring with other nitrogen-based heteroaromatics (Scheme 4). Attachment of the decyl tail was achieved through a hydroboration of **12** with 9-borabicyclo[3.3.1]nonane (9-BBN) and a subsequent one-pot Suzuki–Miyaura cross-coupling with 4-bromoacetophenone to yield **24**. *α*-Bromination of **24** with NBS and tosylic acid afforded the monobrominated compound **25** in excellent yield, which upon cyclization with either *tert*-butyl(4-amino-4-thioxobutyl)-carbamate or *tert*-butyl(4-amino-4-oxobutyl)carbamate provided the thiazole derivative **27** and the oxazole derivative **29**, respectively. Deprotection of the Boc-groups with hydrochloric acid generated the primary ammonium salts **28** and **30**. To synthesize the imidazole analogues, compound **25** was converted to keto-ester intermediate **26** with *N*-Bocgamma aminobutyric acid (GABA) in nearly quantitative yields. Dehydration of **26** with excess ammonium acetate in refluxing

toluene formed the imidazole ring and afforded the *N*-Boc-protected imidazole **31**.[41] This was then subjected to treatment with either acid to afford the ammonium salt **32** or methyl iodide and sodium hydride to afford the methylated imidazole **33** exclusively, as confirmed via HMBC NMR spectroscopy. Compound **33** was then treated with acid to yield **34** as a hydrochloride salt.

Pyrazole analogues were synthesized as described in Scheme 5. Commercially available aryl bromide **35** was reacted with pyrazole boronic acids under Suzuki–Miyaura cross-coupling conditions to afford isomeric pyrazoles **36a** and **36b**. Deprotonation of the pyrazole ring with sodium hydride in THF generated the sodium amide, which was then alkylated with an *N*-Boc-protected alkyl bromide. Alkylation of **36a** yielded a 90 (**39**):10 (**37**) mixture of isomers, which were separable via column chromatography. Due to the symmetric nature of the pyrazole ring in **36b**, alkylation exclusively affords **41** as the lone product. Further treatment with hydrochloric acid afforded compounds **38**, **40**, and **42**.

To determine optimal atom arrangement in the linker region, we replaced the 1,2,4-oxadiazole linker with a 1,3,4-oxadiazole (Scheme 6). Hydrazine hydrate was reacted with 4-iodobenzoyl chloride **43** to afford hydrazide **44**. This intermediate was coupled to *N*-Boc-GABA with HCTU to generate an *N*-acyl intermediate and dehydrated using tosyl chloride in a one-pot fashion, affording 1,3,4-oxadiazole **45**. Attachment of the decyl tail was achieved through a tandem hydroboration Suzuki–Miyaura cross-coupling reaction with 1-decene. Deprotection with hydrochloric acid afforded compound **47**.

Homologation of the linker region was performed as described in Scheme 7. Aryl bromides **48a**–**b** were reacted with hydroxylamine hydrochloride, generating the amidoximes **49a**–**b**. Condensation with *N*-Boc-GABA was facilitated with HCTU to afford the Boc-protected oxadiazoles **50a**–**b**. Terminal alkenes (1-nonene and 1-octene) were hydroborated with 9-BBN and subjected to Suzuki–Miyaura cross-coupling conditions with the appropriate aryl bromide. Following tail attachment, removal of the Boc groups with acid provided the primary ammonium hydrochloride salts **52a**–**b**.

Ideal tail length and placement were interrogated in accordance with Scheme 8. The iodo-substituted benzonitriles **53a**–**b** were converted to amidoximes **54a**–**b** using hydroxylamine hydrochloride. Cyclization of compounds **54a**–**b** with HCTU and *N*-Boc-GABA provided the protected oxadiazoles **55a**–**b**. Terminal alkenes were hydroborated with 9-BBN and subsequently attached to **55a**–**b** under Suzuki–Miyaura cross-coupling conditions. The generated alkyl-substituted structures **56a**–**f** were treated with hydrochloric acid to afford the hydrochloride salts **57a**–**f**.

Incorporation of ether tails and alterations to the phenyl ring of **16d** were accomplished as described in Scheme 9. Starting with either phenols **58a**–**c** or the naphthol **58d**, a Williamson ether reaction was performed by employing the appropriate alkyl bromide to afford aryl nitriles **59a**–**d**. Conversion from the nitrile to the amidoximes **60a**–**d** was facilitated with hydroxylamide hydrochloride. As described in earlier schemes, HCTU was employed to condense amidoximes **60a**–**d** with *N*-Boc-GABA to form the oxadiazoles **61a**–**d**. Removal of the Boc groups afforded products **62a**–**d** as ammonium chloride salts.

Introduction of amide tails to **16d** was performed to increase tail group hydrophilicity and hydrogen bond interactions while simultaneously keeping the overall length consistent at 10 nonhydrogen atoms. Amide bonds were first synthesized through an HCTU-mediated condensation between 4-cyanobenzoic acid and a primary amine (Scheme 10) or 4-cyanoaniline and an aliphatic carboxylic acid (Scheme 11). Treatment of the corresponding benzonitriles with hydroxylamine hydrochloride yielded the amidoximes **65** and **70a**–**b**. Cyclization with HCTU and *N*-Boc-GABA yielded the 1,2,4-oxadiazole **66** and **71a**–**b**, which were subsequently deprotected using hydrochloric acid to yield the primary ammonium salts **67** and **72a**–**b**.

Biological Evaluation.

With putative Spns2 inhibitors in hand, we investigated their ability to inhibit S1P release from mouse Spns2-expressing HeLa cells. In this assay, Spns2 inhibitory activity is inversely proportional to S1P concentration in the assay media. Because intracellular S1P metabolism is due to S1P lyase and S1P phosphatase activities, 4-deoxypyridoxine, sodium fluoride, and sodium vanadate were added to retard S1P degradation. Control experiments revealed about a 20-fold increase in S1P extruded into the media compared to Spns2-expressing cells transfected with Spns2Arg200Ser (transport "dead" mutant)[28] or nontransfected cells. The results obtained with this assay are presented in Table 1. With focus on the azetidine ring (**16a**), we determined the effect of acyclic versions with varying carbon spacers (1–4 methylene units, entries 2–5). A three-carbon unit (**16d**) appeared to be most potent, having 67% inhibition at 2 μM. This activity deteriorated with subsequent *N*-methylations (entries 6–7). As such, carbocyclic amines with varying methylene spacer, ring size, position, and stereochemistry were synthesized and tested for Spns2 inhibition (entries 8–15). Among these, piperidine bearing analogue **16n** had similar activity to **16a**. In contrast, exocyclic primaryamines such as **16p**, **16q**, **16r**, and **16s** had profound negative impact on Spns2 inhibition. To mimic the negatively charged phosphate group in S1P, we synthesized α-aminobutanoic acid derivative **16t** and found no Spns2 inhibitory activity. As **16d** bearing a primary amine is the most potent, we introduced additional functional groups such as chloro, amino, *N*-acetyl, hydroxy, and *O*-acetyl along the alkyl backbone to improve inhibitory activity (entries 21–29), but these compounds did not result in improved activity. Likewise, pyrrolidine, piperidine, and morpholine tertiary amine analogues with and without an additional hydroxy functionality also had poor activity (entries 30–35). Interestingly, compound **23b** with a hydroxy and *N,N*-dimethyl groups restored Spn2 inhibition, albeit lower than **16d**.

Having identified a propyl amine functionality as an optimal head group in this series, our attention focused toward the tail region (Table 2). Thus, we performed a tail homologation, synthesizing C_6—C_{11} analogues of **16d**. As the alkyl chain increased from hexyl to decyl, a corresponding increase in Spns2 inhibitory activity was observed. Because the undecyl chain decreased inhibitory activity, a nonyl or decyl group appears optimal. We then investigated the effect of the substitution pattern on the phenyl ring. In this case, the *meta*-decyl derivative **57f** showed a reduction in activity relative to **16d**. Therefore, subsequent studies had the *para*-substitution pattern and the overall tail length was consistent at 10 atoms.

To probe the linker region of **16d**, we performed a homologation study to gauge the impact of adding additional methylene units between the phenyl and 1,2,4-oxadiazole rings. As a compound length of 21 atoms was identified as the ideal length for Spns2 inhibition in **16d**, for each methylene that was added between the two ring systems, one methylene was removed from the tail region. However, compounds **52a**–**b** showed reduced Spns2 inhibition relative to **16d**. Insertion of an oxygen atom and additional groups on the ring and amide groups to improve physicochemical properties of the compound also led to diminished Spns2 inhibitory activity (compounds **62a**–**d**, **67**, and **72a**–**b**).

As a direct aryl substitution on the 1,2,4-oxadiazole ring in **16d** was preferable to flexible alkyl groups, we replaced 1,2,4-oxadiazole with similarly substituted azole rings (Table 3). These modifications included replacement with thiazole (**28**), oxazole (**30**), 1*H*-imidazole (**32**), *N*-methylimidazole (**34**), and N-alkylated pyrazole (**38**, **40**, and **42**) rings. Additionally, analogue **47** was synthesized, where the 1,2,4-oxadiazole ring was replaced with a 1,3,4-oxadiazole ring to determine optimal heteroatom location within the ring. While these analogues demonstrated moderate Spns2 inhibition, none had superior activity relative to **16d** in the HeLa cell assay.

Overall, we performed a structure–activity study that interrogated the head, linker, and tail region of initial hit compound **11**. The biological screening of this focused library of 60 compounds at 2 and 1 μM (see the Supporting Information) identified several compounds within the margin of error in inhibiting Spns2. Among these, we chose **16d** as a potential Spns2 inhibitor for further investigation. Thus, we asked whether **16d** inhibited Spns2 in a dose-dependent manner using the HeLa cell assay. As shown in Figure 4A, a robust decrease of extruded S1P as a function of increasing **16d** concentration was observed with a calculated IC_{50} of 1.93 ± 0.04 μM. We then investigated whether **16d** inhibits SphK1 and SphK2 using a published protocol.[31] As documented in Figure 4B,C, treatment of recombinant mouse SphKs with **16d** in a dose–response manner suggests at least 15-fold selectivity (SphK1 $IC_{50} \geq 30$ μM; SphK2 $IC_{50} \approx 30$ μM).

As previously indicated, results of mouse studies revealed that inactivating the *Spns2* gene results in peripheral blood lymphopenia and a modest decrease in plasma S1P compared to litter mate control mice. To determine whether an Spns2 inhibitor recapitulates this phenotype, we dosed **16d** into mice and rats. Following administration of 20 mg/kg **16d** by intraperitoneal injection, we observed a statistically significant decrease in circulating lymphocytes (Figure 5A) and plasma S1P (Figure 5B) relative to vehicle-treated control mice after 4 h. These results suggest that **16d**, in addition to inhibiting S1P release from cultured cells, recapitulates the genetic phenotype of Spns2 null mice. While the activity of **16d** has not been tested with Mfsd2b, these pharmacodynamic markers—lymphopenia and a slight decrease in plasma S1P—suggest on-target Spns2 inhibition in vivo.

To investigate its pharmacokinetic–pharmacodynamic relationship, we administered **16d** to rats. A single 10 mg/kg dose (intraperitoneal injection) of **16d** into rats revealed a pharmacokinetic profile, reaching a maximum concentration of 5 μM in blood (total plasma) at 2 h with drug levels sustained at ≥ 2 μM for at least 24 h (Figure 6A). This analysis suggested that **16d** has a favorable profile and a half-life of over 8 h in rats. We determined

also the blood lymphocyte counts in these animals. The appearance of **16d** in circulation correlated with a maximal decrease in lymphocyte count at 4 h, which is approximately 25% lower compared to time = 0 (Figure 6B). Taken together, these results suggest that lymphocyte reductions were test article-related.

CONCLUSIONS

Inhibition of the S1P transporter Spns2 has the potential to be an alternative to S1P receptor agonists for modulating the immune system. In particular, the ability of Spns2 inhibitors to induce lymphopenia without drastic changes to systemic S1P levels or stimulating the S1P1-5 signaling pathways is advantageous and may provide an alternative therapeutic strategy that precludes side effects associated with S1P1-5 modulators while capturing their efficacy. In this report, we detail the discovery of Spns2 inhibitors using S1P levels in cultured cell media as a readout of S1P export activity. To the best of our knowledge, these are the first compounds reported to inhibit Spns2 activity both in vitro and in vivo. Our discovery of Spns2 inhibitors provides chemical tools that are complementary to genetic manipulation for elucidating the function and underlying biology of Spns2. The structure–activity profile suggests that a positively charged moiety (such as an ammonium) and a lipophilic alkyl tail are necessary for potent Spns2 inhibition. We observed a distinct preference for a sterically unhindered nitrogen in the ammonium head group as most compounds bearing tertiary ammonium head groups were less potent Spns2 inhibitors. While it is surprising that a carboxylic acid mimetic of the phosphate group of S1P was inactive, it is possible that such an analogue, which resembles S1P, serves as a substrate for export rather than an inhibitor. The homologation series wherein the alkyl tail was modified from hexyl to undecyl indicated a lipophilic binding site with a distinct pocket that accommodates a nonyl/decyl chain. Similar to S1P, Spns2 inhibitors appear to prefer long hydrophobic lipid tails. Our work ultimately led to the discovery of **16d** with an IC_{50} of 1.93 μM. Administration of **16d** to mice resulted in lymphopenia and concomitant plasma S1P decrease when compared to control animals. These in vivo results recapitulate the phenotype observed in Spns2-deficient mice, suggesting that **16d** functions to inhibit Spns2 in vivo. Based on rat pharmacokinetics (PK), **16d** has a favorable half-life in vivo, which will allow it to serve as a scaffold for further development and as a tool compound for studying Spns2 biology. The extent of lymphopenia evoked by **16d** (*ca.* 25% reduction) is considerably less than that obtained by the S1P receptor agonist prodrug, fingolimod, or even in an Spns2-null mouse. Determination of the maximum reduction in peripheral blood lymphocytes obtainable with an Spns2 inhibitor awaits the discovery of more potent molecules.

EXPERIMENTAL SECTION

General Materials and Synthetic Procedures.

Reactions were performed using the Schlenk technique under an argon or nitrogen atmosphere, unless otherwise specified. All glassware used was flamedried or oven-dried overnight. Chemicals were obtained from commercial sources and used without further purification, unless otherwise noted. THF, toluene, and DCM were dried using the

Innovative Technology Pure SolvMD solvent purification system prior to use. Column chromatography was performed using SiliaFlash P60 40–63 μm, 60 Å. Thin-layer chromatography (TLC) analyses were performed using Silicycle aluminum-backed silica gel F-254 plates. NMR spectroscopic experiments were performed using a Bruker AVANCE II 500 MHz, Agilent 400-MR 400 MHz, or a Varian Inova 400 MHz spectrometer. Chemical shifts are reported in δ ppm and ^{1}H and ^{13}C NMR and referenced using the residual protonated solvent ($CHCl_3$, acetone, or methanol) or an internal standard (TMS). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constants (Hz), and integration. Minor rotamer peaks are denoted by an asterisk (*). ESI mass spectra were obtained using an Agilent 6220 TOF LC–MS. Purity assessments were performed by Agilent HPLC analysis. HPLC conditions: solvent A: water (0.1% TFA); solvent B: acetonitrile (0.1% TFA); column: Zorbax SB-C18, 5 μM, 4.6 × 150 mm; method: isocratic 95% A, 5% B from 0 to 5 min, then linear gradient from 5 to 95% B by 20 min, hold 95% B by 30 min, and return to 5% B by 40 min; UV wavelength = 254 nm; flow rate: 1.5 mL/min. All compounds tested in biological assays were assessed to have ≥95% purity by HPLC, unless otherwise noted. Compounds evaluated in vivo were HPLC-purified prior to injection into animals and were of ≥95% purity by HPLC.

General Procedure 1: One-Pot Hydroboration-Suzuki–Miyaura Cross-Coupling.—To a round-bottom flask a containing alkene (1.1 equiv) in THF was added 9BBN (1.5 equiv) and then heated to reflux until consumption of alkene, as monitored by TLC (30–60 min). Aryl halide (1.0 equiv) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.05 equiv) were then added to the mixture, followed by dropwise addition of a 3M $KOH_{(aq)}$ solution (3.0 equiv). The resulting mixture was then heated to reflux until consumption of aryl iodide, as monitored by TLC (2–6 h). On cooling to room temperature (rt), the reaction mixture was filtered over a pad of Celite, diluted in ethyl acetate, and washed with a brine solution. The organic layer was then dried over sodium sulfate and concentrated in vacuo to afford the crude product as a yellow oil, which was then purified by column chromatography with an appropriate hexanes/ethyl acetate solvent system to afford the pure product.

General Procedure 2: Amidoxime Synthesis.—To a round-bottom flask containing ethanol/water (1:1) were added benzonitrile (1.0 equiv), hydroxylamine hydrochloride (2.0 equiv), and sodium carbonate (5.0 equiv) under ambient air. The reaction mixture was then heated to reflux until complete, as monitored by TLC (1–6 h). The resulting solution was allowed to cool to rt. A white precipitate formed upon cooling, which was vacuum-filtered over a filter frit and washed with water and ethanol to afford the pure product.

General Procedure 3: 1,2,4-Oxadiazole Synthesis.—Amidoxime (1.0 equiv), *N*-Boc protected β-amino acid (1.1 equiv), and *N,N*-diisopropylethylamine (DIEA) (1.8 equiv) were added to a round-bottom flask containing DMF at rt. HCTU (1.1 equiv) was then added, and the resulting mixture was heated to 100 °C until completion, as monitored by TLC (6–16 h). Upon cooling to rt, the resulting mixture was diluted in ethyl acetate and washed with a saturated lithium bromide solution. The resulting aqueous layer was then extracted (three times) with ethyl acetate. The organic layers were combined and washed

with a brine solution (three times), followed by drying over anhydrous sodium sulfate. Concentration in vacuo afforded the crude product, which was then purified by column chromatography using the appropriate ethyl acetate/hexane solvent system to afford the pure 1,2,4-oxadiazole product.

General Procedure 4: HCl-Assisted Boc Deprotection.—To a 6 dram vial containing Boc-protected amine (1.0 equiv) was added hydrogen chloride (10.0 equiv, 4M in dioxane). The resulting mixture was allowed to stir until consumption of the starting material, as monitored by TLC (0.5–6 h). The solvent was removed under reduced pressure and rinsed with diethyl ether until a thick white precipitate formed. This precipitate was subjected to trituration with an appropriate solvent system to afford the pure product as a hydrochloride salt.

General Procedure 5: Base-Assisted Fmoc Removal.—To a 6-dram vial containing Fmoc-protected amine (1.0 equiv) and DMF was added morpholine (10.0 equiv). The mixture was allowed to stir at rt for 16 h at which point TLC analysis showed complete consumption of the starting material. Following completion, the mixture was diluted with ethyl acetate and portioned with saturated lithium bromide. The resulting aqueous layer was then extracted (three times) with ethyl acetate. The organic layers were combined and washed with a brine solution (three times), followed by drying over anhydrous sodium sulfate. Concentration in vacuo afforded the crude product, which was then purified by column chromatography using the appropriate ethyl acetate/hexane solvent system.

General Procedure 6: Microwave-Assisted Cyclization of Primary Amines.—To a microwave vial containing a stir bar were added primary amine salt (1.0 equiv), potassium carbonate (1.1 equiv), dibromoalkane (1.0 equiv), and acetonitrile. The vial was then heated to 120 °C for 20 min in a CEM Discover SP Microwave Synthesizer. Following completion, the reaction mixture was extracted with ethyl acetate and washed with a 50:50 brine/10% NaOH solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude product as a colorless oil. The crude product was dissolved in a hydrochloric acid solution (4 M in dioxane) and concentrated in vacuo to afford a white solid. The white solid was loaded onto Celite and subjected to silica gel chromatography in an appropriate solvent system to yield the purified the cyclic amine hydrochloride salt.

General Procedure 7: Alkylation of Pyrazole Rings.—To an oven-dried round-bottom flask containing a stir bar were added sodium hydride (60% dispersion in mineral oil, 1.1 equiv) and THF. The mixture was then purged with argon and cooled to 0 °C in an ice bath. The appropriate aryl pyrazole (1.0 equiv) was added to the solution and allowed to stir for 15 min. *tert*-Butyl(3-bromopropyl)carbamate (3.0 equiv) was slowly added to the flask and the reaction mixture continued to stir at 0 °C for 18 h. Following completion as monitored by TLC, the reaction mixture was concentrated under reduced pressure and purified via column chromatography with an appropriate ethyl acetate/hexane eluent to afford the desired products.

General Procedure 8: Williamson Ether Synthesis.—The appropriate phenol derivative (1.0 equiv) was added to a dried round-bottom flask containing a stir bar and potassium carbonate (3.0 equiv). The appropriate alkyl bromide (1.2 equiv) and dry acetonitrile were added, and the flask was attached to a condenser and heated to reflux for 4 h. Following completion, the crude reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, and partitioned with brine. The organic layer was rinsed three times with brine, dried over sodium sulfate, and filtered. The product was then either carried forward crude with no additional purification or purified via column chromatography.

General Procedure 9: HCTU Amide Coupling.—To a 6-dram vial containing *N*-Boc-amino acid (1.1 equiv) were added DMF (0.2 M), DIEA (1.8 equiv), and HCTU (1.1 equiv). The resulting mixture was allowed to stir at rt for 5 min, followed by addition of the amine derivative (1.0 equiv). The resulting mixture was allowed to stir at rt until consumption of amine, as monitored by TLC (1–4 h). The resulting reaction mixture was diluted in ethyl acetate and washed with a saturated lithium bromide solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo to afford an orange oil which was then subjected to flash chromatography with an appropriate ethyl acetate in a dichloromethane solvent system to afford the pure product.

