Supporting Information

"Structural requirements and docking analysis of amidine-based sphingosine kinase 1 inhibitors containing oxadiazoles"

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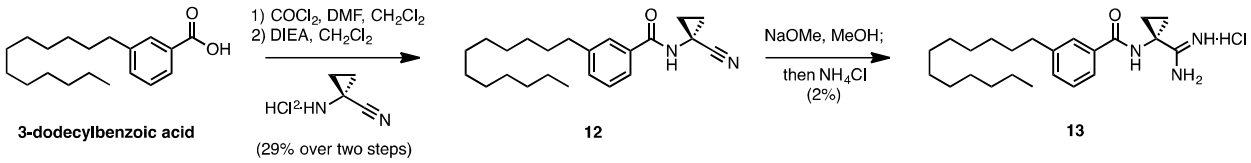
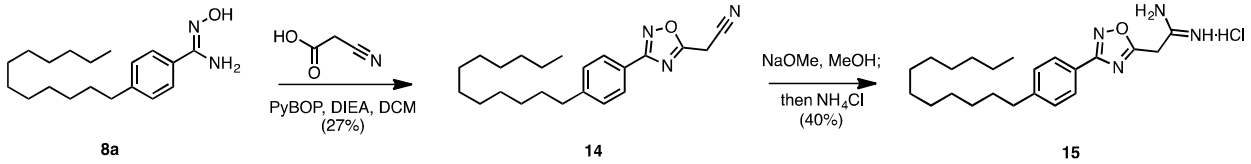
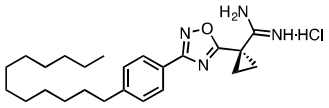
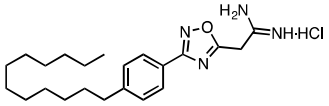


Scheme SI-1: Synthesis of **13**.