4-Decylbenzonitrile (13).—Synthesized according to General Procedure 1. Purified via column chromatography (3% ethyl acetate/hexanes). Off-white solid (96%, 2.05 g). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.55 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 1.61 (p, J = 7.4 Hz, 2H), 1.37–1.18 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 148.7, 132.1, 129.2, 119.2, 109.5, 36.2, 32.0, 31.1, 29.7, 29.6, 29.5, 29.4, 29.3, 22.8, 14.2. Data is consistent with literature.[42]

4-Decyl-N′-hydroxybenzimidamide (14).—Synthesized according to General Procedure 2. Purified via column chromatography (20% ethyl acetate/hexanes). White solid (92%, 10.56 g). Isolated as a mixture of *Z*/*E* (20:1). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.54 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 4.89 (br s, 2H), 2.62 (t, J = 7.7 Hz, 2H), 1.61 (p, J = 7.0 Hz, 2H), 1.36–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 152.8, 145.3, 129.9, 128.8, 125.9, 35.9, 32.0, 31.5, 29.8, 29.7, 29.6, 29.5, 29.4, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{29}N_2O$, 277.2274; observed, 277.2281.

tert-Butyl 3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (15a).—Synthesized according to General Procedure 3. Purified via column chromatography (10–30% ethyl acetate/hexanes). Yellow oil (59%, 94 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.42–4.28 (m, 4H), 4.04 (tt, J = 8.8, 6.2 Hz, 1H), 2.66 (t, J = 7.7 Hz, 2H), 1.64 (p, J = 6.7 Hz, 2H), 1.46 (s, 9H), 1.37–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 178.9, 168.8, 156.0, 146.9, 129.1, 127.5, 124.0, 80.3, 53.4, 36.1, 32.0, 31.3, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5, 25.9, 22.8, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{39}N_3NaO_3$, 464.2884; observed, 464.2882.

tert-Butyl ((3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-carbamate (15b).— Synthesized according to General Procedure 3. Purified via column chromatography (15% ethyl acetate/hexanes). White solid (75%, 281 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.95 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.59 (br s, 1H), 4.66–4.55 (m, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.67–1.57 (m, 2H), 1.46 (br s, 9H), 1.36–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 176.5, 168.4, 155.6, 146.7, 128.9, 127.4, 123.9, 80.6, 37.2, 36.0, 32.0, 31.3, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 28.3, 22.7, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{24}H_{38}N_3O_3$, 416.2908; observed, 416.2925.

tert-Butyl (2-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)-carbamate (15c).— Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Light-yellow solid (50%, 155 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 5.27 (br s, 1H), 3.69–3.62 (m, 2H) 3.12 (t, J = 6.0 Hz, 2H), 2.65 (t, J = 7.7 hz, 2H), 1.68–1.58 (m, 2H), 1.43 (br s, 9H), 1.37–1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 177.8, 168.3, 155.8, 146.6, 129.0, 127.4, 124.1, 79.7, 37.3, 36.0, 32.0, 31.3, 29.7, 29.6, 29.5, 29.4, 29.3, 28.4, 27.6, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_3$, 430.3064; observed, 430.3076.

tert-Butyl (3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (15d).— Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow oil (65%, 260 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 5.07 (br s, 1H), 3.32–3.22 (m, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.11–2.02 (m, 2H), 1.67–1.57 (m, 2H), 1.43 (br s, 9H), 1.36–1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 179.2, 168.2, 156.0, 146.4, 128.9, 127.3, 124.2, 79.2, 39.8, 35.9, 31.9, 31.2, 29.6, 29.6, 29.5, 29.3, 29.3, 28.4, 26.9, 24.1, 22.7, 14.1. HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{41}N_3NaO_3$, 466.3040; observed, 466.3034.

tert-Butyl (4-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)butyl)-carbamate (15e).— Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (69%, 285 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.0 (d, J = 8.2 Hz, 2H), 7.3 (d, J = 8.0 Hz, 2H), 4.8 (t, J = 5.7 Hz, 1H), 3.2 (q, J = 6.7 Hz, 2H), 2.9 (t, J = 7.5 Hz, 2H), 2.6 (t, J = 7.7 Hz, 2H), 1.9 (p, J = 7.5 Hz, 2H), 1.7–1.6 (m, 4H), 1.4 (s, 9H), 1.4–1.2 (m, 14H), 0.9 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.4, 168.2, 156.0, 146.4, 128.9, 127.3, 124.2, 79.1, 39.9, 36.0, 31.9, 31.2, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 28.4, 26.2, 23.8, 22.7, 14.1. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_3$, 458.3383; observed, 458.3390.

tert-Butyl (3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-(methyl)carbamate (15f).— Synthesized according to General Procedure 3. Purified via column chromatography (15% ethyl acetate/hexanes). Yellow oil (54%, 319 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 3.38 (t, J = 6.9 Hz, 2H), 2.94 (t, J = 7.6 Hz, 2H), 2.88 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.10 (p, J = 7.3 Hz, 2H), 1.63 (p, J = 7.5 Hz, 2H), 1.44 (s, 9H), 1.38–1.19 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.0, 168.3, 146.4, 128.9, 127.3, 124.2, 79.3, 47.7, 35.9, 34.2, 31.9, 31.2, 29.6, 29.6,

29.5, 29.3, 29.2, 28.4, 24.7, 23.9, 22.7, 14.1. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_3$, 458.3377; observed, 458.3372.

3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-N,N-dimethylpropan-1-amine (15g).—Synthesized according to General Procedure 3. Crude mixture dried in vacuo and carried forward to the next reaction as a free amine base without further purification.

tert-Butyl 3-((3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-azetidine-1-carboxylate (15h).—Synthesized according to General Procedure 3. Purified via column chromatography (16% ethyl acetate/hexanes). Off-white solid (49%, 160 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 4.16 (t, J = 8.5 Hz, 2H), 3.79–3.74 (m, 2H), 3.24–3.19 (m, 2H), 3.13–3.03 (m, 1H), 2.65 (t, J = 7.8 Hz, 2H), 1.67–1.58 (m, 2H), 1.44 (br s, 9H), 1.37–1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 177.2, 168.4, 156.2, 146.6, 128.9, 127.4, 124.0, 79.6, 53.7, 36.0, 31.9, 31.3, 30.9, 29.6, 29.6, 29.5, 29.4, 29.3, 28.4, 26.4, 22.7, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{27}H_{41}N_3O_3Na$, 478.3046; observed, 478.3029.

tert-Butyl (S)-3-((3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-pyrrolidine-1-carboxylate (15i).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (64%, 273 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 3.77–3.44 (m, 3H), 3.42–3.28 (m, 1H), 3.19–2.94 (m, 3H), 2.84–2.71 (m, 1H), 2.66 (t, J = 7.7 Hz, 2H), 2.19–2.08 (m, 1H), 1.77–1.58 (m, 3H), 1.46 (br s, 9H), 1.38–1.19 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 178.0, 168.4, 154.5, 146.6, 129.0, 127.4,124.1, 79.5, 50.8, 45.0, 36.8, 36.0, 32.0, 31.4, 31.3, 30.9, 29.9, 29.7, 29.7, 29.6, 29.4, 29.3, 28.6, 22.8, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{28}H_{43}N_3NaO_3$, 492.3197; observed, 492.3199.

tert-Butyl (R)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-pyrrolidine-1-carboxylate (15j).—Synthesized according to General Procedure 3. Purified via column chromatography (16% ethyl acetate/hexanes). Off-white solid (75%, 148 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 3.95–3.41 (m, 6H), 2.65 (t, J = 7.7 Hz, 2H), 2.44–2.29 (m, 2H), 1.68–1.58 (m, 2H), 1.48 (br s, 9H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 179.4, 168.4, 154.2, 146.6, 128.9, 127.4, 124.0, 79.8, 49.4, 45.1, 36.6, 36.0, 35.8, 31.9, 30.5, 30.4, 29.6, 29.6, 29.5, 29.4, 29.3, 28.5, 22.7, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{41}N_3NaO_3$, 478.3040; observed, 478.3065.

tert-Butyl (S)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-pyrrolidine-1-carboxylate (15k).—Synthesized according to General Procedure 3. The product was could not be separated from impurity and was carried forward crude to the next reaction.

tert-Butyl (R)-2-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-pyrrolidine-1-carboxylate (15l).—Synthesized according to General Procedure 3. Purified via column chromatography (30% ethyl acetate/hexanes). Yellow oil (61%, 101 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.26–5.02 (m, 1H), 3.80–3.44 (m, 2H), 2.65 (t, J = 7.8 Hz, 2H), 2.47–2.33 (m, 1H), 2.22–2.06 (m, 2H), 2.04–1.93 (m, 1H), 1.63 (p, J = 7.1 Hz, 2H), 1.49–1.21 (m, 23H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101

MHz, $CdCl_3$): δ 180.6, 168.5, 153.7, 146.7, 129.1, 128.9*, 127.6*, 127.5, 124.2, 80.6, 80.4*, 53.9, 46.7*, 46.5, 36.1, 32.5, 32.0, 31.6*, 31.4, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5*, 28.3, 24.5*, 23.8, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{42}N_3O_3$, 456.3221; observed, 456.3219.

tert-Butyl (S)-2-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-pyrrolidine-1-carboxylate (15m).—Synthesized according to General Procedure 3. Purified via column chromatography (30% ethyl acetate/hexanes). Yellow oil (49%, 81 mg). ^1H NMR (400 MHz, $CdCl_3$): δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.21–5.01 (m, 1H), 3.75–3.43 (m, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.44–2.28 (m, 1H), 2.20–2.04 (m, 2H), 2.03–1.93 (m, 1H), 1.62 (p, *J* = 7.9 Hz, 2H), 1.47–1.20 (m, 23H), 0.86 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 180.6, 168.5, 153.7, 146.7, 146.4*, 129.1, 128.9*, 127.6*, 127.5, 124.2, 80.5, 80.4*, 53.9, 46.7*, 46.5, 36.1*, 32.5, 32.0, 31.6, 31.4, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5*, 28.3, 24.4*, 23.8, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{42}N_3O_3$, 456.3221; observed, 456.3212.

tert-Butyl 4-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (15n).—Synthesized according to General Procedure 3. Purified via column chromatography (14% ethyl acetate/hexanes). Yellow oil (76%, 335 mg). ^1H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 4.11 (br s, 2H), 3.18–3.09 (m, 1H), 2.98 (t, *J* = 11.6 Hz, 1H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.14–2.05 (m, 2H), 1.94–1.82 (m, 2H), 1.67–1.56 (m, 2H), 1.48 (br s, 9H), 1.37–1.19 (m, 14H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 181.0, 168.2, 154.5, 146.4, 128.8, 127.3, 124.2, 79.7, 42.8, 35.9, 34.4, 31.9, 31.2, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 28.4, 22.7, 14.1. HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{44}N_3O_3$, 470.3377; observed, 470.3369.

tert-Butyl 4-((3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-piperazine-1-carboxylate (15o).—Synthesized according to General Procedure 3. Purified via column chromatography (35% ethyl acetate/hexanes). White solid (63%, 248 mg). ^1H NMR (400 MHz, $CdCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.93 (s, 2H), 3.5 (t, *J* = 5.0 Hz, 4H), 2.66 (t *J* = 7.7 Hz, 2H), 2.60 (t *J* = 5.0 Hz, 4H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.45 (s, 9H), 1.38–1.19 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 175.8, 168.5, 154.7, 146.8, 129.1, 127.6, 124.0, 80.0, 53.2, 52.7, 43.6, 36.1, 32.0, 31.4, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{45}N_4O_3$, 485.3486; observed, 485.3479.

tert-Butyl ((1S,3R)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-cyclopentyl)carbamate (15p).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (63%, 213 mg). ^1H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 5.67 (br s, 1H), 4.23 (br s, 1H), 3.59–3.48 (m, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.53–2.43 (m, 1H), 2.29–1.91 (m, 4H), 1.85–1.74 (m, 1H), 1.68–1.58 (m, 2H), 1.47 (br s, 9H), 1.38–1.19 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 183.6, 168.2, 155.5, 146.7, 129.0, 127.5, 124.1, 79.2, 52.0, 38.1, 36.1, 35.2, 33.4, 32.0, 31.4, 30.1, 29.7, 29.7, 29.6,

29.4, 29.4, 28.6, 28.6, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{44}N_3O_3$, 470.3377; observed, 470.3372.

tert-Butyl ((1R,3S)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-cyclohexyl)carbamate (15q).—Synthesized according to General Procedure 3. Purified via column chromatography (12% ethyl acetate/hexanes). Yellow solid (72%, 314 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 4.58 (s, 1H), 3.61 (s, 1H), 3.10 (dt, J = 11.6, 5.9 Hz, 1H), 2.71–2.58 (m, 2H), 2.48 (d, J = 12.4 Hz, 1H), 2.15 (d, J = 9.4 Hz, 1H), 2.05 (d, J = 12.7 Hz, 1H), 1.99–1.90 (m, 1H), 1.70–1.49 (m, 6H), 1.45 (s, 9H), 1.38–1.19 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 181.5, 168.2, 155.0, 146.4, 128.9, 127.3, 124.2, 79.3, 48.8, 36.6, 35.9, 35.5, 32.6, 31.9, 31.2, 29.6, 29.6, 29.5, 29.3, 29.2, 28.4, 24.1, 22.7, 14.1. HRMS (ESI): $[M + Na]^+$ calcd for $C_{29}H_{45}N_3NaO_3$, 506.3353; observed, 506.3337.

tert-Butyl ((1R,3S)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-cyclohexyl)carbamate (15q).—Synthesized according to General Procedure 3. Purified via column chromatography (12% ethyl acetate/hexanes). Yellow solid (73%, 318 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 4.63 (br s, 1H), 3.95 (brs 1H), 3.29 (br s, 1H), 2.65 (d, J = 7.7 Hz, 2H), 2.22–1.54 (m, 10H), 1.45 (s, 9H), 1.39–1.22 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 181.9, 168.4, 155.2, 146.5, 129.0, 127.5, 124.4, 79.5, 45.5, 36.1, 34.5, 32.2, 32.0, 31.4, 30.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 28.6, 22.8, 20.6, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{29}H_{45}N_3NaO_3$, 506.3353; observed, 506.3336.

tert-Butyl (3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)benzyl)-carbamate (15s).—Synthesized according to General Procedure 3. Purified via column chromatography (17% ethyl acetate/hexanes). Yellow solid (59%, 232 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.14–8.09 (m, 2H), 8.07 (d, J = 8.2 Hz, 2H), 7.56–7.49 (m, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.99 (br s, 1H), 4.43 (d, J = 6.2 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 1.65 (p, J = 7.4 Hz, 2H), 1.49 (s, 9H), 1.39–1.20 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ175.5, 169.1, 156.0, 146.7, 140.5, 131.8, 129.6, 129.1, 127.6, 127.2, 127.0, 124.8, 124.4, 80.0, 44.4, 36.1, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 29.4, 28.5, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{30}H_{42}N_3O_3$, 492.3221; observed, 492.3209.

tert-Butyl (R)-2-((tert-Butoxycarbonyl)amino)-4-(3-(4-decylphen-yl)-1,2,4-oxadiazol-5-yl)butanoate (15t).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (59%, 290 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.34 (d, J = 8.1 Hz, 1H), 4.34 (q, J = 7.9 Hz, 1H), 3.11–2.91 (m, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.49–2.36 (m, 1H), 2.25–2.11 (m, 1H), 1.62 (p, J = 8.5 Hz, 2H), 1.48 (s, 9H), 1.43 (s, 9H), 1.35–1.21 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 178.8, 171.0, 168.4, 155.5, 146.5, 129.0, 127.4, 124.2, 82.6, 80.0, 53.5, 36.0, 32.0, 31.3, 29.8, 29.7, 29.7, 29.6, 29.4, 29.3, 28.4, 28.1, 23.1, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{31}H_{50}N_3O_5$, 544.3745; observed, 544.3753.

tert-Butyl (E)-(3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)allyl)-carbamate (15u).—Synthesized according to General Procedure 3. Purified via column chromatography (15% ethyl acetate/hexanes). White solid (74%, 143 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.09 (dt, J = 16.1, 4.9 Hz, 1H), 6.58 (d, J = 16.1 Hz, 1H), 5.00 (br s, 1H), 4.03 (br s, 2H), 2.65 (t, J = 7.7 Hz, 2H), 1.63 (p, J = 7.1 Hz, 2H), 1.47 (s, 9H), 1.37–1.19 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 174.2, 168.7, 155.7, 146.6, 143.1, 129.0, 127.4, 124.2, 113.5, 80.0, 41.9, 36.0, 32.0, 31.3, 29.7, 29.7, 29.6, 29.4, 29.3, 28.4, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{40}N_3O_3$, 442.3070; observed, 442.3063.

tert-Butyl (S)-(1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propan-2-yl)carbamate (15v).—Synthesized according to General Procedure 3. Purified via column chromatography (15% ethyl acetate/hexanes). Yellow solid (46%, 110 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.02–4.90 (m, 1H), 4.29–4.17 (m, 1H), 3.15 (d, J = 5.8 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.68–1.57 (m, 2H), 1.43 (br s, 9H), 1.36–1.20 (m, 17H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 177.0, 168.3, 155.0, 146.6, 129.0, 127.5, 124.2, 79.7, 44.5, 36.0, 33.5, 32.0, 31.3, 29.7, 29.7, 29.6, 29.4, 20.3, 28.4, 22.8, 20.30, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{41}N_3NaO_3$, 466.3040; observed, 466.3061.

tert-Butyl (3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-2-hydroxypropyl)carbamate (15w).—Synthesized according to General Procedure 3. Purified via column chromatography (40% ethyl acetate/hexanes). Yellow solid (60%, 452 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.94 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.30 (br s, 1H), 4.30 (br s, 2H), 3.49–3.41 (m, 1H), 3.32–3.22 (m, 1H), 3.14–3.05 (m, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.66–1.58 (m, 2H), 1.44 (br s, 9H), 1.36–1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CdCl_3$): δ 177.3, 168.1, 156.9, 146.7, 129.0, 127.4, 123.8, 80.0, 68.5, 45.7, 36.0, 32.0, 31.7, 31.3, 29.7, 29.7, 29.6, 29.4, 29.3, 28.4, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{42}N_3O_4$, 460.3170; observed, 460.3169.

1-((tert-Butoxycarbonyl)amino)-3-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)propan-2-yl Acetate (15x).—2-To a 6-dram vial containing 15w were added acetic anhydride (50.0 equiv) and TEA (9.0 equiv), and the mixture was allowed to stir at rt for 30 min. The mixture was then diluted with ethyl acetate and washed with a saturated sodium carbonate solution, followed by a brine solution. The organic layer was concentrated in vacuo to afford a crude mixture. The desired product was confirmed via HRMS and carried forward as crude with no further purification. Clear oil (82%, 206 mg). HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{43}N_3NaO_5$, 524.3095; observed, 524.3088.

5-(Azetidin-3-yl)-3-(4-decylphenyl)-1,2,4-oxadiazole Hydrochloride (16a).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (79%, 34 mg). ^{1}H NMR (400 MHz, CD3OD): δ 7.97 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.64–4.46 (m, 5H), 2.66 (t, J = 7.7 Hz, 2H), 1.63 (p, J = 7.5 Hz, 2H), 1.37–1.23 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.9, 169.8,

148.1, 130.1, 128.4, 125.0, 50.8, 36.9, 33.1, 32.4, 30.7, 30.7, 30.6, 30.5, 30.3, 29.9, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{32}N_3O$, 342.2540; observed, 342.2543.

(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)methanamine Hydrochloride (16b).— Synthesized according to General Procedure 4. Purified via column chromatography (10% methanol/dichloromethane). White solid (86%, 250 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 4.60 (br s, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.70–1.57 (m, 2H), 1.39–1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 174.4, 169.7, 148.4, 130.1, 128.5, 124.7, 36.9, 36.1, 33.0, 32.4, 30.7, 30.6, 30.4, 30.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{30}N_3O$, 316.2383; observed, 316.2393.

2-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)ethan-1-amine Hydrochloride (16c).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (76%, 110 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 3.52 (t, J = 6.8 Hz, 2H), 3.38 (t, J = 6.7 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 1.70–1.60 (m, 2H), 1.40–1.22 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 177.6, 169.6, 148.2, 130.1, 28.4, 125.2, 37.3, 36.9, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 25.4, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{32}N_3O$, 330.2540; observed, 330.2529.

3-(3-(4-Decylphenyl)- 1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (16d).—Synthesized according to General Procedure 4. Purified via column chromatography (10% methanol/dichloromethane). White solid (63%, 160 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.93 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2), 3.19–3.07 (m, 4H), 2.64 (t, J = 7.6 Hz, 2H), 2.25 (p, J = 7.5 Hz, 2H), 1.69–1.58 (m, 2H), 1.37–1.20 (m, 14H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 180.1, 169.4, 147.9, 130.0, 128.3, 125.3, 39.8, 36.8, 33.0, 32.4, 30.7, 30.6, 30.4, 30.3, 25.1, 24.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2701.

4-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)butan-1-amine Hydrochloride (16e).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (85%, 190 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.04 (t, J = 7.3 Hz, 2H), 2.98 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.95 (p, J = 7.3 Hz, 2H), 1.79 (p, J = 8.3 Hz, 2H), 1.62 (p, J = 7.5 Hz, 2H), 1.35–1.22 (m, 14H), 0.86 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 181.0, 169.4, 148.0, 130.1, 128.3, 125.4, 40.3, 36.8, 33.1, 32.5, 30.7, 30.7, 30.6, 30.5, 30.3, 27.8, 26.6, 24.4, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3O$, 358.2853; observed, 358.2854.

3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-N-methylpropan-1-amine Hydrochloride (16f).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (79%, 211 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.95 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.7 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.1 Hz, 2H), 2.75 (s, 3H), 2.68 (t, J = 7.6 Hz, 2H), 2.35–2.20 (m, 2H), 1.71–1.59 (m, 2H), 1.42–1.20 (m, 14H), 0.89 (t, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.9, 169.4,

147.9, 130.0, 128.3, 125.3, 49.7, 36.8, 34.4, 33.0, 32.4, 30.6, 30.5, 30.3, 30.2, 24.6, 24.0, 23.6, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3O$, 358.2853; observed, 358.2850.

3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-N,N-dimethylpropan-1-amine Hydrochloride (16g).—The amine-free base of the title compound was prepared according to General Procedure 3. The title compound was prepared by dissolving the amine-free base **15g** in methanolic HCl, followed by concentration in vacuo. It was purified via column chromatography (10% methanol/dichloromethane). White solid (33%, 80 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 7.34 (d, J = 8.2 Hz, 2H), 3.40–3.30 (m, 2H), 3.14 (t, J = 7.3 Hz, 2H), 2.97 (s, 6H), 2.69 (t, J = 7.7 Hz 2H), 2.40–2.29 (m, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.42–1.22 (m, 14H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.9, 169.5, 148.0, 130.1, 128.3, 125.3, 57.8, 43.6, 36.8, 33.0, 32.4, 30.7, 30.5, 30.4, 30.3, 24.2, 23.7, 22.4, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{38}N_3O$, 372.3009; observed, 372.3005.

5-(Azetidin-3-ylmethyl)-3-(4-decylphenyl)-1,2,4-oxadiazole Hydrochloride (16h).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (63%, 164 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.34–4.24 (m, 2H), 4.14–4.04 (m, 2H), 3.54 (hept, J = 8.2 Hz, 1H), 3.37 (d, J = 7.6 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 1.64 (p, J = 7.5 Hz, 2H), 1.42–1.21 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.5, 169.5, 148.1, 130.1, 128.3, 125.2, 52.1, 36.8, 33.1, 32.4, 30.8, 30.7, 30.6, 30.4, 30.3, 29.9, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O$, 356.2696; observed, 356.2729.

(S)-3-(4-Decylphenyl)-5-(pyrrolidin-3-ylmethyl)-1,2,4-oxadiazole Hydrochloride (16i).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (75%, 210 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.66–3.59 (m, 1H), 3.47–3.40 (m, 1H), 3.34–3.25 (m, 1H), 3.21–3.14 (m, 2H), 3.09 (dd, J = 11.8, 8.9 Hz, 1H), 3.00–2.83 (m, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.39–2.30 (m, 1H), 1.83 (dq, J = 13.2, 8.8 Hz, 1H), 1.62 (p, J = 7.2 Hz, 2H), 1.36–1.19 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 179.3, 169.5, 148.1, 130.1, 128.3, 125.3, 50.7, 46.3, 36.8, 33.1, 32.4, 31.0, 30.7, 30.6, 30.5, 30.3, 29.7, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{36}N_3O$, 370.2853; observed, 370.2856.

(R)-3-(4-Decylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole Hydrochloride (16j).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (72%, 90 mg). ^{1}H NMR (400 MHz, cd_3od): δ 7.94 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 4.04–3.92 (m, 1H), 3.77–3.69 (m, 1H), 3.67–3.60 (m, 1H), 3.49–3.36 (m, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.61–2.49 (m, 1H), 2.44–2.31 (m, 1H), 1.62 (p, J = 7.5 Hz, 2H), 1.38–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 179.3, 169.5, 163.1, 147.9, 130.0, 128.3, 125.3, 119.6, 116.7, 50.6, 46.2, 36.8, 36.8, 33.0, 32.4, 31.0, 30.7, 30.6, 30.4, 30.3, 29.7, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O$, 356.2696; observed, 356.2716.

(S)-3-(4-Decylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole Hydrochloride (16k).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether.

White solid (75%, 210 mg). ^{1}H NMR (400 MHz, cd$_3$od): δ 7.94 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 4.02–3.90 (m, 1H), 3.75–3.66 (m, 1H), 3.64–3.57 (m, 1H), 3.46–3.32 (m, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.60–2.47 (m, 1H), 2.43–2.30 (m, 1H), 1.62 (p, J = 7.1 Hz, 2H), 1.37–1.22 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 179.3, 169.5, 148.1, 130.1, 128.3, 125.3, 50.7, 46.3, 36.8, 33.1, 32.4, 31.0, 30.7, 30.6, 30.5, 30.3, 29.7, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O$, 356.2696; observed, 356.2700.

(R)-3-(4-Decylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole Hydrochloride (16l).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (76%, 88 mg). ^{1}H NMR (400 MHz, CD$_3$OD): δ 8.00 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 5.21 (t, J = 7.8 Hz, 1H), 3.67–3.49 (m, 2H), 2.75–2.62 (m, 3H), 2.49–2.36 (m, 1H), 2.36–2.20 (m, 2H), 1.64 (p, J = 7.4 Hz, 2H), 1.39–1.24 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD$_3$OD): δ 175.9, 169.8, 148.6, 130.2, 128.5, 124.6, 55.6, 47.3, 36.9, 33.0, 32.4, 30.7, 30.7, 30.5, 30.4, 30.3, 30.2, 24.5, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O$, 356.2696; observed, 356.2711.

(S)-3-(4-Decylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole Hydrochloride (16m).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (79%, 55 mg). ^{1}H NMR (400 MHz, CD$_3$OD): δ 8.00 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 5.21 (t, J = 7.7 Hz, 1H), 3.67–3.49 (m, 2H), 2.75–2.62 (m, 3H), 2.49–2.36 (m, 1H), 2.36–2.20 (m, 2H), 1.65 (p, J = 7.6 Hz, 2H), 1.40–1.23 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD$_3$OD): δ 175.9, 169.8, 148.6, 130.2, 128.5, 124.6, 55.6, 47.3, 36.9, 33.0, 32.4, 30.7, 30.7, 30.5, 30.4, 30.3, 30.2, 24.5, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O$, 356.2696; observed, 356.2698.

3-(4-Decylphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole Hydrochloride (16n).— Synthesized according to General Procedure 4. Purified via column chromatography (7% methanol/dichloromethane). White solid (89%, 330 mg). ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.96 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 3.56–3.43 (m, 3H), 3.27–3.16 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.48–2.35 (m, 2H), 2.21–2.06 (m, 2H), 1.73–1.57 (m, 2H), 1.42–1.16 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 181.5, 169.5, 148.1, 130.1, 128.3, 125.3, 44.0, 36.9, 33.1, 32.9, 32.5, 30.7, 30.6, 30.5, 30.3, 27.2, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{36}N_3O$, 370.2853; observed, 370.2826.

3-(4-Decylphenyl)-5-(piperazin-1-ylmethyl)-1,2,4-oxadiazole Hydrochloride (16o).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (49%, 100 mg). ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.91 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.03 (s, 2H), 4.03–3.16 (m, 4H), 2.96–2.82 (m, 4H), 2.61 (t J = 7.7 Hz, 2H), 1.66 (p, J = 7.5 Hz, 2H), 1.42–1.45 (m, 14H), 0.84 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, cd$_3$od): δ 175.4, 169.7, 148.4, 130.2, 128.4, 125.0, 52.4, 50.3, 44.0, 36.8, 33.1, 32.4, 30.7, 30.5, 30.4, 30.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{37}N_4O$, 385.2962; observed, 385.2980.

(1S,3R)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)cyclopentan-1-amine Hydrochloride (16p).— Synthesized according to General Procedure 4. Purified via

trituration with diethyl ether. White solid (54%, 122 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 3.87–3.78 (m, 1H), 3.72–3.58 (m, 1H), 2.78–2.64 (m, 3H), 2.38–2.07 (m, 4H), 1.98–1.88 (m, 1H), 1.65 (p, J = 7.5 Hz, 2H), 1.38–1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 183.1, 169.4, 148.0, 130.1, 128.3, 125.4, 52.6, 36.9, 36.8, 36.8, 36.8, 33.1, 32.5, 31.3, 30.7, 30.6, 30.5, 30.3, 30.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{36}N_3O$, 370.2853; observed, 370.2859.

(1R,3S)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)cyclohexan-1-amine Hydrochloride (16q).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (87%, 226 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 3.71–3.52 (m, 2H), 2.67 (t, J = 7.7 Hz, 2H), 2.58–2.47 (m, 1H), 2.27–2.19 (m, 1H), 2.18–2.09 (m, 1H), 2.08–2.00 (m, 1H), 1.77 (q, J = 12.3 Hz, 1H), 1.71–1.51 (m, 5H), 1.40–1.20 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 182.4, 169.5, 148.0, 130.1, 128.3, 125.4, 48.0, 36.8, 33.3, 33.1, 32.9, 32.4, 30.8, 30.7, 30.5, 30.4, 30.3, 28.5, 23.7, 21.3, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{24}H_{38}N_3O$, 384.3009; observed, 384.2967.

(1R,3R)-3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)cyclohexan-1-amine Hydrochloride (16r).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (74%, 192 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.93 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 3.39–3.32 (m, 1H), 3.29–3.19 (m, 1H), 2.66 (t, J = 7.8 Hz, 2H), 2.57–2.50 (m, 1H), 2.28–2.19 (m, 1H), 2.17–2.09 (m, 1H), 2.08–2.01 (m, 1H), 1.77 (q, J = 12.3 Hz, 1H), 1.70–1.41 (m, 5H), 1.39–1.21 (m, 14H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 182.6, 169.5, 148.0, 130.1, 128.3, 125.4, 50.5, 36.8, 35.9, 34.8, 33.0, 32.4, 31.0, 30.7, 30.5, 30.4, 30.3, 30.1, 24.4, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{24}H_{38}N_3O$, 384.3009; observed, 384.2970.

(3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)phenyl)methanamine Hydrochloride (16s).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (91%, 174 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.37 (t, J = 1.8 Hz, 1H), 8.29 (dt, J = 7.7, 1.5 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.79 (dt, J = 7.8, 1.6 Hz, 1H), 7.77–7.68 (m, 1H), 7.38 (d, J = 8.3 Hz, 2H), 4.28 (s, 2H), 2.71 (t, J = 7.5 Hz, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.44–1.21 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, cd_3od): δ 176.46, 170.34, 148.25, 136.04, 134.59, 131.38, 130.18, 129.72, 129.58, 128.41, 126.35, 125.39, 43.86, 36.88, 33.07, 32.45, 30.69, 30.56, 30.44, 30.30, 23.73, 14.43. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{34}N_3O$, 392.2696; observed, 392.2698.

(R)-2-Amino-4-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)butanoic Acid Hydrochloride (16t).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (69%, 145 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 4.19 (t, J = 6.6 Hz, 1H), 3.24–3.11 (m, 2H), 2.61 (t J = 7.7 Hz, 2H), 2.55–2.35 (m, 2H), 1.59 (p, J = 7.2 Hz, 2H), 1.35–1.15 (m, 14H), 0.83 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 179.7, 171.1, 169.5,

148.0, 130.1, 128.3, 125.3, 53.0, 36.8, 33.1, 32.4, 30.7, 30.6, 30.4, 30.3, 28.1, 28.0, 23.7, 23.5, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O3$, 388.2595; observed, 388.2595.

3-Chloro-3-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (16u).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (58%, 54 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.84–4.76 (m, 1H), 3.72–3.55 (m, 3H), 3.44 (dd, J = 13.7, 9.9 Hz, 1H), 2.69 (t, J = 7.7 Hz, 2H), 1.66 (p, J = 7.7 Hz, 2H), 1.43–1.18 (m, 14H), 0.89 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 176.9, 169.7, 148.2, 130.1, 128.3, 125.2, 55.6, 46.0, 36.8, 33.9, 33.1, 32.4, 30.7, 30.5, 30.4, 30.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{33}ClN_3O$, 378.2312; observed, 378.2312.

(S)-1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propan-2-amine Hydrochloride (16v).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (67%, 76 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.03–3.87 (m, 1H), 3.36 (d, J = 6.3 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.71–1.56 (m, 2H), 1.47 (d, J = 6.7 Hz, 3H), 1.39–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 177.0, 169.6, 148.1, 130.1, 128.4, 125.1, 46.6, 36.9, 33.1, 32.4, 32.0, 30.7, 30.6, 30.5, 30.3, 23.7, 18.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2705.

1-Amino-3-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)propan-2-ol Hydrochloride (16w).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (87%, 298 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.43–4.34 (m, 1H), 3.30–3.15 (m, 3H), 3.05 (dd, J = 12.9, 9.5 Hz, 1H), 2.67 (t, J = 7.7 Hz, 2H), 1.64 (p, J = 7.5 Hz, 2H), 1.38–1.21 (m, 14H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 178.2, 169.6, 148.1, 130.1, 128.3, 125.4, 66.5, 45.2, 36.9, 33.3, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O_2$, 360.2646; observed, 360.2654.

1-Amino-3-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)propan-2-yl Acetate Hydrochloride (16x).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (71%, 93 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 5.57 (q, J = 7.5 Hz, 1H), 3.59–3.35 (m, 4H), 2.69 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 1.66 (p, J = 7.5 Hz, 2H), 1.43–1.22 (m, 14H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 176.9, 171.9, 169.6, 148.2, 130.1, 128.3, 125.2, 68.8, 43.1, 36.8, 33.1, 32.4, 30.7, 30.5, 30.4, 30.3, 30.0, 23.7, 20.8, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{36}N_3O_3$, 402.2751; observed, 402.2747.

(9H-Fluoren-9-yl)methyl tert-Butyl (1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propane-1,3-diyl)(S)-dicarbamate (17a).—Synthesized according to General Procedure 3. Purified via column chromatography (25% ethyl acetate/hexanes). White solid (0.36 g, 74%). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.69–7.59 (m, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.33 (dd, J = 7.1, 2.7 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.00 (d, J = 9.0 Hz, 1H), 5.24 (q, J = 7.9 Hz, 1H), 4.93 (t, J = 6.7 Hz, 1H), 4.49 (d, J = 7.0 Hz, 2H), 4.26 (t, J = 7.0 Hz, 1H), 3.59–3.36 (m, 1H), 3.16–2.98 (m, 1H),

2.66 (t, J = 7.7 Hz, 2H), 2.32–2.19 (m, 1H), 2.19–2.02 (m, 1H), 1.64 (p, J = 7.2 Hz, 2H), 1.42 (s, 9H), 1.35–1.19 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 178.8, 168.5, 156.3, 156.2, 146.9, 143.9, 143.7, 141.5, 129.1, 127.9, 127.6, 127.2, 125.2, 123.9, 120.1, 79.8, 67.4, 47.3, 46.8, 36.5, 36.1, 34.4, 32.0, 31.3, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5, 22.8, 14.3.

(9H-Fluoren-9-yl)methyl tert-Butyl (1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)butane-1,4-diyl)(S)-dicarbamate (17b).—Synthesized according to General Procedure 3. Purified via column chromatography (30% ethyl acetate/hexanes). Yellow solid (0.20 g, 40%). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.34–7.30 (m, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.85–5.70 (m, 1H), 5.27–5.09 (m, 1H), 4.64 (s, 1H), 4.51–4.42 (m, 2H), 4.24 (t, J = 7.0 Hz, 1H), 3.27–3.13 (m, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.14–2.00 (m, 1H), 1.99–1.87 (m, 1H), 1.70–1.62 (m, 2H), 1.61–1.54 (m, 2H), 1.45 (s, 9H), 1.39–1.19 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 178.8, 168.5, 156.2, 155.9, 146.9, 143.9, 143.7, 141.5, 129.1, 127.9, 127.6, 127.2, 125.2, 123.9, 120.1, 79.6, 67.3, 48.9, 47.3, 39.9, 36.1, 32.0, 31.3, 31.3, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5, 26.3, 22.81, 14.2.

(9H-Fluoren-9-yl)methyl tert-butyl (1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)pentane-1,5-diyl)(S)-dicarbamate (17c).—Synthesized according to General Procedure 3. Purified via column chromatography (30% ethyl acetate/hexane). White solid (0.36 g, 73%). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.0 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.32 (dd, J = 7.2, 2.7 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.71 (d, J = 8.6 Hz, 1H), 5.15 (q, J = 7.7 Hz, 1H), 4.62 (t, J = 6.8 Hz, 1H), 4.49 (dd, J = 10.6, 6.9 Hz, 1H), 4.46–4.37 (m, 1H), 4.24 (t, J = 7.0 Hz, 1H), 3.13 (q, J = 7.2 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.13–1.89 (m, 2H), 1.65 (p, J = 14.8, 7.4 Hz, 2H), 1.58–1.48 (m, 2H), 1.43 (s, 11H), 1.36–1.18 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.0, 168.4, 156.3, 156.0, 146.8, 143.9, 143.7, 141.4, 129.0, 127.8, 127.6, 127.2, 125.2, 125.2, 123.9, 120.1, 79.4, 67.3, 48.9, 47.3, 40.0, 36.1, 33.6, 32.0, 31.3, 29.7, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5, 22.8, 22.5, 14.3. HRMS (ESI$^+$): calcd for $C_{43}H_{57}N_4O_5$ $[M + H]^+$, 709.4323; observed, 709.4322.

(9H-Fluoren-9-yl)methyl tert-Butyl(1-(3-(4-decylphenyl)-1,2,4-ox-adiazol-5-yl)pentane-1,5-diyl)(R)-dicarbamate (17d).—Synthesized according to General Procedure 3. The product could not be separated from the unreacted starting material and was carried forward crude to the next reaction.

tert-Butyl (S)-(3-Amino-3-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (18a).—Synthesized according to General Procedure 5. Purified by silica gel (5% methanol/dichloromethane). Yellow oil (0.02 g, 34%). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.06 (s, 1H), 4.28 (dd, J = 8.7, 5.0 Hz, 1H), 3.38–3.20 (m, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.28–1.90 (m, 2H), 1.63 (p, J = 7.2 Hz, 2H), 1.42 (s, 9H), 1.34–1.13 (m, 14H), 0.87 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 182.1, 168.4, 156.2, 146.8, 129.1, 127.5, 124.1, 79.6, 47.7, 37.6, 36.1, 35.8, 32.0,

31.4, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5, 22.8, 14.3. HRMS (ESI^+): calcd for $C_{26}H_{43}N_4O_3$ $[M + H]^+$, 459.3330; observed, 459.3325.

tert-Butyl (S)-(4-Amino-4-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)butyl)carbamate (18b).—Synthesized according to General Procedure 5. Purified via column chromatography (5% methanol/dichloromethane). Yellow oil (0.03 g, 83%). ^1H NMR (400 MHz, $CdCl_3$): δ 7.97 (d, J =8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.69 (br s, 1H), 4.24 (t, J = 6.9 Hz, 1H), 3.18 (q, J = 6.7 Hz, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.22–1.80 (m, 2H), 1.74–1.63 (m, 2H), 1.63–1.57 (m, 2H), 1.43 (s, 9H), 1.36–1.14 (m, 14H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 182.3, 168.4, 156.1, 146.8, 129.1, 127.5, 124.1, 79.4, 49.1, 40.2, 36.1, 33.1, 32.0, 31.4, 29.7, 29.7, 29.6, 29.4, 29.4, 28.4, 26.4, 22.8, 14.3. HRMS (ESI^+): calcd for $C_{27}H_{45}N_4O_3$ $[M + H]^+$, 473.3486; observed, 473.3476.

tert-Butyl (S)-(5-Amino-5-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)pentyl)carbamate (18c).—Synthesized according to General Procedure 5. Purified via column chromatography (5% methanol/dichloromethane). Yellow oil (0.06 g, 85%). ^1H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 4.58 (s, 1H), 4.19 (t, J = 6.8 Hz, 1H), 3.12 (q, J = 6.5 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.01–1.92 (m, 2H), 1.62 (p, J = 7.4 Hz, 2H), 1.58–1.51 (m, 2H), 1.50–1.44 (m, 2H), 1.41 (s, 9H), 1.34–1.20 (m, 14H), 0.86 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 182.5, 168.3, 156.1, 146.7, 129.0, 127.5, 124.1, 79.2, 49.3, 40.4, 36.1, 35.7, 32.0, 31.4, 29.9, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5, 23.0, 22.8, 14.2. HRMS (ESI^+): calcd for $C_{28}H_{47}N_4O_3$ $[M + H]^+$, 487.3643; observed, 487.3632.

tert-Butyl (R)-(5-Amino-5-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)pentyl)carbamate (18d).—Synthesized according to General Procedure 5. Purified by silica gel (50% ethyl acetate/hexanes). Yellow solid (0.12 g, 44%). ^1H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 4.59 (br s, 1H), 4.19 (t, J = 6.8 Hz, 1H), 3.11 (q, J = 6.4 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.05–1.85 (m, 2H), 1.62 (p, J = 7.4 Hz, 2H), 1.58–1.50 (m, 2H), 1.50–1.43 (m, 2H), 1.41 (s, 9H), 1.33–1.16 (m, 14H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 182.5, 168.3, 156.1, 146.7, 129.0, 127.5, 124.2, 79.2, 49.3, 40.4, 36.1, 35.7, 32.0, 31.3, 29.9, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5, 23.0, 22.8, 14.2. HRMS (ESI^+): calcd for $C_{28}H_{47}N_4O_3$ $[M + H]^+$, 487.3643; observed, 487.3634.

(S)-1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propane-1,3-diamine Hydrochloride (19a).—Synthesized according to General Procedure 4. Purified via column chromatography (0–20% methanol/dichloromethane). White solid (0.02 g, 67%). ^1H NMR (400 MHz, CD_3OD): δ 7.97 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.39 (dd, J = 8.8, 5.1 Hz, 1H), 3.28–3.15 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.38–2.08 (m, 2H), 1.66 (p, J = 7.5 Hz, 2H), 1.42–1.19 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 182.8, 169.5, 148.1, 130.1, 128.4, 125.3, 48.6, 38.6, 36.8, 33.3, 33.1, 32.4, 30.7, 30.6, 30.4, 30.3, 23.7, 14.4. HRMS (ESI^+): calcd for $C_{21}H_{35}N_4O$ $[M + H]^+$, 359.2805; observed, 359.2798.

(S)-1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)butane-1,4-diamine Hydrochloride (19b).—Synthesized according to General Procedure 4. Purified via column

chromatography (0–20% methanol/dichloromethane). White solid (0.01 g, 57%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.54 (t, J = 6.8 Hz, 1H), 3.02 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.24–1.99 (m, 2H), 1.94–1.75 (m, 2H), 1.65 (p, J = 7.3 Hz, 2H), 1.42–1.19 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.8, 169.6, 148.3, 130.2, 128.4, 125.1, 49.3, 40.2, 36.8, 33.1, 32.4, 32.3, 30.7, 30.5, 30.4, 30.3, 24.9, 23.7, 14.4. HRMS (ESI^+): calcd for $C_{22}H_{37}N_4O$ $[M + H]^+$, 373.2962; observed, 373.2955.