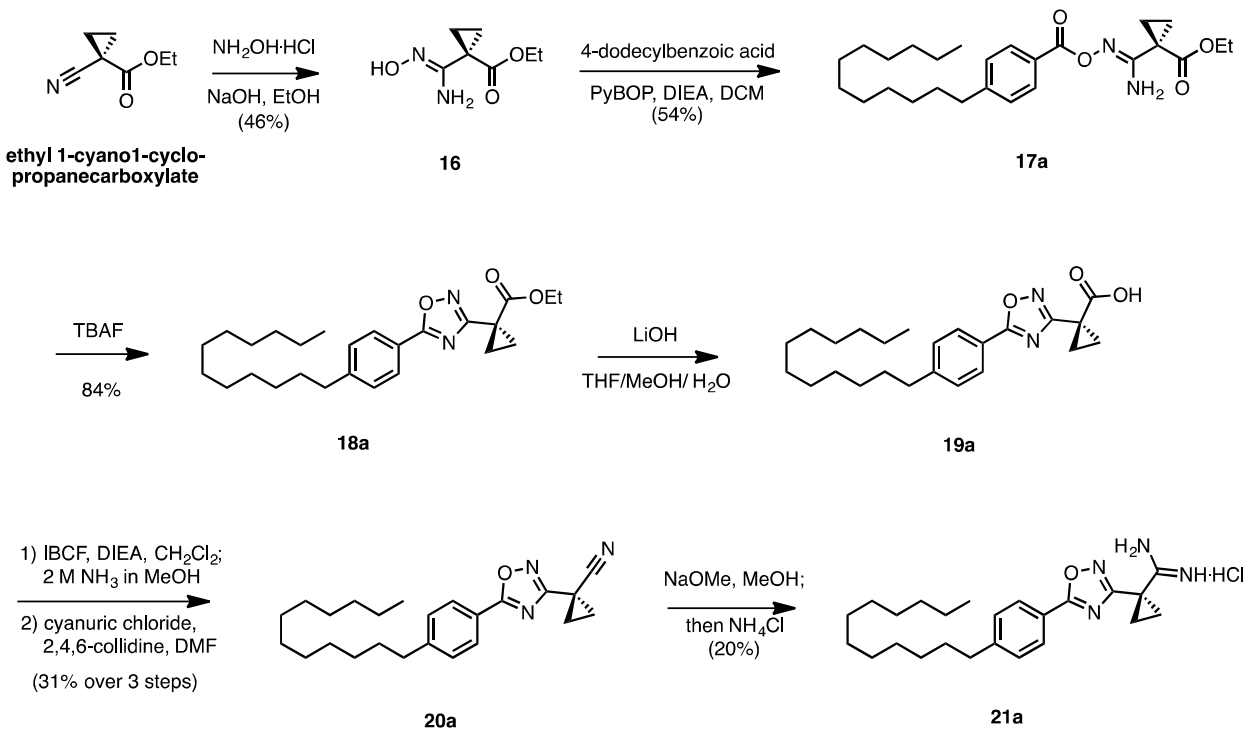
Scheme SI-2: Synthesis of **15.**

Table SI-1. Compound **15** compared to **11c**.

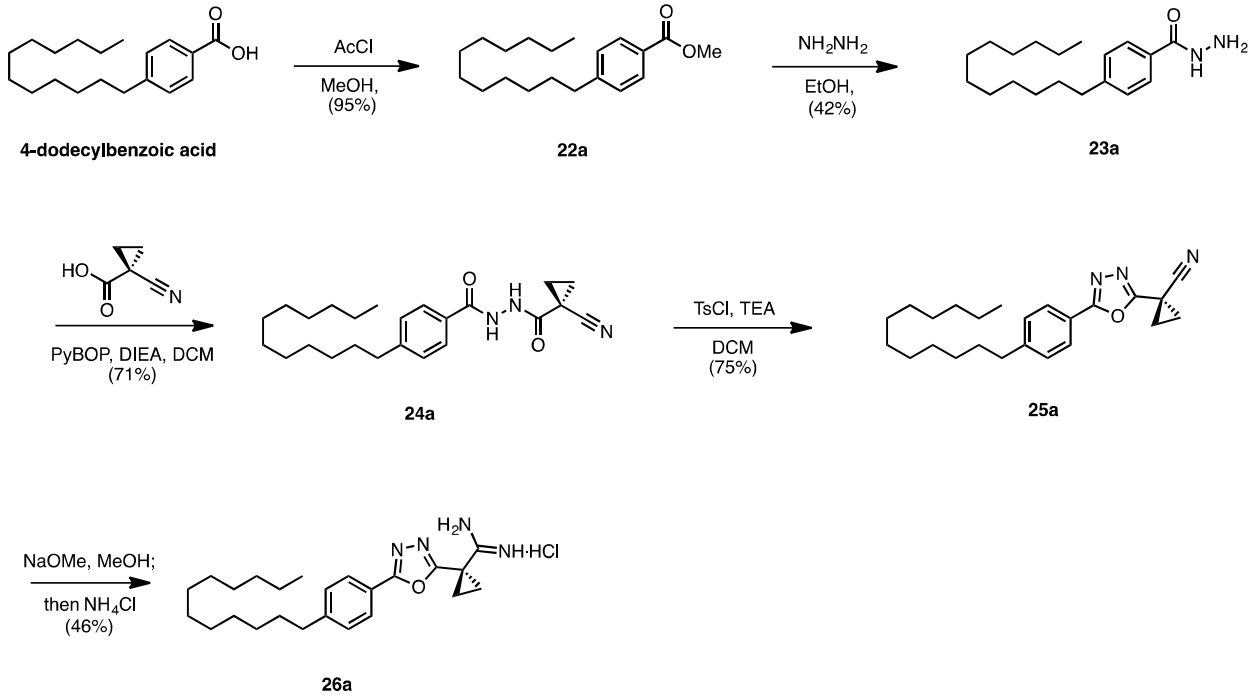
Compound	Structure	K_I (μM)[a] SphK1	SphK2	SphK1 Selectivity[b]
11c		0.32	6	40
15		13	15	2.3

[a] $K_I = [I] / (K_M / K_M - 1)$; K_M of sphingosine at SphK1 = 10 μM; K_M of sphingosine at SphK2 = 5 μM

[b] Selectivity = $(K_I / K_M)^{SphK2} / (K_I / K_M)^{SphK1}$



Scheme SI-3: Synthesis of 21a.