(S)-1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)pentane-1,5-diamine Hydrochloride (19c).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (0.02 g, 37%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.97 (d, J = 8.1 Hz, 2H), 7.34 (d, J =8.1 Hz, 2H), 4.29 (t, J = 6.8 Hz, 1H), 3.01–2.89 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.09–1.87 (m, 2H), 1.78–1.65 (m, 2H), 1.70–1.59 (m, 2H), 1.62–1.41 (m, 2H), 1.39–1.19 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 183.1, 169.4, 148.1, 130.1, 128.3, 125.4, 49.7, 40.5, 36.8, 35.7, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 28.2, 23.7, 23.5, 14.5. HRMS (ESI^+): calcd for $C_{23}H_{39}N_4O$ $[M + H]^+$, 387.3118; observed, 387.3124.

(R)-1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)pentane-1,5-diamine Hydrochloride (19d).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (0.09 g, 79%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.01 (d, J = 8.0 Hz, 2H), 7.35 (d, J =8.1 Hz, 2H), 4.98 (t, J = 6.9 Hz, 1H), 2.99 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.34–2.14 (m, 2H), 1.80 (p, J = 7.6 Hz, 2H), 1.72–1.63 (m, 2H), 1.63–1.53 (m, 2H), 1.40–1.20 (m, 14H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 176.7, 169.8, 148.5, 130.2, 128.5, 124.6, 48.9, 40.2, 36.8, 33.0, 32.4, 30.6, 30.5, 30.4, 30.3, 27.8, 23.7, 23.1, 14.5. HRMS (ESI^+): calcd for $C_{23}H_{39}N_4O$ $[M + H]^+$, 387.3118; observed, 387.3106.

tert-Butyl (S)-(5-Acetamido-5-(3-(4-decylphenyl)-1,2,4-oxadia-zol-5-yl)pentyl)carbamate (20).—To a round-bottom flask containing dry DCM and a stir bar were added **18c** (1.0 equiv) and TEA (3.0 equiv). Acetyl chloride (1.1 equiv) was added dropwise, and the reaction mixture was stirred at rt for 4 h. The crude reaction mixture was concentrated under reduced pressure and subjected to silica gel chromatography. It was purified via column chromatography (60% ethyl acetate/hexanes). White solid (0.08 g, 48%). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.93 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.1 Hz, 1H), 5.36 (q, J = 7.3 Hz, 1H), 4.67 (t, J = 6.2 Hz, 1H), 3.09 (q, J = 6.5 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 2.07 (s, 3H), 2.04–1.84 (m, 2H), 1.61 (p, J = 7.3 Hz, 2H), 1.54–1.46 (m, 2H), 1.41 (s, 9H), 1.39–1.33 (m, 2H), 1.33–1.20 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 178.9, 170.2, 168.4, 156.3, 146.8, 129.0, 127.5, 123.9, 79.3, 46.8, 39.9, 36.0, 33.3, 32.0, 31.3, 29.7, 29.7, 29.6, 29.4, 29.3, 28.5, 23.1, 22.8, 22.4, 14.2.

(S)-N-(5-Amino-1-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)-pentyl)acetamide Hydrochloride (21).—Synthesized according to General Procedure 4. Purified via column chromatography (0–20% methanol/dichloromethane). White solid (0.06 g, 85%). ^{1}H NMR

(400 MHz, CD_3OD): δ 7.95 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.28 (dd, J = 8.8, 5.9 Hz, 1H), 2.95 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 2.17–2.07 (m, 1H), 2.05 (s, 3H), 2.04–1.94 (m, 1H), 1.80–1.70 (m, 2H), 1.69–1.60 (m, 2H), 1.60–1.46 (m, 2H), 1.38–1.17 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.6, 173.4, 169.6, 148.1, 130.1, 128.3, 125.2, 47.8, 40.4, 36.8, 33.3, 33.1, 32.4, 30.7, 30.6, 30.5, 30.3, 27.9, 23.7, 23.7, 22.4, 14.5. HRMS (ESI^+): calcd for $C_{25}H_{41}N_4O2$ $[M + H]^+$, 429.3224; observed, 429.3225.

3-(4-Decylphenyl)-5-(3-(pyrrolidin-1-yl)propyl)-1,2,4-oxadiazole Hydrochloride (22a).—Synthesized according to General Procedure 6. Purified via column chromatography (5–10% methanol/dichloromethane). White solid (68%, 56 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.40–3.29 (m, 6H), 3.13 (t, J = 7.3 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.37–2.27 (m, 2H), 2.14–2.04 (m, 4H), 1.65 (p, J = 7.3 Hz, 2H), 1.40–1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.1, 169.5, 148.1, 130.1, 128.3, 125.4, 55.3, 55.1, 36.8, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 24.4, 24.0, 24.0, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O$, 398.3166; observed, 398.3155.

3-(4-Decylphenyl)-5-(3-(piperidin-1-yl)propyl)-1,2,4-oxadiazole Hydrochloride (22b).—Synthesized according to General Procedure 6. Purified via column chromatography (5–10% methanol/dichloromethane). White solid (38%, 32 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.05 (t, J = 7.3 Hz, 2H), 2.94–2.75 (m, 6H), 2.66 (t, J = 7.7 Hz, 2H), 2.26–2.14 (m, 2H), 1.72 (p, J = 5.7 Hz, 4H), 1.69–1.51 (m, 4H), 1.39–1.18 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.7, 169.4, 147.9, 130.1, 128.3, 125.5, 58.2, 55.0, 36.9, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 25.5, 24.9, 24.0, 23.8, 23.2, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{42}N_3O$, 412.3322; observed, 412.3315.

4-(3-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)propyl)morpholine Hydrochloride (22c).—Synthesized according to General Procedure 6. Purified via column chromatography (5–10% methanol/dichloromethane). White solid (73%, 62 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.13–3.76 (m, 4H), 3.63–3.48 (m, 2H), 3.41–3.33 (m, 2H), 3.27–3.12 (m, 4H), 2.68 (t, J = 7.7 Hz, 2H), 2.43–2.32 (m, 2H), 1.65 (p, J = 7.2 Hz, 2H), 1.39–1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 179.9, 169.5, 148.1, 130.1, 128.3, 125.4, 65.1, 57.3, 63.3, 36.8, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 24.3, 23.7, 21.6, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_2$, 414.3115; observed, 414.3113.

1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-3-(pyrrolidin-1-yl)-propan-2-ol Hydrochloride (22d).—Synthesized according to General Procedure 6. Purified via column chromatography (5–15% methanol/dichloromethane). White solid (40%, 30 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.55–4.47 (m, 1H), 3.39–3.32 (m, 6H), 3.21 (qd, J = 15.5, 6.2 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.11–2.03 (m, 4H), 1.65 (p, J = 7.4 Hz, 2H), 1.40– 1.22 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.2, 169.6, 148.1, 130.1, 128.3, 125.4, 65.8, 60.7,

55.5, 36.8, 33.6, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 24.0, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_2$, 414.3115; observed, 414.3133.

1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-3-(piperidin-1-yl)-propan-2-ol Hydrochloride (22e).—Synthesized according to General Procedure 6. Purified via column chromatography (10% methanol/dichloromethane). White solid (19%, 10 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.68–4.59 (m, 1H), 3.68–3.53 (m, 2H), 3.39 (dd, J = 13.3, 3.0 Hz, 1H), 3.33–3.15 (m, 3H), 3.14–2.96 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.02–1.47 (m, 8H), 1.40–1.19 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 176.5, 168.2, 146.7, 128.7, 126.9, 123.9, 62.5, 60.4, 54.8, 51.7, 35.4, 32.1, 31.6, 31.0, 29.3, 29.1, 29.0, 28.9, 22.4, 22.4, 22.3, 21.2, 13.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{42}N_3O_2$, 428.3272; observed, 428.3264.

1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-3-morpholinopropan-2-ol Hydrochloride (22f).—Synthesized according to General Procedure 6. Purified via column chromatography (5–10% methanol/dichloromethane). White solid (64%, 84 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.73–4.65 (m, 1H), 4.11–3.98 (m, 2H), 3.93–3.76 (m, 2H), 3.65–3.52 (m, 2H), 3.51–3.63 (m, 2H), 3.34–3.17 (m, 4H), 2.68 (t, J = 7.7 Hz, 2H), 1.64 (p, J = 7.4 Hz, 2H), 1.39–1.21 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ ^{13}C NMR (101 MHz, CD_3OD): δ 177.9, 169.6, 148.06, 130.1, 128.3, 125.4, 64.7, 63.7, 62.2, 54.8, 52.3, 36.8, 33.5, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_3$, 430.3064; observed, 430.3061.

1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-3-(ethylamino)-propan-2-ol (23a).—To a round-bottom flask containing **16w** (1.0 equiv) were added methanol (0.1 M), glacial acetic acid (2.0 equiv), and sodium cyanoborohydride (6.0 equiv) at rt. Acetaldehyde (1.2 equiv) was then added and the mixture stirred for 16 h at rt under argon. The reaction mixture was diluted in dichloromethane and washed with 2 M sodium bicarbonate solution and brine. The aqueous layer was washed with dichloromethane (three times). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure before being subjected to silica gel chromatography. The product was then dissolved in methanolic HCl and concentrated to afford the title compound as a hydrochloride salt. Purified via column chromatography (10% methanol/dichloromethane). White solid (27%, 20 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 4.54–4.41 (m, 1H), 3.39–3.06 (m, 5H), 2.68 (t, J = 7.8 Hz, 2H), 1.65 (p, J = 7.2 Hz, 2H), 1.41–1.20 (m, 17H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.1, 169.6, 148.1, 130.1, 128.3, 125.4, 65.7, 52.5, 44.1, 36.8, 33.4, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 23.7, 14.5, 11.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{38}N_3O_2$, 388.2959; observed, 388.2977.

1-(3-(4-Decylphenyl)-1,2,4-oxadiazol-5-yl)-3-(dimethylamino)-propan-2-ol Hydrochloride (23b).—To a round-bottom flask was added **16w** (1.0 equiv), followed by paraformaldehyde (10.0 equiv) and methanol (0.2 M). Sodium borohydride (6.0 equiv) was then added, and the mixture was heated to reflux for 16 h. The reaction mixture was

diluted in dichloromethane and washed with 2 M sodium bicarbonate solution and brine. The aqueous layer was washed with dichloromethane three times. The combined organic layers were dried over sodium sulfate and concentrated. The product was then dissolved in methanolic HCl and concentrated to afford the title compound as a HCl salt. Purified via column chromatography (0–15% methanol/dichloromethane). White solid (20%, 16 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.53–4.44 (m, 1H), 3.26–3.10 (m, 2H), 3.09–3.04 (m, 2H), 2.73 (s, 6H), 2.68 (t, J = 7.7 Hz, 2H), 1.65 (p, J = 7.6 Hz, 2H), 1.39–1.22 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.4, 169.6, 148.0, 130.1, 128.3, 125.4, 65.4 63.7, 44.6, 36.8, 33.6, 33.1, 32.5, 30.7, 30.6, 30.5, 30.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{38}N_3O_2$, 388.2959; observed, 388.2953.

1-(4-Decylphenyl)ethan-1-one (24).—Synthesized according to General Procedure 1. Purified via column chromatography (5% ethyl acetate/hexanes). White solid (70%, 1.15 g). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.88 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.58 (s, 3H), 1.62 (p, J = 8.8 Hz, 2H), 1.38–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 198.0, 149.0, 135.1, 128.7, 128.6, 36.1, 32.0, 31.3, 29.7, 29.7, 29.6, 29.5, 29.4, 26.7, 22.8, 14.3. HRMS (ESI): $[2M + H]^+$ calcd for $C_{36}H_{57}O_2$, 521.4353; observed, 521.4331.

2-Bromo-1-(4-decylphenyl)ethan-1-one (25).—Compound **24** (1.0 equiv) was dissolved in acetonitrile and added to a round-bottom flask containing a stir bar. NBS (1.0 equiv) and *p*-toluenesulfonic acid monohydrate (1.6 equiv) were added, and the reaction mixture was heated to reflux for 2 h. The flask was then removed from the heating source and allowed to stir at rt for an additional 18 h. The crude reaction mixture was concentrated under reduced pressure, dissolved in DCM, and partitioned with brine. The organic layer was further rinsed three times with brine, dried over sodium sulfate, filtered, loaded onto Celite, and subjected to silica chromatography. It was purified via column chromatography (5% ethyl acetate/hexanes). Light-pink solid (88%, 2.40 g). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.90 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.43 (s, 2H), 2.67 (t, J = 7.7 Hz, 2H), 1.63 (p, J = 8.0 Hz, 2H), 1.29 (d, J = 23.7 Hz, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 191.1, 150.1, 131.8, 129.2, 129.0, 36.2, 32.0, 31.1, 31.1, 29.7, 29.7, 29.6, 29.4, 29.4, 22.8, 14.2. HRMS (ESI): $[2M + Na]^+$ calcd for $C_{36}H_{54}Br_2NaO_2$, 701.2362; observed, 701.2361.

2-(4-Decylphenyl)-2-oxoethyl 4-((tert-Butoxycarbonyl)amino)-butanoate (26).—Compound **25** (1.0 equiv), *N*-Boc-GABA (1.1 equiv), and potassium carbonate (3.0 equiv) were added to a round-bottom flask. The flask was purged with argon, and acetonitrile was added. The mixture was allowed to stir overnight at rt. The crude mixture was loaded onto Celite, concentrated under reduced pressure, and subjected to silica gel chromatography. Purified via column chromatography (30% ethyl acetate/hexanes). Off-white solid (91%, 248 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.82 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.34 (s, 2H), 4.82 (t, J = 6.1 Hz, 1H), 3.23 (q, J = 6.7 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.91 (p, J = 7.1 Hz, 2H), 1.62 (p, J = 7.6 Hz, 2H), 1.44 (s, 9H), 1.38–1.18 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 191.9, 172.8, 156.1,

150.0, 131.9, 129.0, 128.0, 79.2, 66.0, 39.8, 36.2, 32.0, 31.3, 31.1, 29.7, 29.6, 29.5, 29.4, 29.3, 28.5, 25.4, 22.8, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{27}H_{43}NNaO_5$, 484.3033; observed, 484.3032.

tert-Butyl(3-(4-(4-decylphenyl)thiazol-2-yl)propyl)carbamate (27).—To an oven-dried pressure tube containing a stir bar were added **25** (1.0 equiv) and *tert*-butyl(4-amino-4-thioxobutyl)carbamate (1.2 equiv). The flask was sealed and purged with argon. A 2:1 DMF/EtOH solution was syringed into the flask, and the reaction mixture was heated to 80 °C for 4 h. The resulting solution was concentrated under reduced pressure, loaded onto Celite, and subjected to silica gel chromatography. It was purified via column chromatography (20–30% ethyl acetate/hexanes). Yellow oil (34%, 97 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.78 (d, J = 8.2 Hz, 2H), 7.26 (s, 1H), 7.21 (d, J = 8.1 Hz, 2H), 4.95 (br s, 1H), 3.26 (q, J = 6.6 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 2.03 (p, J = 7.1 Hz, 2H), 1.61 (p, J = 7.3 Hz, 2H), 1.44 (s, 9H), 1.37–1.21 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 170.0, 156.1, 155.4, 143.1, 132.1, 128.9, 126.4, 111.4, 79.3, 40.1, 35.9, 32.0, 31.6, 30.9, 30.0, 29.8, 29.7, 29.7, 29.5, 29.4, 28.6, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{43}N_2O_2S$, 459.3040; observed, 459.3035.

3-(4-(4-Decylphenyl)thiazol-2-yl)propan-1-amine Hydrochloride (28)—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. Off-white solid (94%, 80 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.86 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.36 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.7 Hz, 2H), 2.25 (p, J = 7.6 Hz, 2H), 1.64 (p, J = 7.2 Hz, 2H), 1.39–1.21 (m, 14H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 173.7, 153.1, 145.7, 130.2, 130.0, 127.7, 115.5, 39.8, 36.6, 33.0, 32.5, 30.7, 30.7, 30.6, 30.4, 30.3, 29.7, 28.4, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{35}N_2S$, 359.2515; observed, 359.2500.

tert-Butyl (3-(4-(4-Decylphenyl)oxazol-2-yl)propyl)carbamate (29)—To an oven-dried pressure tube containing a stir bar were added **25** (1.0 equiv) and *tert*-butyl(4-amino-4-oxobutyl)carbamate (2.0 equiv). The flask was sealed and purged with argon. NMP was syringed into the flask, and the reaction mixture was heated to 100 °C for 4 h. The resulting solution was diluted with ethyl acetate and portioned with a saturated sodium bicarbonate solution. The organic layer was further rinsed three times with brine, dried over sodium sulfate, and filtered. The concentrated residue was loaded onto Celite and subjected to silica gel chromatography. It was purified via column chromatography (20–30% ethyl acetate/hexanes). Yellow solid (10%, 42 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.77 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.02 (br s, 1H), 3.24 (q, J = 6.5 Hz, 2H), 2.86 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.00 (p, J = 7.0 Hz, 2H), 1.61 (p, J = 7.0 Hz, 2H), 1.44 (s, 9H), 1.35–1.21 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 164.6, 156.1, 143.0, 140.8, 132.8, 128.9, 128.6, 125.5, 79.3, 40.2, 35.9, 32.0, 31.5, 29.7, 29.7, 29.6, 29.5, 29.4, 28.5, 27.3, 25.9, 22.8, 14.2. HRMS (ESI): $[M\text{-Boc}]^+$ calcd for $C_{22}H_{35}N_2O$, 343.2744; observed, 343.2745.

3-(4-(4-Decylphenyl)oxazol-2-yl)propan-1-amine Hydrochloride (30)—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether.

White solid (22 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.13 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 3.10 (t, J = 7.4 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.18 (p, J = 7.2 Hz, 2H), 1.61 (p, J = 7.0 Hz, 2H), 1.36–1.20 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 165.3, 144.1, 141.8, 135.2, 129.8, 129.5, 126.4, 40.1, 36.6, 33.0, 32.6, 30.7, 30.7, 30.5, 30.4, 30.2, 25.9, 25.6, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{35}N_2O$, 343.2744; observed, 343.2744.

tert-Butyl (3-(4-(4-Decylphenyl)-1H-imidazol-2-yl)propyl)-carbamate (31).—To a round-bottom flask attached to a condenser were added alpha acyl ketone **26** (1.0 equiv) and ammonium acetate (20.0 equiv). Dry toluene was then added and the mixture heated to reflux for 5 h. The mixture was then concentrated in vacuo and diluted in ethyl acetate, followed by washing with a saturated sodium bicarbonate solution. The organic layer was then dried over anhydrous sodium sulfate, concentrated in vacuo, and subjected to silica chromatography. Purified via column chromatography (100% ethyl acetate). White solid (85%, 270 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 11.32 (s, 1H), 7.58 (s, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.9 Hz, 1H), 5.02 (s, 1H), 3.22 (q, J = 6.2 Hz, 2H), 2.83–2.75 (m, 2H), 1.85–1.75 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 157.9, 148.7, 131.8, 126.3, 120.0, 111.8, 80.3, 38.7, 29.7, 28.5, 24.7. HRMS (ESI): $[M + Na]^+$ calcd for $C_{17}H_{22}BrN_3NaO_2$, 402.0788; observed, 402.0768.

3-(4-(4-Decylphenyl)-1H-imidazol-2-yl)propan-1-amine Hydrochloride (32).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (86%, 177 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.76 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.20 (t, J = 7.8 Hz, 2H), 3.09 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.24 (p, J = 7.9 Hz, 2H), 1.72–1.57 (m, 2H), 1.31 (d, J = 21.9 Hz, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 147.9, 146.1, 135.0, 130.5, 126.6, 125.4, 115.1, 39.7, 36.6, 33.0, 32.5, 30.7, 30.7, 30.6, 30.4, 30.3, 26.5, 23.9, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3$, 342.2904; observed, 342.2905.

tert-Butyl (3-(4-(4-Decylphenyl)-1-methyl-1H-imidazol-2-yl)-propyl)carbamate (33).—Compound **31** was dissolved in a solution of dry THF and added to an oven-dried round-bottom flask containing a stir bar. The flask was purged with argon and cooled to 0 °C in an ice bath. Sodium hydride (1.1 equiv, 60% dispersion in mineral oil) was added, and the reaction mixture was allowed to stir for 15 min. Methyl iodide (1.5 equiv) was added to the reaction mixture dropwise and slowly warmed to rt over the course of 18 h. Following the completion of the reaction, the mixture was loaded onto Celite and subjected to silica gel chromatography. Purified via column chromatography (100% ethyl acetate). White solid (63%, 65 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.57 (d, J = 8.3 Hz, 2H), 7.22 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 3.63 (s, 3H), 3.12 (t, J = 6.7 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.85 (p, J = 7.6 Hz, 2H), 1.59 (p, J = 7.3 Hz, 2H), 1.44 (s, 9H), 1.36–1.22 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 158.5, 149.8, 142.4, 140.8, 132.8, 129.5, 125.8, 117.9, 79.9, 40.8, 36.6, 33.1, 33.1, 32.7, 30.7, 30.7, 30.6, 30.5, 30.3, 29.4, 28.8, 24.7, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{46}N_3O_2$, 456.3585; observed, 456.3592.

3-(4-(4-Decylphenyl)-1-methyl-1H-imidazol-2-yl)propan-1-amine Hydrochloride (34).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether and ethyl acetate. White solid (75%, 42 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.93 (s, 3H), 3.22 (t, J = 7.9 Hz, 2H), 3.13 (t, J = 7.7 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.20 (p, J = 7.9 Hz, 2H), 1.64 (p, J = 6.8 Hz, 2H), 1.38–1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 147.6, 146.2, 134.0, 130.5, 126.6, 125.1, 119.9, 39.7, 36.6, 35.1, 33.0, 32.5, 30.7, 30.7, 30.6, 30.4, 30.3, 26.0, 23.7, 22.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{38}N_3$, 356.3060; observed, 356.3057.

3-(4-Decylphenyl)-1H-pyrazole (36a).—Compound **35** (1.0 equiv), (1*H*-pyrazol-3-yl)boronic acid (4.0 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.2 equiv), and sodium bicarbonate (6.0 equiv) were added to a two-neck round-bottom flask containing a stir bar and attached to a reflux condenser. The system was purged with argon, and DMF was added (0.2 M). An additional 0.2 mL of DI water was then syringed into the flask and the mixture was heated to 100 °C for 16 h. Upon completion, the flask was cooled to rt, filtered through Celite, and subjected to silica gel chromatography. It was then purified via column chromatography (30–40% ethyl acetate/hexanes). Off-white solid (46%, 1.043 g). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.64 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.58 (d, J = 2.2 Hz, 1H), 2.63 (t, J = 7.7 Hz, 2H), 1.63 (p, J = 7.3 Hz, 2H), 1.40– 1.21 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{29}N_2$, 285.2325; observed, 285.2323.

4-(4-Decylphenyl)-1H-pyrazole (36b).—Compound **35** (1.0 equiv), (1*H*-pyrazol-4-yl)boronic acid (4.0 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.2 equiv), and sodium bicarbonate (6.0 equiv) were added to a two-neck round-bottom flask containing a stir bar and attached to a reflux condenser. The system was purged with argon, and DMF was added (0.2 M). An additional 0.2 mL of DI water was then syringed into the flask, and the mixture was heated to 100 °C for 16 h. Upon completion, the flask was cooled to rt, filtered through Celite, and subjected to silica gel chromatography. It was then purified via column chromatography (30–40% ethyl acetate/hexanes). White solid (53%, 761 mg). ^{1}H NMR (500 MHz, CD_3OD): δ 8.00–7.78 (m, 3H), 7.47 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 2.60 (t, J = 7.7 Hz, 2H), 1.61 (p, J = 7.4 Hz, 2H), 1.39–1.23 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 142.2, 131.4, 129.9, 126.5, 123.8, 36.6, 33.1, 32.7, 30.7, 30.7, 30.6, 30.5, 30.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{29}N_2$, 285.2325; observed, 285.2333.

tert-Butyl (3-(5-(4-Decylphenyl)-1H-pyrazol-1-yl)propyl)-carbamate (37).—Synthesized according to General Procedure 7. Purified via column chromatography (20% ethyl acetate/dichloromethane). Clear oil (16%, 50 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.52 (d, J = 1.9 Hz, 1H), 7.32–7.22 (m, 4H), 6.25 (d, J = 1.9 Hz, 1H), 4.70 (br s, 1H), 4.20 (t, J = 6.7 Hz, 2H), 3.02 (q, J = 6.4 Hz, 2H), 2.65 (d, J = 7.8, 2H), 1.92 (p, J = 6.6 Hz, 2H), 1.65 (p, J = 7.4 Hz, 2H), 1.41 (s, 9H), 1.37–1.22 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 156.0, 143.9, 143.8, 138.9, 128.9, 128.9, 128.1, 106.3, 79.2, 47.0, 37.8,

35.9, 32.1, 31.5, 30.6, 29.8, 29.7, 29.7, 29.5, 29.5, 28.5, 22.8, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_2$, 442.3428; observed, 442.3422.

3-(5-(4-Decylphenyl)-1H-pyrazol-1-yl)propan-1-amine Hydrochloride (38).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (89%, 38 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.67 (d, J = 2.0 Hz, 1H), 7.44–7.33 (m, 4H), 6.41 (d, J = 2.0 Hz, 1H), 4.32 (t, J = 6.7 Hz, 2H), 2.88 (t, J = 7.7 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.11 (p, J = 7.3 Hz, 2H), 1.66 (p, J = 7.1 Hz, 2H), 1.40–1.22 (m, 14H), 0.90 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 146.3, 145.6, 139.6, 130.2, 130.0, 128.2, 107.8, 47.6, 38.4, 36.7, 33.1, 32.6, 30.7, 30.7, 30.6, 30.5, 30.4, 29.2, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3$, 342.2904; observed, 342.2910.

tert-Butyl (3-(3-(4-Decylphenyl)-1H-pyrazol-1-yl)propyl)-carbamate (39).— Synthesized according to General Procedure 7. Purified via column chromatography (20% ethyl acetate/dichloromethane). Clear oil (77%, 240 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.69 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 2.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.49 (d, J = 2.3 Hz, 1H), 5.07 (t, J = 6.2 Hz, 1H), 4.19 (t, J = 6.5 Hz, 2H), 3.15 (q, J = 6.4 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 2.03 (p, J = 6.5 Hz, 2H), 1.61 (p, J = 7.0 Hz, 2H), 1.43 (s, 9H), 1.36–1.21 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 156.2, 151.8, 142.5, 131.0, 130.7, 128.7, 125.5, 102.6, 79.2, 49.8, 38.0, 35.8, 32.0, 31.6, 30.8, 29.7, 29.7, 29.6, 29.4, 29.4, 28.5, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_2$, 442.3428; observed, 442.3419.

3-(3-(4-Decylphenyl)-1H-pyrazol-1-yl)propan-1-amine Hydrochloride (40).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (83%, 172 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.73–7.63 (m, 3H), 7.20 (d, J = 8.2 Hz, 2H), 6.60 (d, J = 2.3 Hz, 1H), 4.31 (t, J = 6.5 Hz, 2H), 3.01–2.93 (m, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.29–2.17 (m, 2H), 1.62 (p, J =7.6 Hz, 2H), 1.39–1.20 (m, 14H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 153.5, 143.9, 133.0, 132.0, 129.7, 126.6, 103.8, 49.8, 38.4, 36.6, 33.1, 32.6, 30.7, 30.7, 30.6, 30.4, 30.3, 29.6, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3$, 342.2904; observed, 342.2922.

tert-Butyl (3-(4-(4-Decylphenyl)-1H-pyrazol-1-yl)propyl)-carbamate (41).— Synthesized according to General Procedure 7. Purified via column chromatography (20–60% ethyl acetate/hexanes). White solid (64%, 148 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 7.76 (s, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 3.04 (d, J = 6.6 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 2.00 (p, J = 6.8 Hz, 2H), 1.59 (p, J = 7.5 Hz, 2H), 1.42 (s, 9H), 1.33–1.23 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 158.4, 142.1, 137.3, 131.1, 129.9, 128.1, 126.3, 124.4, 80.0, 50.5, 38.5, 36.6, 33.1, 32.7, 31.7, 30.7, 30.7, 30.6, 30.5, 30.3, 28.8, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_2$, 442.3428; observed, 442.3428.

3-(4-(4-Decylphenyl)-1H-pyrazol-1-yl)propan-1-amine Hydrochloride (42).— Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (78%, 99 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (s, 1H), 7.89 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 4.36 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 7.2 Hz,

2H), 2.66 (t, J = 7.6 Hz, 2H), 2.27 (p, J = 7.2 Hz, 2H), 1.68 (p, J = 7.4 Hz, 2H), 1.44–1.32 (m, 14H), 0.95 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 142.5, 137.8, 131.0, 130.0, 128.3, 126.4, 124.8, 49.9, 38.5, 36.6, 33.1, 32.7, 30.7, 30.7, 30.6, 30.4, 30.3, 29.8, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3$, 342.2904; observed, 342.2908.

4-Iodobenzohydrazide (44).—To a round-bottom flask were added 4-iodobenzoyl chloride (**43**, 1.0 equiv) and ethanol to make a 0.24 M solution. Hydrazine (6.0 equiv, 35% in water) was then added, and then the mixture was allowed to stir at 80 °C under ambient air for 20 h. The reaction mixture was removed from heating, cooled to rt, and the product recrystallized from ethanol. The crude product was then filtered and washed with deionized water and cold ethanol to afford the pure product. The material was carried forward as crude without any additional purification. White solid (67%, 1.01 g).

tert-Butyl (3-(5-(4-Iodophenyl)-1,3,4-oxadiazol-2-yl)propyl)-carbamate (45).—To a round-bottom flask containing a stir bar were added *N*-Boc-GABA (1.0 equiv), **44** (1.0 equiv), DIEA (3.0 equiv), and acetonitrile. The resulting solution was allowed to stir for 10 min before HCTU (1.1 equiv) was added. The reaction mixture was stirred at rt for 2 h. A second portion of DIEA (2.0 equiv) was then added, followed by tosyl chloride (3.0 equiv) addition. The mixture was continued to be stirred at rt for 16 h. Following completion, the reaction mixture was added to a beaker containing 15% ammonium hydroxide solution and stirred for 10 min. The mixture was extracted with dichloromethane (2 × 50 mL), and the organic layer was dried over anhydrous sodium sulfate. The dried organic layer was concentrated under reduced pressure, loaded onto Celite, and subjected to silica gel chromatography. It was then purified via column chromatography (30–50% ethyl acetate/hexanes). White solid (79%, 498 mg). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.01 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.6 Hz, 2H), 6.14 (s, 1H), 3.27 (q, J = 6.5 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.10–2.03 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, acetone): δ 167.8, 164.7, 156.7, 139.3, 129.0, 124.9, 98.4, 78.6, 40.3, 28.6, 27.6, 23.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{21}IN_3O_3$, 430.0622; observed, 430.0620.

tert-Butyl (3-(5-(4-Decylphenyl)-1,3,4-oxadiazol-2-yl)propyl)-carbamate (46).—Synthesized according to General Procedure 1. Purified via column chromatography (30–45% ethyl acetate/hexanes). Light-brown solid (79%, 163 mg). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.97 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 6.13 (s, 1H), 3.28 (q, J = 6.6 Hz, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.8 Hz, 2H), 2.11–2.04 (m, 2H), 1.70 (p, J = 7.3 Hz, 2H), 1.43 (s, 9H), 1.42–1.23 (m, 14H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 167.2, 165.3, 156.7, 147.7, 130.1, 127.4, 122.8, 78.6, 40.3, 36.4, 32.6, 32.0, 30.3, 30.3, 30.2, 30.0, 29.9, 28.6, 27.6, 23.3, 14.3. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{42}N_3O_3$, 444.3221; observed, 444.3219.

3-(5-(4-Decylphenyl)-1,3,4-oxadiazol-2-yl)propan-1-amine Hydrochloride (47).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (76%, 85 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 3.20–3.04 (m, 4H), 2.70 (t, J = 7.7 Hz, 2H), 2.24 (p, J = 7.4 Hz, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.41–1.22 (m, 14H), 0.89 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz,

CD_3OD): δ 167.3, 166.7, 149.1, 130.5, 127.9, 122.2, 39.8, 36.9, 33.1, 32.3, 30.7, 30.7, 30.5, 30.4, 30.3, 24.9, 23.7, 23.3, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2693.

2-(4-Bromophenyl)-N′-hydroxyacetimidamide (49a).—Synthesized according to General Procedure 2. The reaction mixture was removed from heating, cooled to rt, and the product recrystallized from ethanol. The crude product was then filtered and washed with deionized water and cold ethanol to afford the pure product. White solid (62%, 542 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.44 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.34 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD): δ 155.5, 137.7, 132.5, 131.6, 121.5, 37.5. HRMS (ESI): $[M + H]^+$ calcd for $C_8H_{10}BrN_2O$, 228.9971; observed, 228.9977.

3-(4-Bromophenyl)-N′-hydroxypropanimidamide (49b).—The compound was synthesized according to General Procedure 2. The reaction mixture was removed from heating and cooled to rt, and the product was recrystallized from ethanol. The crude product was then filtered and washed with deionized water and cold ethanol to afford the pure product. White solid (41%, 352 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 2.84 (d, J = 7.7 Hz, 2H), 2.34 (d, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD): δ 156.4, 141.5, 132.4, 131.5, 120.8, 33.8, 33.7. HRMS (ESI): $[M + H]^+$ calcd for $C_9H_{12}BrN_2O$, 243.0128; observed, 243.0135.

tert-Butyl (3-(3-(4-Bromobenzyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (50a).—Synthesized according to General Procedure 3. Purified via column chromatography (35% ethyl acetate/hexanes). Yellow oil (68%, 292 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.65 (s, 1H), 3.99 (s, 2H), 3.21 (q, J = 6.3 Hz, 2H), 2.89 (t, J = 7.6 Hz, 2H), 1.97 (p, J = 7.0 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.7, 169.1, 156.0, 134.5, 132.0, 130.8, 121.3, 79.6, 39.8, 31.9, 28.5, 27.0, 24.1. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{23}BrN_3O_3$, 418.0737; observed, 418.0746.

tert-Butyl (3-(3-(4-Bromophenethyl)-1,2,4-oxadiazol-5-yl)-propyl)carbamate (50b).—Synthesized according to General Procedure 3. Purified via column chromatography (35% ethyl acetate/hexanes). Yellow oil (76%, 322 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.40 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 4.71 (s, 1H), 3.22 (q, J = 6.2 Hz, 2H), 3.00 (q, J = 3.1, 2.2 Hz, 4H), 2.90 (t, J = 7.5 Hz, 2H), 1.99 (p, J = 7.1 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.3, 169.6, 156.1, 139.3, 131.7, 130.2, 120.3, 79.6, 39.8, 32.5, 28.5, 27.7, 27.0, 24.0. HRMS (ESI): $[M + Na]^+$ calcd for $C_{18}H_{24}BrN_3O_3Na$, 432.0893; observed, 432.0894.

tert-Butyl (3-(3-(4-Nonylbenzyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (51a).—Synthesized according to General Procedure 1. Purified via column chromatography (25% ethyl acetate/hexanes). Colorless oil (48%, 149 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.21 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 4.69 (s, 1H), 4.00 (s, 2H), 3.20 (q, J = 6.2 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.56 (d, J = 7.7 Hz, 2H), 1.97 (p, J = 7.0 Hz, 2H), 1.58 (p, J = 7.4 Hz, 2H), 1.43 (s, 9H), 1.27 (d, J = 14.6 Hz, 12H), 0.86 (t, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.4, 169.7, 156.0, 141.9, 132.7, 128.9, 128.9, 79.5, 39.8, 35.7, 32.0, 32.0,

31.6, 29.7, 29.6, 29.5, 29.4, 28.5, 27.0, 24.1, 22.8, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{41}N_3O_3Na$, 466.3040; observed, 466.3049.

tert-Butyl (3-(3-(4-Octylphenethyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (51b).—Synthesized according to General Procedure 1. Purified via column chromatography (20% ethyl acetate/hexanes). Colorless oil (50%, 166 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.16–7.06 (m, 4H), 4.72 (s, 1H), 3.23 (q, J = 6.3 Hz, 2H), 3.05–2.98 (m, 4H), 2.91 (t, J = 7.5 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H), 2.01 (p, J = 6.9 Hz, 2H), 1.58 (p, J = 7.5 Hz, 2H), 1.44 (s, 9H), 1.38–1.20 (m, 10H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.1, 170.1, 156.0, 141.1, 137.6, 128.7, 128.3, 79.5, 39.8, 35.7, 32.8, 32.0, 31.7, 29.6, 29.5, 29.4, 28.5, 28.1, 27.0, 24.0, 22.8, 14.2. HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{41}N_3O_3Na$, 466.3040; observed, 466.3044.

3-(3-(4-Nonylbenzyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (52a).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (45%, 50 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.19 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.01 (s, 2H), 3.13–2.97 (m, 4H), 2.57 (t, J = 7.8 Hz, 2H), 2.13 (p, J = 7.5 Hz, 2H), 1.58 (p, J = 7.5 Hz, 2H), 1.40–1.22 (m, 12H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.8, 169.5, 141.5, 132.7, 128.4, 128.3, 38.4, 35.1, 31.6, 31.3, 31.0, 29.3, 29.2, 29.0, 28.9, 23.6, 22.8, 22.3, 13.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2703.

3-(3-(4-Octylphenethyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (52b).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (46%, 49 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.13–7.06 (m, 4H), 3.12–2.97 (m, 8H), 2.55 (t, J = 7.7 Hz, 2H), 2.17 (p, J = 7.5 Hz, 2H), 1.59 (p, J = 7.5, 6.6 Hz, 2H), 1.37–1.21 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 179.9, 171.1, 142.1, 138.8, 129.6, 129.2, 39.8, 36.5, 33.5, 33.0, 32.8, 30.6, 30.4, 30.3, 28.7, 25.1, 24.2, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2700.

tert-Butyl (3-(3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (55a).—Synthesized according to General Procedure 3. Purified via column chromatography (25% ethyl acetate/hexanes). Off-white solid (67%, 985 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.84–7.77 (m, 4H), 4.77 (br s, 1H), 3.28 (q, J = 6.5 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.07 (p, J = 7.1 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.7, 167.8, 156.1, 138.2, 129.0, 126.5, 98.0, 79.6, 39.9, 28.5, 27.1, 24.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{21}IN_3O_3$, 430.0622; observed, 430.0614.

tert-Butyl (3-(3-(3-Iodophenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (55b).—Synthesized according to General Procedure 3. Purified via column chromatography (25% ethyl acetate/hexanes). White solid (58%, 333 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.42 (t, J = 1.7 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 4.75 (s, 1H), 3.28 (q, J = 6.5 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.07 (p, J = 7.1 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.8, 167.1, 156.1, 140.2, 136.3, 130.6, 128.8, 126.6, 94.5, 79.6, 39.8, 28.5, 27.1, 24.2.

tert-Butyl (3-(3-(4-Hexylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56a).— Synthesized according to General Procedure 1. Purified by silica chromatography (25% ethyl acetate/hexanes). White solid (86%, 135 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.94 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 4.79 (s, 1H), 3.26 (q, J = 6.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.11–1.99 (m, 2H), 1.92–1.74 (m, 2H), 1.49 (s, 9H), 1.38–1.20 (m, 6H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.1, 168.1, 155.9, 146.4, 128.9, 127.3, 124.1, 80.9, 39.7, 35.9, 32.0, 31.6, 31.1, 28.9, 28.3, 26.1, 24.0, 22.5, 21.1, 14.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{34}N_3O_3$, 388.2595; observed, 388.2617.

tert-Butyl (3-(3-(4-Heptylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56b).—Synthesized according to General Procedure 1. Purified by silica chromatography (25% ethyl acetate/hexanes). White solid (93%, 120 mg). ^{1}H NMR (400 MHz, chloroform-d): δ 7.95 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 4.77 (s, 1H), 3.27 (q, J = 6.6 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.05 (p, J = 7.0 Hz, 2H), 1.63 (p, J = 7.3 Hz, 2H), 1.42 (s, 9H), 1.31–1.20 (m, 8H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.26, 168.45, 156.08, 146.64, 129.05, 127.49, 124.27, 36.10, 32.22, 31.94, 31.38, 29.36, 29.29, 28.53, 26.37, 22.80, 22.16, 14.24.

tert-Butyl (3-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56c).— Synthesized according to General Procedure 1. Purified by silica chromatography (25% ethyl acetate/hexanes). White solid (48%, 70 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.95 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.80 (s, 1H), 3.27 (q, J = 6.4 Hz, 2H), 2.97 (d, J = 7.5 Hz, 2H), 2.64 (t, J = 6.9 Hz, 2H), 2.06 (p, J = 7.0 Hz, 2H), 1.68–1.58 (m, 2H), 1.43 (s, 9H), 1.36–1.15 (m, 10H), 0.85 (t, J = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.1, 168.2, 155.9, 146.4, 128.8, 127.3, 124.1, 79.3, 39.7, 35.9, 31.8, 31.1, 29.4, 29.2, 29.2, 28.3, 26.9, 24.1, 22.6, 14.0. HRMS (ESi): $[M + H]^+$ calcd for $C_{24}H_{38}N_3O_3$, 416.2908; observed, 416.2890.

tert-Butyl (3-(3-(4-Nonylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56d).— Synthesized according to General Procedure 1. Purified by silica chromatography (25% ethyl acetate/hexanes). White solid (67%, 100 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.96 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 4.79 (s, 1H), 3.27 (q, J = 6.5 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 2.06 (p, J = 7.0 Hz, 2H), 1.68–1.56 (m, 2H), 1.43 (s, 9H), 1.36–1.17 (m, 12H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.0, 168.9, 155.9, 146.4, 128.8, 127.3, 124.1, 79.3, 39.7, 35.3, 31.8, 31.2, 29.5, 29.4, 29.2, 29.2, 28.3, 26.9, 24.0, 22.6, 14.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_3$, 430.3064; observed, 430.3050.

tert-Butyl (3-(3-(4-Undecylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56e).—Synthesized according to General Procedure 1. Purified by silica chromatography (20% ethyl acetate/hexanes). White solid (59%, 100 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.95 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.78 (s, 1H), 3.27 (q, J = 6.5 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 8.7 Hz, 2H), 2.06 (p, J =7.1 Hz, 2H), 1.62 (p, J = 7.4 Hz, 2H), 1.43 (s, 9H), 1.36–1.18 (m, 16H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$):

δ 179.0, 168.2, 155.9, 146.4, 128.8, 127.3, 124.1, 79.5, 39.7, 35.9, 31.8, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.5, 26.9, 24.0, 22.6, 14.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{44}N_3O_3$, 458.3377; observed, 458.3359.

tert-Butyl (3-(3-(3-Decylphenyl)-1,2,4-oxadiazol-5-yl)propyl)-carbamate (56f).— The compound was synthesized according to General Procedure 1. The crude mixture was passed through a silica plug (25% ethyl acetate/hexane eluent) and concentrated under reduced pressure. The desired product was confirmed via HRMS and carried forward as crude with no further purification. Yellow oil (60%, 199 mg). HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{42}N_3O_3$, 444.3221; observed, 444.3205.

3-(3-(4-Hexylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57a).—Synthesized according to General Procedure 4. White solid (30%, 50 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 3.18–3.09 (m, 4H), 2.69 (t, J = 7.7 Hz, 2H), 2.24 (p, J = 7.4 Hz, 2H), 1.66 (p, J = 7.6 Hz, 2H), 1.42–1.25 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.1, 169.5, 148.1, 130.1, 128.3, 125.4, 39.9, 36.8, 32.8, 32.4, 30.0, 25.2, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{26}N_3O$, 288.2070; observed, 288.2125.