Scheme SI-4: Synthesis of 26a

EXPERIMENTAL METHODS

Sphingosine Kinase Assay. Human SphK1 and mouse SphK2 cDNAs were used to generate mutant baculoviruses that encoded these proteins. Infection of Sf9 insect cells with the viruses for 72 h resulted in >1000-fold increases in SphK activity in 10000g supernatant fluid from homogenized cell pellets. The enzyme assay conditions were exactly as described,[1] except infected Sf9 cell extract containing 2-3 μg of protein was used as a source of enzyme.

Pharmacokinetic Analysis. Groups of 8-12-week-old mice (strain C57BL/6J) were injected (intraperitoneally) with either compounds (at a dose of 10 mg/kg) or an equal volume of vehicle [2% solution of hydroxypropyl-β-cyclodextrin (Cargill Cavitron 82004)]. After injection, animals were bled at the specified time points [ASAP (as soon as possible) time points were 1-2 min after dosing]. Whole blood was processed immediately for LC-MS analysis as described below.

U937 Cell Culture Assay. U937 cells were grown according to a previously described literature procedure.[2] In general, cells were grown in RPMI 1640 medium enriched with L-glutamine, 10% penicillin and streptomycin, and 10% fetal bovine serum (FBS). Twenty-four hours before dosing with SphK inhibitors, the medium was replaced with medium containing 2% FBS. All cell cultures were grown at a stable temperature of 37 °C, and the SphK inhibitors were dosed for 2 h.

S1P Extraction and LCMS Quantification. Extraction protocols and LCMS procedures were adapted from a previously reported study.[3] Samples of pelleted cells (approximately 4 million) were taken up in 2 mL of 3:1 methanol/chloroform mixture and transferred to a capped glass vial. To this suspension was added 10 μL of internal standard solution containing 1 μM C17 S1P (purchased from Avanti Polar Lipids). The mixture was homogenized via sonication for 10 min

and immediately incubated at 48 °C for 16 h. After this time, the mixture was cooled to ambient temperature and 200 μL of 1 M KOH in methanol was added to the suspension. The samples were again sonicated and incubated at 37 °C for an additional 2 h. After this time, the samples were neutralized through the addition of 30 μL of glacial acetic acid and transferred to 2 mL microcentrifuge tubes. Samples were then centrifuge at 10000g for 10 min at 4 °C. The supernatant fluid was collected in a separate glass vial, and the pellets were discarded. The resulting solution was evaporated (to a solid) with a stream of nitrogen. Immediately prior to LCMS analysis, the solid material was taken up in 300 μL of methanol and centrifuged at 12000g for 12 min at 4 °C. An autosampler vial was loaded with 150 μL of the resulting supernatant for LCMS analysis. S1P analysis from cellular extracts was performed on an Applied Biosystems 4000 QTrap LC/MS/MS instrument. Chromatographic resolution of analytes was achieved with a Shimadzu LC-20AD system. A binary solvent gradient with a flow rate of 1 mL/min was used to separate sphingolipid analytes by reverse phase chromatography (Supelco Discovery C18 column; 50 mm, 2.1 mm (length, i.d.); 5 μm bead size). Mobile phase A consisted of water/methanol/formic acid (79:20:1), and mobile phase B consisted of methanol/formic acid (99:1). The run started with 100% A for 0.5 min. Solvent B was then increased linearly for 5.1 min to 100% of the total solvent composition and held at 100% for an additional 4.3 min. The column was finally reequilibrated to 100% for 0.1 min and held for an additional 1 min. The following analytes (and fragmentation patterns) were monitored simultaneously for identification. C17S1P (366.4, 250.4); S1P (380.4, 264.4).