3-(3-(4-Heptylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57b).—Synthesized according to General Procedure 4. White solid (27%, 70 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 3.18–3.09 (m, 4H), 2.69 (t, J = 7.7 Hz, 2H), 2.24 (p, J = 7.4 Hz, 2H), 1.65 (p, J = 6.9 Hz, 2H), 1.41– 1.23 (m, 8H), 0.90 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.2, 169.5, 148.1, 130.1, 128.3, 125.4, 39.9, 36.8, 33.0, 32.5, 30.3, 30.3, 25.2, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{28}N_3O$, 302.2227; observed, 302.2230.

3-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57c).—Synthesized according to General Procedure 4. White solid (74%, 25 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 3.17–3.08 (m, 4H), 2.67 (t, J = 8.6 Hz, 2H), 2.29–2.17 (m, 2H), 1.70–1.58 (m, 2H), 1.38–1.22 (m, 10H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.7, 168.0, 146.6, 128.6, 126.8, 123.9, 38.4, 35.4, 31.5, 31.0, 29.0, 28.9, 28.8, 23.7, 22.8, 22.2, 12.9. HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{30}N_3O$, 316.2383; observed, 316.2368.

3-(3-(4-Nonylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57d).—Synthesized according to General Procedure 4. White solid (52%, 40 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 3.18–3.09 (m, 4H), 2.69 (t, J = 7.7 Hz, 2H), 2.24 (p, J = 7.4 Hz, 2H), 1.66 (p, J = 7.3 Hz, 2H), 1.41– 1.24 (m, 12H), 0.89 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 178.7, 168.0, 146.6, 128.6, 126.8, 123.9, 38.4, 35.4, 31.5, 31.1, 29.2, 29.1, 28.9, 28.8, 23.8, 22.3, 22.8, 12.9. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{32}N_3O$, 330.2540; observed, 330.2529.

3-(3-(4-Undecylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57e).—Synthesized according to General Procedure 4. White solid (58%, 50 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 3.17–3.08 (m, 4H),

2.67 (t, J = 8.6 Hz, 2H), 2.29–2.17 (m, 2H), 1.71–1.58 (m, 2H), 1.42–1.19 (m, 16H), 0.87 (t, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.2, 169.5, 148.1, 130.1, 128.3, 125.4, 39.9, 36.8, 33.1, 32.4, 30.7, 30.7, 30.5, 30.5, 30.3, 25.2, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{36}N_3O$, 358.2853; observed, 358.2839.

3-(3-(3-Decylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (57f).—Synthesized according to General Procedure 4. White solid (53%, 90 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.87–7.81 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 3.21–3.09 (m, 4H), 2.64 (t, J = 7.7 Hz, 2H), 2.27 (p, J = 7.5 Hz, 2H), 1.62 (p, J = 7.2 Hz, 2H), 1.39–1.17 (m, 14H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.2, 169.5, 144.9, 132.5, 129.9, 128.1, 127.8, 125.7, 39.8, 36.7, 33.0, 32.6, 30.7, 30.6, 30.4, 30.3, 28.8, 25.1, 24.3, 23.7, 14.5. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{34}N_3O$, 344.2696; observed, 344.2685.

4-(Nonyloxy)benzonitrile (59a).—Synthesized according to General Procedure 8. Purified via column chromatography (5% ethyl acetate/hexanes). White solid (80%, 827 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.57 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 1.79 (p, J = 6.6 Hz, 2H), 1.44 (p, J = 7.7 Hz, 2H), 1.38–1.24 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 162.6, 134.1, 119.5, 115.3, 103.8, 68.6, 32.0, 29.6, 29.5, 29.4, 29.1, 26.1, 22.8, 14.2.

3-Fluoro-4-(nonyloxy)benzonitrile (59b).—Synthesized according to General Procedure 8. Purified via column chromatography (7% ethyl acetate/hexanes). White solid (88%, 846 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.43–7.32 (m, 2H), 6.99 (t, J = 8.3 Hz, 1H), 4.07 (t, J = 6.6 Hz, 2H), 1.84 (p, J = 6.7 Hz, 2H), 1.45 (p, J = 7.3 Hz, 2H), 1.39–1.24 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 152.0 (d, J = 249.9 Hz), 151.6 (d, J = 10.3 Hz), 129.7 (d, J = 3.8 Hz), 119.7 (d, J = 21.4 Hz), 118.3 (d, J =2.6 Hz), 114.5 (d, J = 2.4 Hz), 103.7 (d, J = 8.3 Hz), 69.7, 32.0, 29.6, 29.4, 29.3, 29.0, 25.9, 22.8, 14.2.

4-(Nonyloxy)-3-(trifluoromethyl)benzonitrile (59c).—Synthesized according to General Procedure 8. Purified via column chromatography (7% ethyl acetate/hexanes). White solid (77%, 625 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.85 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 8.7, 2.1 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 4.11 (t, J = 6.3 Hz, 2H), 1.84 (p, J = 6.4 Hz, 2H), 1.47 (p, J = 7.0 Hz, 2H), 1.39–1.23 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 160.4, 137.6, 131.5 (q, J = 5.4 Hz), 122.6 (q, J = 273.0 Hz), 120.3 (q, J = 32.1 Hz), 118.1, 113.5, 103.6, 69.6, 32.0, 29.6, 29.3, 29.3, 28.8, 25.8, 22.8, 14.2.

6-(Heptyloxy)-2-naphthonitrile (59d).—Synthesized according to General Procedure 8. Purified via column chromatography (5% ethyl acetate/hexanes). White solid (99%, 1.21 g). ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.12 (d, J =1.6 Hz, 1H), 7.80–7.73 (m, 2H), 7.55 (dd, J = 8.5, 1.7 Hz, 1H), 7.24 (dd, J = 9.0, 2.5 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 4.09 (t, J = 6.6 Hz, 2H), 1.86 (p, J =6.7 Hz, 2H), 1.50 (p, J = 7.1 Hz, 2H), 1.43–1.27 (m, 6H), 0.94–0.87 (m, 3H). ^{13}C NMR (126 MHz, $CdCl_3$): δ 159.7, 136.6, 133.9, 130.0, 127.9, 127.7, 127.1, 121.1, 106.7,

68.4, 31.9, 29.2, 29.2, 26.2, 22.8, 14.2. HRMS (ESI): $[M + NH_4]^+$ calcd for $C_{18}H_{25}N_2O$, 285.1961; observed, 285.1962.

N′-Hydroxy-4-(nonyloxy)benzimidamide (60a).—Synthesized according to General Procedure 2. Purified via column chromatography (40% ethyl acetate/hexanes). White solid (35%, 320 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.76 (s, 1H), 7.64 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.38 (s, 2H), 4.01 (t, J = 6.5 Hz, 2H), 1.82–1.72 (m, 2H), 1.53–1.43 (m, 2H), 1.42–1.22 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 160.9, 152.0, 127.6, 126.8, 114.8, 68.6, 32.6, 30.3, 30.1, 30.0, 30.0, 26.8, 23.3, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{27}N_2O_2$, 279.2073; observed, 279.2061.

3-Fluoro-N′-hydroxy-4-(nonyloxy)benzimidamide (60b).—The compound was synthesized according to General Procedure 2. The crude mixture was concentrated under reduced pressure, redissolved in ethyl acetate, and partitioned with brine. The aqueous layer was rinsed three times with ethyl acetate. The organic layers were combined, rinsed further three times with brine, dried over sodium sulfate, and concentrated in vacuo. The product was carried forward as crude with no further purification. White solid (78%, 727 mg).

N′-Hydroxy-4-(nonyloxy)-3-(trifluoromethyl)benzimidamide (60c).—Synthesized according to General Procedure 2. Purified via column chromatography (40% ethyl acetate/hexanes).White solid (89%, 616 mg). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 9.09 (s, 1H), 8.1 (d, J = 2.3 Hz, 1H), 7.92 (dd, J = 8.7, 2.0 Hz, 1H), 7.22 (d, J = 8.72 Hz, 1H), 5.60 (s, 2H), 4.21 (t, J = 6.3 Hz, 2H), 1.94–1.78 (m, 2H), 1.61–1.50 (m, 2H), 1.39–1.22 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 157.6 (q, J = 1.6 Hz), 150.1, 130.7, 125.5, 124.0 (q, J = 5.4 Hz), 123.9 (q, J = 271.7 Hz), 117.7 (q, J = 30.6 Hz), 112.9, 68.7, 31.7, 29.0, 28.8, 25.6, 22.4, 13.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{26}N_2OF_3$, 347.1946; observed, 347.1944.

6-(Heptyloxy)-N′-hydroxy-2-naphthimidamide (60d).—Synthesized according to General Procedure 2. Purified via silica plug (dichloromethane wash, followed by elution with 100% ethyl acetate). Gray solid (93%, 2.1 g). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.98 (s, 1H), 8.13 (d, J = 1.7 Hz, 1H), 7.85 (dd, J = 8.7, 1.8 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.16 (dd, J = 8.9, 2.5 Hz, 1H), 5.56 (s, 2H), 4.12 (t, J = 6.5 Hz, 2H), 1.89–1.79 (m, 2H), 1.57–1.47 (m, 2H), 1.45–1.28 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 158.6, 152.1, 136.1, 130.6, 129.6, 129.3, 127.3, 125.0, 124.8, 120.1, 107.4, 69.6, 32.6, 30.0, 29.8, 26.8, 23.3, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2$, 301.1911; observed, 301.1912.

tert-Butyl (3-(3-(4-(Nonyloxy)phenyl)-1,2,4-oxadiazol-5-yl)-propyl)carbamate (61a).—Synthesized according to General Procedure 3. Purified via column chromatography (15% ethyl acetate/hexanes). White solid (79%, 316 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 4.81 (s, 1H), 4.00 (t, J = 6.6 Hz, 2H), 3.28 (q, J = 6.1 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H), 2.6 (p, J = 7.0 Hz, 2H), 1.88–1.71 (m, 2H), 1.50–1.41 (m, 11H), 1.36–1.26 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.1, 168.2, 161.7, 156.1, 129.1, 119.1, 114.9, 79.6, 68.3, 39.9,

32.0, 29.7, 29.5, 29.4, 29.3, 28.5, 27.1, 26.2, 24.2, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_4$, 446.3013; observed, 446.3004.

tert-Butyl (3-(3-(3-Fluoro-4-(nonyloxy)phenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (61b).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (87%, 360 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.82–7.75 (m, 2H), 7.02 (t, J = 8.6 Hz, 1H), 4.79 (s, 1H), 4.08 (t, J = 6.6 Hz, 2H), 3.28 (q, J = 6.1 Hz, 2H), 2.98 (t, J = 7.4 Hz, 2H), 2.07 (p, J = 7.0 Hz, 2H), 1.85 (p, J = 6.7 Hz, 2H), 1.52–1.42 (s, 11H), 1.40–1.24 (m, 10H), 0.88 (t, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.4, 167.5, 156.1, 152.6 (d, J = 246.7 Hz), 149.8 (d, J = 10.7 Hz), 124.0 (d, J = 3.6 Hz), 119.5 (d, J = 7.4 Hz), 115.4 (d, J = 20.7 Hz), 114.5 (d, J = 2.3 Hz), 79.6, 69.5, 39.9, 32.0, 29.6, 29.5, 29.4, 29.2, 28.5, 27.0, 26.0, 24.2, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{23}H_{39}FN_3O_4$, 464.2919; observed, 464.2910.

tert-Butyl (3-(3-(4-(Nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (61c).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). Yellow solid (57%, 260 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.27 (d, J = 1.9 Hz, 1H), 8.16 (dd, J = 8.7, 2.0 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 4.74 (s, 1H), 4.10 (t, J = 6.4 Hz, 2H), 3.28 (q, J = 6.1 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.07 (p, J = 7.0 Hz, 2H), 1.83 (p, J = 6.4 Hz, 2H), 1.52–1.41 (m, 11H), 1.36–1.24 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.6, 167.4, 159.3, 156.1, 132.5, 126.8 (q, J = 5.3 Hz), 123.4 (q, J = 272.6 Hz), 119.6 (q, J = 31.4 Hz), 118.7, 113.0, 79.6, 69.2, 39.9, 32.0, 29.6, 29.3, 29.3, 29.0, 28.5, 27.1, 25.9, 24.1, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{39}F_3N_3O4$, 514.2887; observed, 514.2881.

tert-Butyl (3-(3-(6-(Heptyloxy)naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (61d).—Synthesized according to General Procedure 3. Purified via column chromatography (20% ethyl acetate/hexanes). White solid (68%, 265 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.49 (s, 1H), 8.06 (dd, J = 8.6, 1.7 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.18 (dd, J = 8.9, 2.5 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 4.82 (s, 1H), 4.08 (t, J = 6.6 Hz, 2H), 3.35–3.23 (m, 2H), 3.01 (t, J = 7.5 Hz, 2H), 2.10 (p, J =7.1 Hz, 2H), 1.85 (p, J = 6.7 Hz, 2H), 1.55–1.25 (m, 17H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.3, 168.6, 158.6, 156.1, 136.2, 130.4, 128.4, 127.8, 127.5, 124.4, 121.8, 120.0, 106.7, 79.5, 68.2, 39.9, 31.9, 29.3, 29.2, 28.5, 27.1, 26.2, 24.2, 22.7, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{27}H_{38}N_3O_4$, 468.2857; observed, 468.2857.

3-(3-(4-(Nonyloxy)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (62a).—Synthesized according to General Procedure 4. White solid (88%, 226 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 4.04 (t, J = 6.4 Hz, 2H), 3.17–3.08 (m, 4H), 2.23 (p, J = 7.4 Hz, 2H), 1.79 (p, J = 6.5 Hz, 2H), 1.49 (p, J = 6.7 Hz, 2H), 1.44–1.23 (m, 10H), 0.90 (t, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.0, 169.3, 163.2, 129.9, 120.0, 115.9, 69.3, 39.9, 33.0, 30.7, 30.5, 30.4, 30.3, 27.1, 25.2, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{32}N_3O_2$, 346.2489; observed, 346.2480.

3-(3-(3-Fluoro-4-(nonyloxy)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (62b).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (79%, 236 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.8 (dt, J = 8.6, 1.5 Hz, 1H), 7.7 (dd, J = 11.9,2.0 Hz, 1H), 7.2 (t, J = 8.5 Hz, 1H), 4.1 (t, J = 6.4 Hz, 2H), 3.1 (q, J = 7.4 Hz, 2H), 2.2 (p, J = 7.4 Hz, 2H), 1.9 1.7 (m, 2H), 1.6–1.4 (m, 2H), 1.4–1.2 (m, 10H), 0.9 (d, J = 6.8 Hz, 3H).^{13}C NMR (101 MHz, CD_3OD): δ 180.3, 168.6 (d, J = 2.6 Hz), 153.7 (d, J = 245.8 Hz), 151.2 (d, J = 10.7 Hz), 125.1 (d, J = 3.7 Hz), 120.5 (d, J = 7.4 Hz), 115.8, 115.7 (d, J = 23.9 Hz), 70.4, 39.9, 33.0, 30.6, 30.4, 30.4, 30.2, 27.0, 25.2, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{31}FN_3O_2$, 364.2395; observed, 364.2387.

3-(3-(4-(Nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine Hydrochloride (62c).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (72%, 155 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.25–8.20 (m, 2H), 7.30 (d, J = 9.2 Hz, 1H), 4.17 (t, J = 6.2 Hz, 2H), 3.22–3.11 (m, 4H), 2.26 (p, J = 7.5 Hz, 2H), 1.83 (p, J = 6.3 Hz, 2H), 1.52 (p, J = 7.0 Hz, 2H), 1.41–1.26 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.5, 168.4, 160.7 (q, J = 1.6 Hz), 133.8, 127.0 (q, J = 5.5 Hz), 124.8 (q, J = 271.8 Hz), 120.2 (q, J = 31.3 Hz), 119.8, 114.8, 70.3, 39.8, 33.0, 30.6, 30.3, 30.3, 30.0, 26.9, 25.1, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{31}F_3N_3O_2$, 414.2363; observed, 414.2355.

3-(3-(6-(Heptyloxy)naphthalen-2-yl)-1,2,4-oxadiazol-5-yl)-propan-1-amine Hydrochloride (62d).—Synthesized according to General Procedure 4. White solid (85%, 166 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.50 (d, J = 1.6 Hz, 1H), 8.03 (dd, J = 8.6 Hz, 1H), 7.88 (d, J = 3.5 Hz, 1H), 7.86 (d, J = 3.8 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 4.13 (t, J = 6.4 Hz, 2H), 3.21–3.11 (m, 4H), 2.27 (p, J = 7.4 Hz, 2H), 1.86 (p, J = 6.7 Hz, 2H), 1.54 (p, J = 6.9 Hz, 2H), 1.47–1.31 (m, 6H), 0.93 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.2, 169.7, 160.1, 137.8, 131.2, 129.8, 128.7, 128.6, 125.0, 122.8, 121.1, 107.7, 69.2, 39.9, 33.0, 30.4, 30.2, 27.2, 25.3, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{21}H_{31}F_3N_3O_2$, 414.2363; observed, 414.2355.

4-Cyano-N-octylbenzamide (64).—Synthesized according to General Procedure 9. Purified by silica chromatography (30% ethyl acetate in hexanes). Orange solid (94%, 822 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.85 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 6.29 (t, J = 5.9 Hz, 1H), 3.44 (q, J = 7.3 Hz, 2H), 1.61 (p, J = 7.4 Hz, 2H), 1.40–1.22 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 165.8, 138.9, 132.5, 127.7, 118.2, 115.0, 40.5, 31.9, 29.6, 29.4, 29.3, 27.1, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1805; observed, 259.1804.

4-(N′-Hydroxycarbamimidoyl)-N-octylbenzamide (65).—Synthesized according to General Procedure 2. Purified by silica chromatography (90% ethyl acetate in hexanes). White solid (52%, 555 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.87 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 3.41 (t, J = 7.2 Hz, 2H), 1.66 (p, J = 7.1 Hz, 2H), 1.47–1.30 (m, 10H), 0.93 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 169.5, 162.6, 137.2, 136.8,

128.3, 127.3, 41.1, 33.0, 30.5, 30.4, 30.4, 28.1, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_2$, 292.2020; observed, 292.2030.

tert-Butyl (3-(3-(4-(Octylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (66).—Synthesized according to General Procedure 3. Purified by silica chromatography (60% ethyl acetate in hexanes). White solid (48%, 188 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 8.04 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 6.68 (t, J = 5.6 Hz, 1H), 4.97 (s, 1H), 3.40 (q, J = 6.8 Hz, 2H), 3.24 (q, J = 6.5 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H), 2.03 (p, J = 7.0 Hz, 2H), 1.57 (p, J = 7.3 Hz, 2H), 1.39 (s, 9H), 1.36–1.17 (m, 10H), 0.83 (t, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.7, 167.6, 166.9, 156.1, 137.2, 129.4, 127.5, 127.5, 79.4, 40.3, 39.8, 31.8, 29.7, 29.3, 29.3, 28.4, 27.1, 26.9, 24.1, 22.7, 14.1. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{39}N_4O4$, 459.2966; observed, 459.2962.

4-(5-(3-Aminopropyl)-1,2,4-oxadiazol-3-yl)-N-octylbenzamide Hydrochloride (67).—Synthesized according to General Procedure 4. Purified via trituration with diethyl ether. White solid (96%, 155 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.15 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 3.40 (t, J = 7.2 Hz, 2H), 3.19–3.13 (m, 4H), 2.26 (p, J = 7.5 Hz, 2H), 1.64 (p, J = 7.2 Hz, 2H), 1.44–1.28 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 179.2, 167.7, 167.5, 137.1, 129.3, 127.5, 126.9, 39.7, 38.4, 31.6, 29.0, 29.0, 28.9, 26.7, 23.8, 22.8, 22.3, 13.0. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{31}N_4O_2$, 359.2442; observed, 359.2432.

N-(4-Cyanophenyl)nonanamide (69a).—Synthesized according to General Procedure 9. Purified via column chromatography (20% ethyl acetate/hexanes). White solid (84%, 551 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.51 (br s, 1H), 2.39 (t, J = 7.6 Hz, 2H), 1.72 (p, J = 7.4 Hz, 2H), 1.40–1.20 (m, 10H), 0.88 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 171.9, 142.2, 133.4, 119.6, 119.0, 107.0, 38.0, 31.9, 29.4, 29.4, 29.2, 25.5, 22.8, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1805; observed, 259.1802.

N-(4-Cyanobenzyl)octanamide (69b).—Synthesized according to General Procedure 9. Purified via column chromatography (60% ethyl acetate/hexanes). White solid (89%, 873 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.68 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 4.42 (s, 2H), 2.25 (t, J = 7.5 Hz, 2H), 1.63 (p, J = 7.5 Hz, 2H), 1.37–1.23 (m, 8H), 0.90 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 176.4, 146.2, 133.4, 129.3, 119.7, 111.9, 43.6, 37.0, 32.9, 30.3, 30.1, 27.0, 23.6, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1805; observed, 259.1798.

N-(4-(N′-Hydroxycarbamimidoyl)phenyl)nonanamide (70a).—The compound was synthesized according to General Procedure 2. The crude mixture was concentrated under reduced pressure, redissolved in ethyl acetate, and partitioned with brine. The aqueous layer was rinsed three times with ethyl acetate. The organic layers were combined, rinsed further three times with brine, dried over sodium sulfate, and concentrated in vacuo. The desired product was confirmed via HRMS and carried forward as crude with no further purification. White solid (88%, 545 mg). HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_2$, 292.2020; observed, 292.2003.

N-(4-(N′-Hydroxycarbamimidoyl)benzyl)octanamide (70b).—The compound was synthesized according to General Procedure 2. The crude mixture concentrated under reduced pressure, redissolved in ethyl acetate, and partitioned with brine. The aqueous layer was rinsed three times with ethyl acetate. The organic layers were combined, rinsed further three times with brine, dried over sodium sulfate, and concentrated in vacuo. The desired product was confirmed via HRMS and carried forward as crude with no further purification. White solid (95%, 937 mg). HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_2$, 292.2020; observed, 292.2010.

tert-Butyl (3-(3-(4-Nonanamidophenyl)-1,2,4-oxadiazol-5-yl)-propyl)carbamate (71a).—Synthesized according to General Procedure 3. Purified via column chromatography (60% ethyl acetate/hexanes). White solid (22%, 191 mg). ^{1}H NMR (400 MHz, $CdCl_3$): δ 7.98 (d, J = 8.7 Hz, 2H), 7.87 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 4.92 (t, J = 7.7 Hz, 1H), 3.26 (q, J = 6.6 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.6 Hz, 2H), 2.05 (p, J = 7.1 Hz, 2H), 1.70 (p, J = 7.5 Hz, 2H), 1.42 (s, 9H), 1.37–1.19 (m, 10H), 0.89–0.81 (m, 3H). ^{13}C NMR (101 MHz, $CdCl_3$): δ 179.3, 172.1, 167.9, 156.2, 140.9, 128.4, 122.3, 119.7, 79.6, 39.9, 37.9, 31.9, 29.4, 29.4, 29.2, 28.5, 27.0, 25.7, 24.1, 22.7, 14.2. HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{39}N_4O4$, 459.2966; observed, 459.2966.

tert-Butyl (3-(3-(4-(Octanamidomethyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate (71b).—Synthesized according to General Procedure 3. Purified via column chromatography (40–60% ethyl acetate/hexanes). White solid (77%, 1129 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 4.43 (s, 2H), 3.20 (t, J = 6.7 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.04 (p, J = 7.2 Hz, 2H), 1.65 (p, J = 7.5 Hz, 2H), 1.42 (s, 9H), 1.37–1.23 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 181.4, 176.3, 169.2, 158.5, 143.8, 129.0, 128.5, 126.9, 80.1, 43.7, 40.5, 37.0, 32.9, 30.2, 30.1, 28.7, 27.7, 27.0, 24.7, 23.6, 14.4. HRMS (ESI): $[M + Na]^+$ calcd for $C_{25}H_{38}N_4NaO_4$, 481.2785; observed, 481.2785.

N-(4-(5-(3-Aminopropyl)-1,2,4-oxadiazol-3-yl)phenyl)-nonanamide Hydrochloride (72a).—Synthesized according to General Procedure 4. Purified via trituration with ethyl acetate and diethyl ether. White solid (68%, 111 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 3.16–3.07 (m, 4H), 2.40 (t, J = 7.5 Hz, 2H), 2.23 (p, J = 7.4 Hz, 2H), 1.71 (p, J = 7.4 Hz, 2H), 1.44–1.25 (m, 10H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.3, 174.9, 169.1, 142.9, 129.0, 123.1, 120.9, 40.1, 38.1, 32.9, 30.4, 30.3, 30.3, 26.8 25.7, 24.3, 23.7, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{31}N_4O_2$, 359.2442; observed, 359.2444.

N-(4-(5-(3-Aminopropyl)-1,2,4-oxadiazol-3-yl)benzyl)-octanamide Hydrochloride (72b).—Synthesized according to General Procedure 4. Purified via trituration with ethyl acetate and diethyl ether. White solid (80%, 782 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 4.42 (s, 2H), 3.18–3.09 (m, 4H), 2.30–2.18 (m, 4H), 1.63 (p, J = 7.3 Hz, 2H), 1.36–1.23 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD): δ 180.3, 176.3, 169.3, 144.0, 129.1, 128.5, 126.8, 43.7,

39.9, 37.1, 32.9, 30.2, 30.1, 27.0, 25.2, 24.3, 23.6, 14.4. HRMS (ESI): $[M + H]^+$ calcd for $C_{20}H_{31}N_4O_2$, 359.2442; observed, 359.2446.

Sphingosine Kinase Assays.

Recombinant baculovirus encoding either mSphK1 or mSphK2 was used to infect Sf9 insect cells, cleared lysates were prepared after 48 h, and 1–2 μL (0.02–0.03 mg protein) was used in each assay. Alternately, plasmids encoding mouse SphK1 or SphK2 were used to transfect HEK293T cells and cleared lysates were prepared after 48 h. SphK activity was measured in kinase assay buffer that consisted of 20 mM Tris–Cl (pH 7.4), 1 mM 2-mercaptoethanol, 1 mM EDTA, 5 mM sodium orthovanadate, 40 mM β-glycerophosphate, 15 mM NaF, 1 mM phenylmethylsulfonyl fluoride, 10 mM $MgCl_2$, 0.5 mM 4-deoxypyridoxine, 10% glycerol, and 0.01 mg/mL each leupeptin, aprotinin, and soybean trypsin inhibitor. To achieve optimal activity of SphK1 or SphK2, the buffer was supplemented with either 0.5% Triton X-100 or 1 M KCl, respectively. To ascertain any inhibitory effect of **16d**, the assay was supplemented with the substrate (D-*erythro*-sphingosine, 10 μM for SphK1 and 5 μM for SphK2), appropriate amount of compounds [(to achieve 10–30,000 nM); γ-[^{32}P]ATP (10 μM, specific activity = 8.3 Ci/mmol)], and recombinant enzyme (0.02–0.03 mg of total protein). After 20 min at 37 °C, the reaction mixture was extracted with 2 volumes of chloroform/methanol/1 N HCl (100:200:1), and the components in the organic phase were separated by TLC using a 1-butanol/glacial acetic acid/water (3:1:1) solvent system. Radio-labeled enzyme products were detected by autoradiography and identified by migration relative to authentic standards. For quantification, the silica gel containing radiolabeled lipid was scraped into a scintillation vial and measured by liquid scintillation counting.

In Vitro Spns2 Assay.

HeLa cells were transfected with pcDNA3.1 plasmids encoding mouse Spns2 or mouse Spns2Arg200Ser (transport dead mutant). Transfected cell pools were selected by inclusion of geneticin (G418) in the cell media. To assess S1P release, HeLa cells were plated onto 12-well plates and grown to near confluence. Growth media were removed by aspiration and 1.5 mL of release assay medium (RPMI 1640 with 0.2% fatty acid-free BSA) supplemented with 4-deoxypyridoxine (to 1 mM), NaF (2 mM), and Na_3VO_4 (0.2 mM) to retard degradation of S1P by S1P lyase and S1P phosphatases was added to each well. Test articles were introduced into duplicate wells (to 2 μM), and plates were placed in a tissue culture incubator for 18–20 h. Following this incubation, the medium was collected, internal standard (5 μL of 0.5 μM d_7-S1P in methanol) and 150 μL of 100% trichloroacetic acid were added, and the mixture was held on ice for 30–60 min. The precipitated material was collected by centrifugation, the pellets washed with water, recentrifuged, and the final pellet mixed vigorously after adding 0.3 mL methanol. After further centrifugation, 0.15 mL of the supernatant fluid was added to UPLC vials and S1P and d_7-S1P were quantified by MS/MS by injecting 9 μL into the column. Spns2-expressing cells were found to release S1P into the culture media in ca. 20-fold excess of Spns2R200S-transfected or nontransfected cells.

In Vivo Studies.

Compound **16d** (10 or 20 mg/kg) or an equal volume of vehicle (36.1% PEG400/9.1% ethanol/4.6% Solutol/50% H_2O) was administered by intraperitoneal injection into mice (C57BL/6j strain) or rats (Sprague-Dawley strain). Blood samples were analyzed via LC–MS/MS as described for analysis using the in vitro Spns2 assay above. Lymphocyte counts were obtained from 20 μL of mouse or rat blood using a Heska HT5 Element blood analyzer. For PK analysis in rats, whole blood collections via tail nick (*ca.* 70 μL) were performed at 0, 0.5, 1, 2, 4, 6, and 24 h postdose and plasma samples prepared for LC–MS/MS analysis for drug and S1P levels. All animal protocols were approved prior to experimentation by the University of Virginia School of Medicine's Animal Care and Use Committee.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

dppf	1,1′-bis(diphenylphosphino)ferrocene
EAE	experimental autoimmune encephalomyelitis
HCTU	2-(6-chloro-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
MFS	major facilitator superfamily
MS	mass spectrometry
mSphK1	mouse sphingosine kinase 1
mSphK2	mouse sphingosine kinase 2
S1P	sphingosine-1-phosphate
S1P1-5	sphingosine-1-phosphate receptors 1–5
SphK1	sphingosine kinase 1
SphK2	sphingosine kinase 2
Spns2	spinster homologue 2

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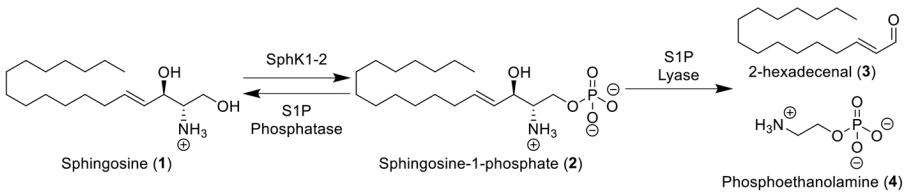


Figure 1.
S1P metabolic pathway.

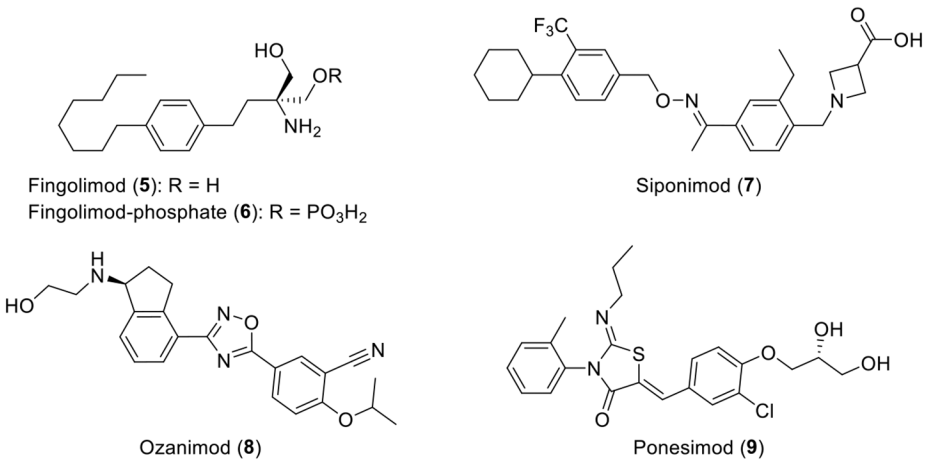


Figure 2.

FDA-approved therapies targeting S1P signaling through S1P1 functional antagonism.

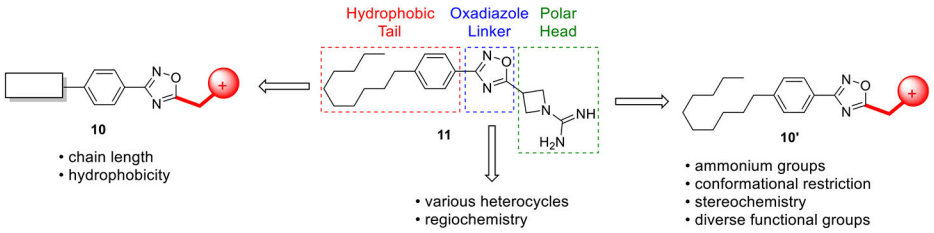


Figure 3.

Initial hit generated from our screening of SphK2 inhibitors with proposed structural delineations outlined.

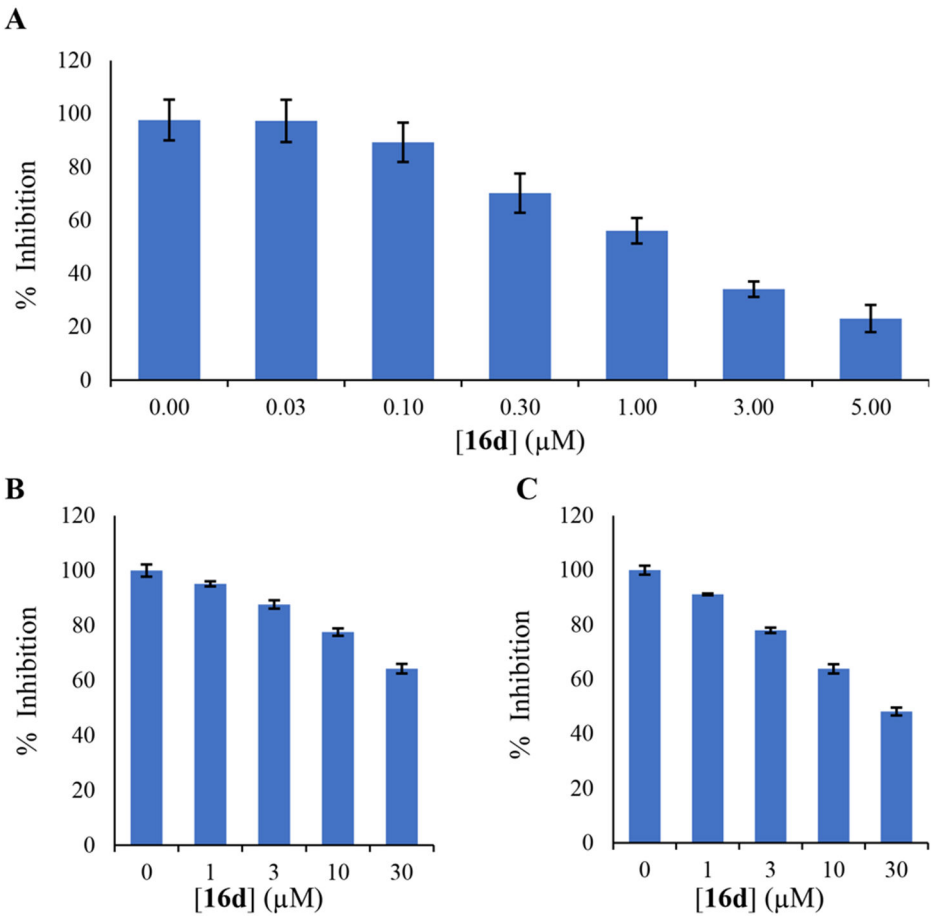


Figure 4.

Concentration–effect assessment of **16d** against Spns2 and sphingosine kinases. S1P release decreased as a function of increased concentrations of **16d** in Spn2-transfected Hela cells (A). Inhibition of recombinant mSphK1 (B) and mSphK2 (C) inhibition using a standard TLC-based assay. The assays were performed in duplicate.

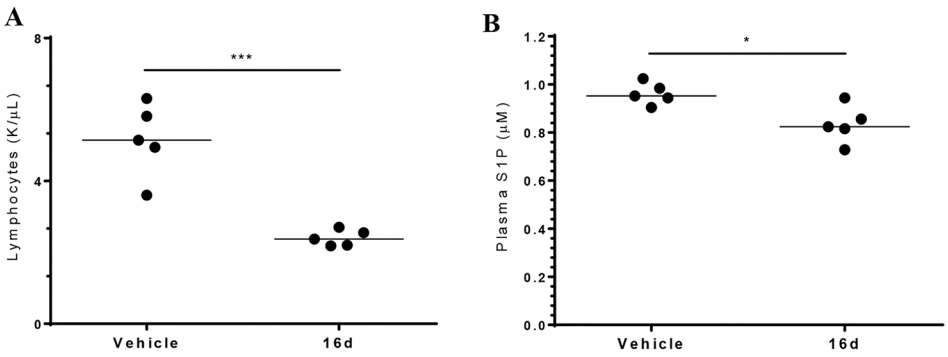


Figure 5.

Biological evaluation of **16d** in mice. Dosing with **16d** resulted in both a decrease in circulating lymphocytes (A) and plasma S1P (B). Age- and gender-matched mice (C57BL/6j strain) were injected (intraperitoneal route) with **16d** or the vehicle. Blood was drawn 4 h postdose (20 mg/kg). Lymphocyte counts were determined using a Heska Element HT5 blood analyzer, and plasma S1P was quantified via LC/MS. *t*-test: *≤0.05; ***≤0.001.

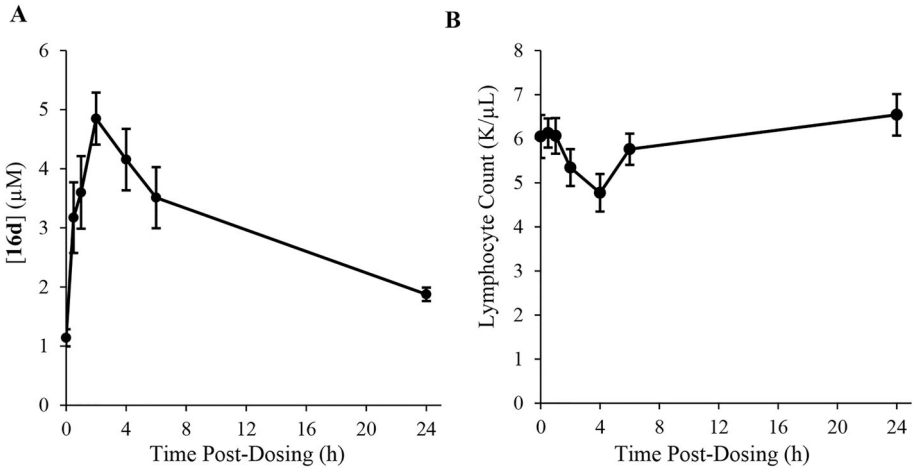
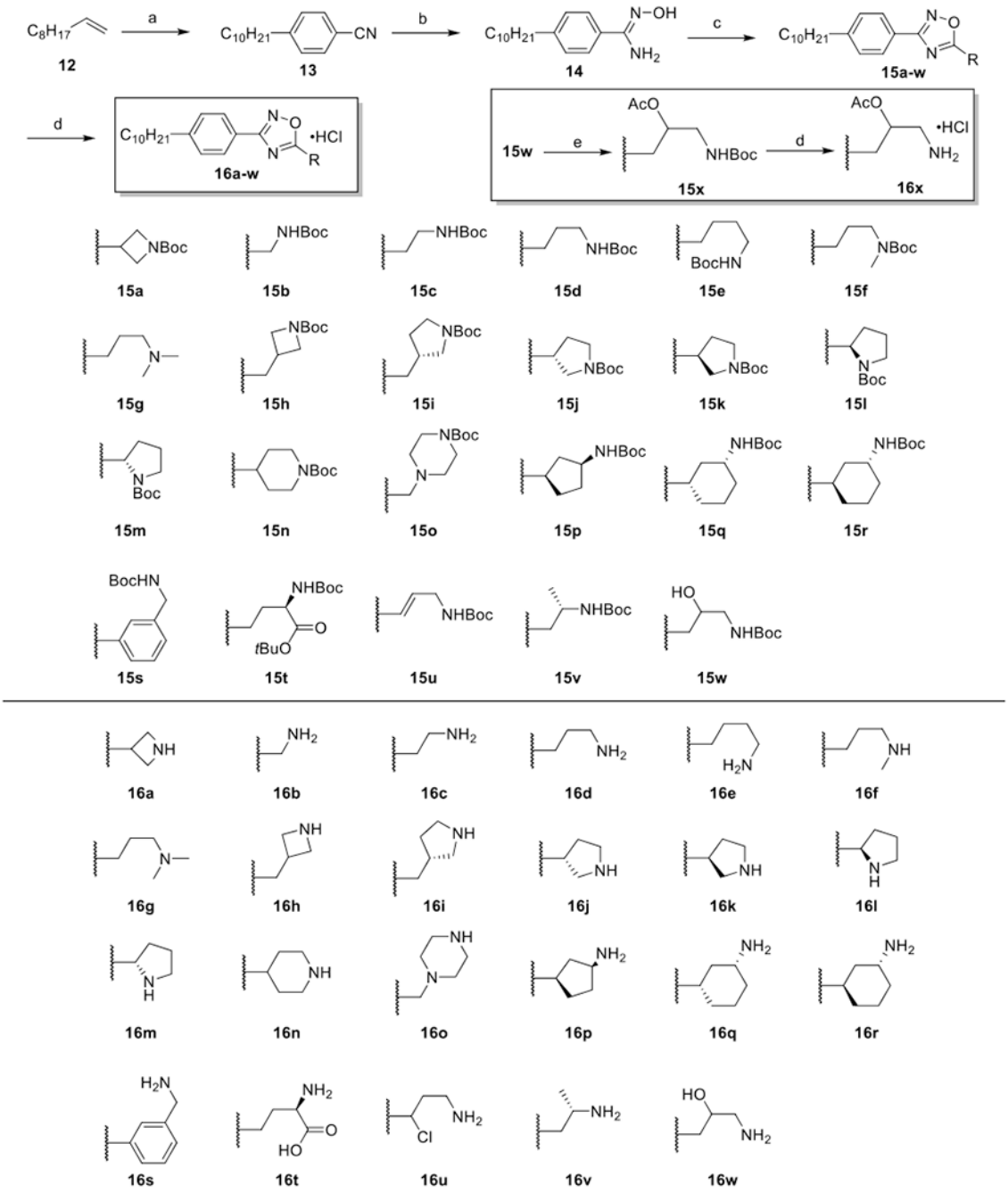


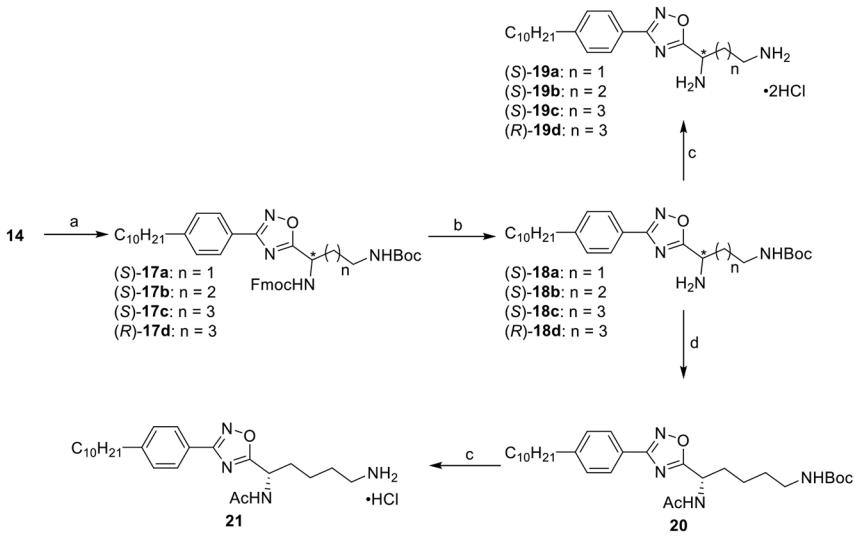
Figure 6.