General Synthetic Materials and Methods. All nonaqueous reactions were carried out in oven or flame-dried glassware under an argon or nitrogen atmosphere with dry solvents and magnetic stirring, unless otherwise stated. The argon and nitrogen were dried by passing through

a tube of Drierite. Anhydrous diethyl ether (Et_2O), chloroform ($CHCl_3$), Dimethyl sulfoxide (DMSO), toluene (PhMe), dichloromethane (CH_2Cl_2), methanol (MeOH), ethanol (EtOH), and tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) were purchased from Aldrich or VMR Chemicals and used as received. THF was dried over activated molecular sieves (4 Å) prior to use. All other reagents were purchased from Acros chemicals and Aldrich chemicals. Except as indicated otherwise, reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Whatman precoated silica gel plates. Flash chromatography was performed with the indicated solvents and Dynamic Adsorbents silica gel (particle size 0.023 – 0.040 mm). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian UnityInova 500/51 or Varian UnityInova 300/54 at 300K unless otherwise noted. Chemical shifts are reported in ppm (δ) values relative to the solvent as follows: $CDCl_3$ (δ 7.24 for proton and δ 77.0 for carbon NMR), DMSO-d_6 (δ 2.50 for proton and δ 39.5 for carbon NMR) CD_3OD (δ 3.31 for proton and δ 47.6 for carbon NMR). All high-resolution mass spectrometry was carried out by the Mass Spectrometry Laboratory in the School of Chemical Sciences at the University of Illinois Urbana-Champagne (Urbana, IL).

TLC Stains: KMnO4; 3 g $KMnO_4$ and 20 g K_2CO_3 in 300 mL water and 5 mL 5% NaOH. Seebach's Dip; To a solution of 25 g phosphomolybdic acid and 7.5 g cerium (IV) sulfate in 479 mL water was added 25 mL conc. sulfuric acid dropwise. Ninhydrin; 1.5 g ninhydrin in 5 mL AcOH and 500 mL 95% EtOH. All stains required TLC development on a hot plate set to 80 ºC.

Other abbreviations: 1,1'-bis(diphenylphosphino)ferrocene (dppf), 4-dimethylaminopyridine (DMAP), 9-borabicyclo[3.3.1]nonane (9-BBN), acetic acid (AcOH), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), di-tert-butyl dicarbonate (Boc_2O), ethyl acetate (EtOAc), N,Ndiisopropylethylamine (DIEA), tert-butanol (tBuOH), triethylamine

(TEA), trifluoroacetic acid (TFA), trifluoroacetic anhydride (TFAA), tetrabutylammonium fluoride (TBAF).

Liquid Chromatography and Mass Spectrometry for Evaluation of Chemical Purity. All compounds submitted for biological evaluation were determined to be > 95% pure by LCMS evaluation performed by the Mass Spectrometry Laboratory in the School of Chemical Sciences at the University of Illinois Urbana-Champagne (Urbana, IL). High performance liquid chromatography - mass spectrometry (LCMS) was carried out using an Agilent 2.1x50 mm C-18 column and a Micromass Q-tof Ultima mass spectrometer. Mobile phase A consisted of HPLC grade H2O and 0.01% TFA; mobile phase B consisted of MeCN and 0.01% TFA. LCMS identification and purity utilized a binary gradient starting with 90% A and 10% B and linearly increasing to 100% B over the course of 6 min, followed by an isocratic flow of 100% B for an additional 3 min. A flow rate of 0.5 mL / min was maintained throughout the HPLC method. The purity of all products was determined by integration of the total ion count (TIC) spectra and integration of the ultraviolet (UV) spectra at 214 nm. Retention times are abbreviated as t_R; mass to charge ratios are abbreviated as *m/z*.