Pharmacodynamic and pharmacokinetic analysis of **16d** in rats following a 10 mg/kg IP injection. All rats were 4 week old (Sprague-Dawley strain, $n = 4$) males. (A) Levels of **16d** in blood. (B) Blood lymphocyte concentrations reached a minimum 4 h after treatment with **16d**. Lymphocyte counts were determined using a Heska Element HT5 blood analyzer, while **16d** levels were determined by LC/MS using **57e** as an internal standard.



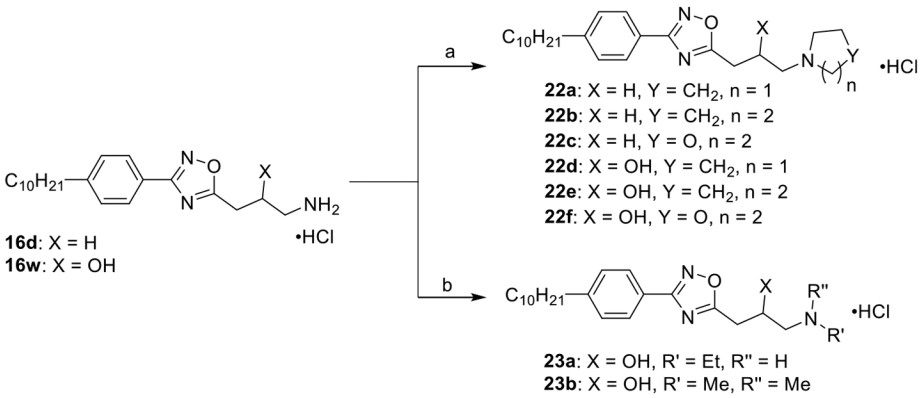
Scheme 1. Synthesis of Cyclic and Acyclic Amino Acid Derivatives 16a–x[a]

[a](a) (i) 9-BBN, THF, 66 °C, 1 h; (ii) 4-iodobenzonitrile, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $KOH_{(aq)}$, THF, 66 °C, 4 h, 96%; (b) $NH_2OH \cdot HCl$, EtOH, 78 °C, 2 h, 92%; (c) *N*-Boc-amino acid or *N,N*-dimethylglycine, DIEA, HCTU, DMF, 100 °C, 6 h, 46–76%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 33–89%; (e) Ac_2O, TEA, neat, rt, 0.5 h, 82%.



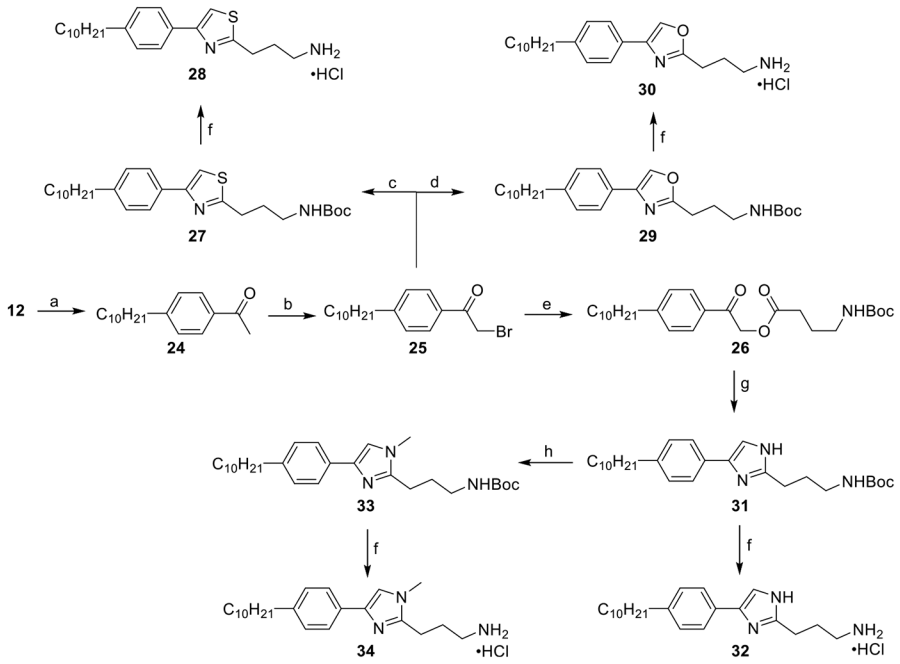
Scheme 2. Synthesis of Diamine Analogues 19a–d and 21[a]

[a](a) Diprotected amino acid, DIEA, HCTU, THF, 80 °C, 4 h, 40–74%; (b) morpholine, DMF, rt, 18 h, 34–85%; (c) 4 M HCl/dioxane, DCM, rt, 2 h, 37–85%; (d) Ac_2O, TEA, neat, rt, 0.5 h, 48%.



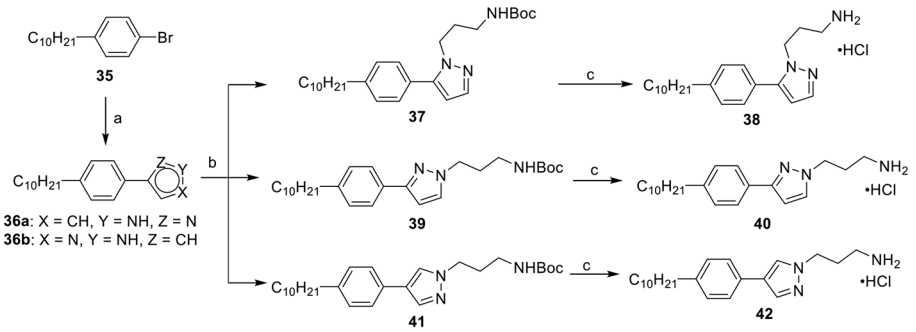
Scheme 3. Synthesis of 22a–f and 23a–b[a]

[a](a) (i) dibromoalkane, K_2CO_3, H_2O, 120 °C, 0.5 h; (ii) 4 M HCl/dioxane, DCM, rt, 2 h, 19–73%; (b) (i) aldehyde, AcOH, MeOH, 0 °C, 0.5 h; (ii) $NaBH_3CN$, MeOH, rt, 4 h, (iii) 4 M HCl/dioxane, DCM, rt, 2 h, 20–27%.



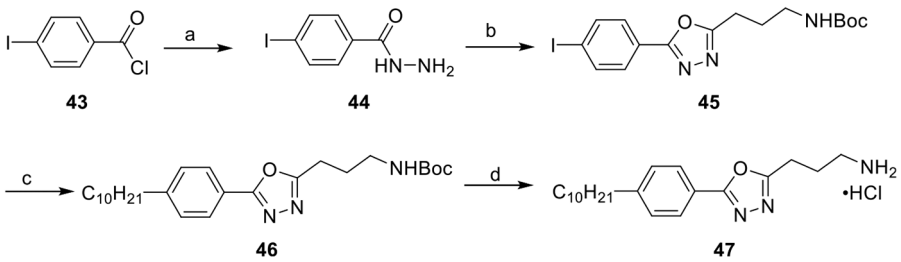
Scheme 4. Heterocyclic Analogues of the Linker Region[a]

[a](a) (i) 9-BBN, THF, 66 °C, 1 h; (ii) 1-(4-iodophenyl)ethan-1-one, Pd(dppf)Cl_2·CH_2Cl_2, $KOH_{(aq)}$, THF, 66 °C, 4 h, 70%; (b) NBS, TsOH, MeCN, 82 °C, 18 h, 88%; (c) *tert*-butyl(4-amino-4-thioxobutyl)carbamate, 2:1 DMF/EtOH, 78 °C, 4 h, 34%; (d) *tert*-butyl(4-amino-4-oxobutyl)carbamate, NMP, 100 °C, 6 h, 10%; (e) *N*-Boc-GABA, K_2CO_3, MeCN, rt, 18 h, 91%; (f) 4 M HCl/dioxane, DCM, rt, 2 h, 60–94%; (g) ammonium acetate, toluene, 110 °C, 5 h, 85%; (h) (i) NaH, THF, 0 °C, 0.5 h; (ii) MeI, THF, 0–25 °C, 18 h, 63%.



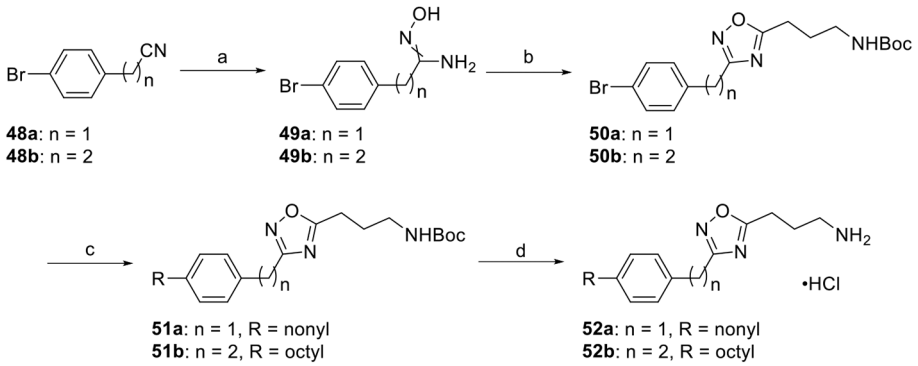
Scheme 5. Synthesis of Pyrazole Analogues 38, 40, and 42[a]

[a](a) Pyrazole boronic acid, $NaHCO_3$, DMF, 105 °C, 24 h, 46–53%; (b) (i) NaH, THF, 0 °C, 0.5 h; (ii) *tert*-butyl(3-bromopropyl)carbamate, THF 0–25 °C, 18 h, 16–77%; (c) 4 M HCl/dioxane, DCM, rt, 2 h, 78–89%.



Scheme 6. Synthesis of 1,3,4-Oxadiazole 47[a]

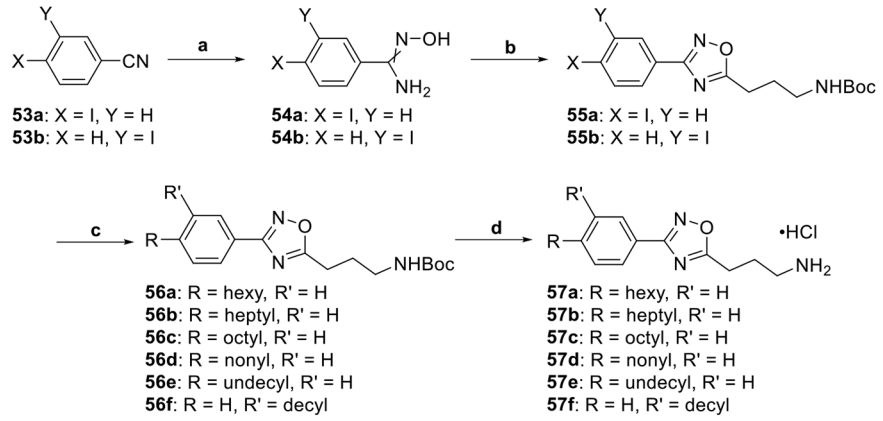
[a](a) Hydrazine hydrate, EtOH, 80 °C, 20 h, 67%; (b) (i) *N*-Boc-GABA, DIEA, HCTU, MeCN, rt, 18 h; (ii) DIEA, TsCl, MeCN, rt, 18 h, 79%; (c) (i) 1-decene, 9-BBN, THF, 66 °C, 1 h; (ii) aryl iodide, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, $KOH_{(aq)}$, THF, 66 °C, 4 h, 79%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 76%.



48a: n = 1
48b: n = 2
49a: n = 1
49b: n = 2
50a: n = 1
50b: n = 2
51a: n = 1, R = nonyl
51b: n = 2, R = octyl
52a: n = 1, R = nonyl
52b: n = 2, R = octyl

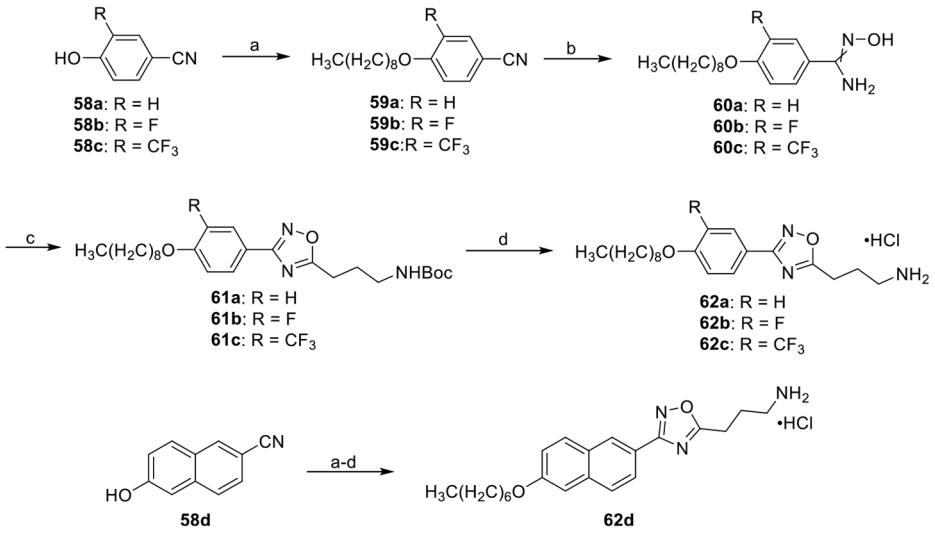
Scheme 7. Linker Group Homologation Series Synthesis[a]

[a](a) $NH_2OH{\cdot}HCl$, EtOH, 78 °C, 2 h, 41–62%; (b) *N*-Boc-GABA, DIEA, HCTU, DMF, 100 °C, 6 h, 68–76%; (c) (i) alkene, 9-BBN, THF, 66 °C, 1 h; (ii) aryl iodide, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, $KOH_{(aq)}$, THF, 66 °C, 4 h, 48–50%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 45–46%.



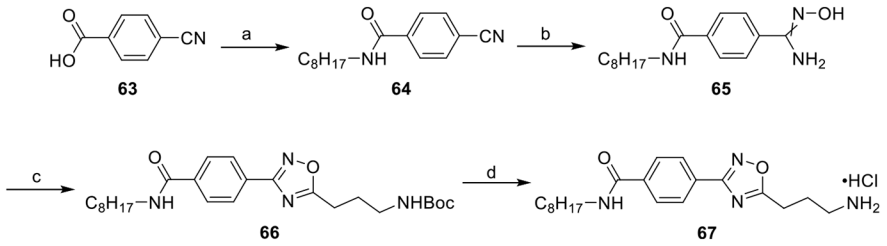
Scheme 8. Synthesis of Compounds 57a–f[a]

[a](a) $NH_2OH{\cdot}HCl$, EtOH, 78 °C, 2 h, 61–92%; (b) *N*-Boc-GABA, DIEA, HCTU, DMF, 100 °C, 6 h, 58–67%; (c) (i) alkene, 9-BBN, THF, 66 °C, 1 h; (ii) aryl iodide, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, $KOH_{(aq)}$, THF, 66 °C, 4 h, 48–93%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 27–74%.



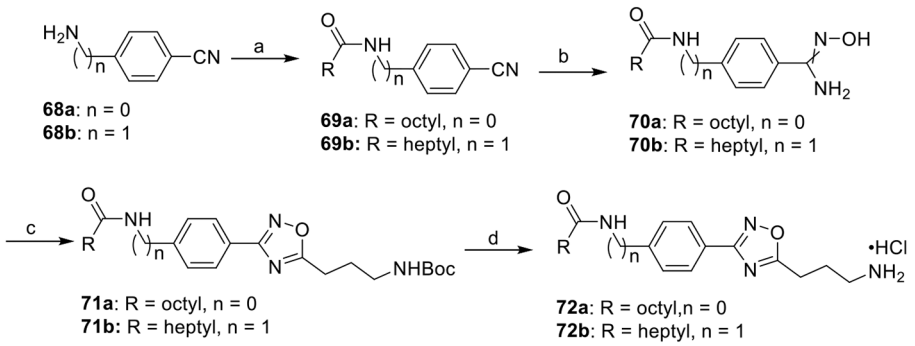
Scheme 9. Synthesis of Ether Tail Derivatives 62a–d[a]

[a](a) Alkyl bromide, K_2CO_3, THF, rt, 2 h, 77–99%; (b) $NH_2OH{\cdot}HCl$, EtOH, 78 °C, 2 h, 34–93%; (c) *N*-Boc-GABA, DIEA, HCTU, DMF, 100 °C, 6 h, 57–87%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 72–88%.



Scheme 10. Synthesis of the Benzamide Analogue 67[a]

[a](a) Octylamine, DIEA, HCTU, DCM, rt, 18 h, 94%; (b) $NH_2OH{\cdot}HCl$, EtOH, 78 °C, 2 h, 52%; (c) *N*-Boc-GABA, DIEA, HCTU, DMF, 100 °C, 6 h, 48%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 96%.

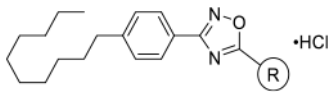


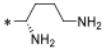
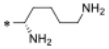
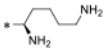
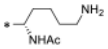
Scheme 11. Synthesis of Amide Derivatives 72a–b[a]

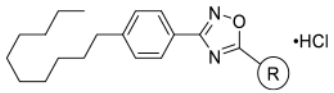
[a](a) Carboxylic acid, DIEA, HCTU, DCM, rt, 18 h, 84–89%; (b) $NH_2OH{\cdot}HCl$, EtOH, 78 °C, 2 h, 88–95%; (c) *N*-Boc-GABA, DIEA, HCTU, DMF, 100 °C, 6 h, 22–77%; (d) 4 M HCl/dioxane, DCM, rt, 2 h, 68–80%.

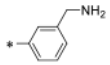
Table 1.

Spns2 Inhibitory Activity of Head Group Analogues[a]



Entry	Cmpd	R	% Inhibition	Entry	Cmpd	R	% Inhibition
1	**16a**		65 ± 3	20	**16t**		5 ± 7
2	**16b**		62 ± 1	21	**16u**		5 ± 4
3	**16c**		59 ± 3	22	**16v**		44 ± 3
4	**16d** (SLF1081851)		67 ± 1	23	**16w**		59 ± 4
5	**16e**		55 ± 3	24	**16x**		0 ± 6
6	**16f**		45 ± 0	25	**19a**		14 ± 10
7	**16g**		8 ± 9	26	**19b**		40 ± 4
8	**16h**		63 ± 0	27	**19c**		43 ± 3
9	**16i**		44 ± 4	28	**19d**		50 ± 1
10	**16j**		62 ± 2	29	**21**		40 ± 5

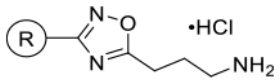


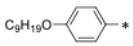
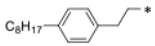
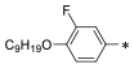
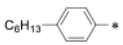
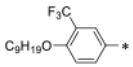
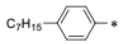
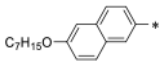
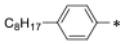
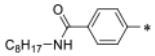
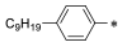
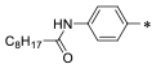
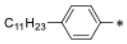
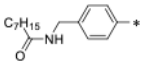
Entry	Cmpd	R	% Inhibition	Entry	Cmpd	R	% Inhibition
11	**16k**		26 ± 2	30	**22a**		3 ± 8
12	**16l**		12 ± 5	31	**22b**		0 ± 9
13	**16m**		21 ± 5	32	**22c**		2 ± 4
14	**16n**		66 ± 3	33	**22d**		21 ± 7
15	**16o**		19 ± 1	34	**22e**		2 ± 6
16	**16p**		38 ± 2	35	**22f**		0 ± 3
17	**16q**		29 ± 2	36	**23a**		5 ± 2
18	**16r**		13 ± 2	37	**23b**		61 ± 3
19	**16s**		2 ± 1				

[a]Spns2 inhibition is presented as percent inhibition relative to the control, during which no inhibitor is introduced. All compounds were assayed with a 2 μM inhibitor. Cell media were extracted, and S1P concentrations were measured by LC/MS. Measurements were performed in duplicate.

Table 2.

Spns2 Inhibitory Activity of the Tail and Homologation of the Linker Region[a]

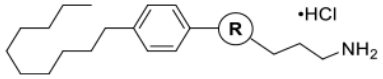


Cmpd	R	% Inhibition	Cmpd	R	% Inhibition
52a		34 ± 8	**62a**		49 ± 3
52b		40 ± 5	**62b**		50 ± 2
57a		55 ± 7	**62c**		24 ± 3
57b		52 ± 4	**62d**		8 ± 0
57c		70 ± 4	**67**		0 ± 14
57d		61 ± 4	**72a**		35 ± 5
57e		49 ± 1	**72b**		11 ± 6
57f		26 ± 4			

[a]Spns2 inhibition is presented as percent inhibition relative to the control, during which no inhibitor is introduced. All compounds were assayed with a 2 μM inhibitor. Cell media were extracted, and S1P concentrations were measured by LC/MS. Compound measurements were performed in duplicate.

Table 3.

Spns2 Inhibitory Activity of Heteroaromatic Linkers[a]



Cmpd	R	% Inhibition	Cmpd	R	% Inhibition
28		45 ± 4	**38**		45 ± 4
30		49 ± 4	**40**		44 ± 5
32		63 ± 3	**42**		50 ± 4
34		51 ± 3	**47**		59 ± 3

[a]Spns2 inhibition is presented as a percent inhibition relative to the control, during which no inhibitor is introduced. All compounds were assayed with a 2 μM inhibitor. Cell media were extracted, and S1P concentrations were measured by LCMS. Compound measurements were performed in duplicate.