General Procedure A: Conversion of Nitriles to Amidines. To a solution of a nitrile (1.0 eq.) in MeOH (0.10 M) was added a 0.5 M solution of sodium methoxide in MeOH (0.50 eq.) at rt and then heated to 50 ºC for 24 h. The intermediate imidate was detectable by TLC; however, being in equilibrium with the nitrile, full conversion does not occur. Ammonium chloride (4.0 eq.) was then added in one portion at that temperature and allowed to react until the imidate was completely consumed by TLC analysis. The reaction was then cooled to rt and evacuated to dryness to yield a crude solid. The solid was reconstituted with $CHCl_3$ and filtered through a fine glass fritted funnel in order to remove excess ammonium chloride, and the filtrate was again

evacuated to dryness. The material was then recrystallized in Et_2O to yield the pure amidine hydrochloride salt. The yields varied greatly depending upon substrate, because amidine formation is dependant upon the equilibrium ratio between nitrile and imidate established under the sodium methoxide conditions.

General Procedure B: PyBOP Mediated Couplings of Amines, Anilines, and Amide oximes to Carboxylic Acids. To a suspension of an amine or aniline (1.0 eq.), carboxylic acid (1.0 eq.), and PyBOP (1.0 eq.), in CH_2Cl_2 at rt was added DIEA (4.0 eq.) and was stirred for 4 h unless otherwise stated. The reaction was then evaporated to dryness and immediately purified by flash chromatography. In the case of amide oximes, a small amount of oxadiazole was formed in the reaction.

General Procedure C: Suzuki Coupling. To a solution of alkene (1.5 eq.) at rt was added a 0.5 M solution of 9-BBN in THF (1.5 eq.) and was stirred until consumption of the alkene was evident by TLC analysis (4 h unless otherwise stated). The reaction was then treated with 3 M NaOH, and diluted with THF (0.2 M relative to the starting alkene). The aryl bromide (1.0 eq.) and $Pd(PPh_3)_4$ were then sequentially added and the reaction was heated to reflux and was stirred for 4 h. The reaction was reduced to a dark oil, diluted with EtOAc and washed 1x with sat. $NaHCO_3$. The organic layer was then dried with $MgSO_4$, evaporated to a dark oil, and immediately purified by flash chromatography.

General Procedure D: Pinnick Oxidation. To a solution of an aldehyde (1.0 eq.),

NaH_2PO_4 (8.0 eq.), and 2-methyl-2-butene (10 eq.) in THF, water, and tBuOH (4:4:1) (0.04 M) at rt was added sodium chlorite (4 eq.) and was stirred for 1 h. The reaction was diluted with EtOAc (10x the volume of the reaction's mixture of solvents), and washed 3x with 1 N HCl (5x

the volume of the reaction's mixture of solvents). The organic layer was then dried with $MgSO_4$, and evaportated to a white solid. No further purification was necessary.

General procedure E: Deprotection of N-Boc and O-tBu Ester Protecting Groups. To a solution of either a N-Boc or O-tBu protecting group (1.0 eq.) in CH_2Cl_2 (0.2 M) at rt was added TFA (0.2 M) and the reaction was reacted until judged complete by TLC analysis (30 min unless otherwise stated). The reaction was then evaporated to dryness and taken on crude.

General Procedure F: Conversion of Nitriles to Amide Oximes. To a solution of nitrile (1 eq.) and hydroxylamine hydrochloride (5 eq.) in EtOH (0.2 M) was added TEA (10 eq.). The reaction was heated to 50 °C for 5 h. The EtOH was evaporated and the crude white solid was immediately purified via flash chromatography.

General Procedure G: Synthesis of 3,5-disubstituted-1,2,4-oxadiazoles Using Tetrabutylammonium Fluoride from Acylated Amide Oximes. To a solution of O-acyl amidoxime (1.0 eq.) in THF (0.1 M) at rt was added a 1.0 M solution of TBAF in THF (1.0 eq.) and was stirred for 1 h. The reaction was evaporated to dryness and immediately purified by flash chromatography.

General Prcedure H: **Coupling of Amines to N,N'-Di-Boc-1H-pyrazole-1-carboxamidine.** To a solution of amine (1.0 eq.) and N,N'-Di-Boc-1H-pyrazole-1-carboxamidine (1.1 eq.) in MeOH (0.1 M) was added a catalytic amount of DMAP followed by DIEA (3.0 eq.). The reaction was heated to 50 °C overnight, cooled to rt, and evaporated. The resulting solid was immediately purified via flash chromatography.

General Procedure I: **Esterification of Benzoic Acids to Methyl Benzoates.**

A 2 M solution of HCl in MeOH was prepared by adding acetyl chloride dropwise to MeOH (1.0 M relative to the benzoic acid) at 0 °C. This mixture was removed from the ice bath and

stirred for 15 min. A benzoic acid (1 equiv) was added neat and the mixture was heated to reflux for 14 h. The mixture was then cooled to room temperature and evaporated to a yellow oil and immediately purified by flash chromatography.

General Procedure J: Benzohydrazide Formation.

To a solution of a methyl benzoate (1 equiv) in EtOH (0.6 M) at room tempurature was added hydrazine (3 equiv), and the mixture was heated to reflux for 14 h. The mixture was then cooled to room temperature, evaporated to a white solid, and immediately purified by flash chromatography.

General Procedure K: Conversion of N-acylbenzohydrazides to 1,3,4-oxadiazoles.

To a solution of a N-acylbenzohydrazide (1.0 equiv) and *p*-toluenesulfonylchloride (2.0 equiv) in CH_2Cl_2 (0.2 M) was added TEA (3.0 equiv) dropwise. The mixture was allowed to stir at room temperature for 12 h. The reaction was evaporated to dryness and immediately purified by flash chromatography.

General Procedure L: Acid Chloride Formation. To a solution of a carboxylic acid (1.0 eq.) and DMF (0.05 eq.) in CH_2Cl_2 (0.1 M) at 0 °C was added oxalyl chloride (2.0 eq.) dropwise and let warm to rt. The reaction progresses to a yellow green color and after 3 h the reaction was evaporated to dryness, and then immediately purified by flash chromatography.

General Procedure M: Acid Chloride and Amine Coupling. To a solution of an acid chloride)1.0 eq). in CH_2Cl_2 (0.3 M) at rt was added DIEA (4.0 eq.) followed by an amine HCl salt (1.5 eq.) and the reaction was left stirring for 12 h. The reaction was then evaporated to dryness and immediately purified by flash chromatography.

General Procedure N: Williamson Ether Synthesis. To a solution of an alcohol (2 eq.) in DMF (0.3 M) at 0 ºC was added 60 % sodium hydride dispersed in mineral oil (2.0 eq.) at 0 ºC,

then let warm to rt, and then let react for 45 min. The alkyl bromide was then added in one portion and the reaction was stirred for 12 h. The reaction was quenched with sat. $NaHCO_3$ (100x the volume of DMF) and extracted into EtOAc (100x the volume of DMF). The organic layer was washed 3x with neat water (100x the volume of DMF), dried with Na_2SO_4, evaporated to a yellow oil, and immediately purified by flash chromatography.

4-decylbenzonitrile (7a). General procedure C was used to couple 1-decene (1.20 mL, 6.16 mmol) and 4-bromobenxonitrile (750 mg, 4.11 mmol) to yield the title product. 98%. Clear and colorless oil. R_f = 0.47 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1, 2H), 7.24 (d, *J* = 8.0, 2H), 2.62 (t, *J* = 7.6, 2H), 1.68 – 1.48 (m, 2H), 1.37 – 1.13 (m, 14H), 0.85 (t, *J* = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.77, 132.24, 129.38, 119.31, 109.68, 36.31, 32.12, 31.20, 29.81, 29.77, 29.65, 29.55, 29.40, 22.91, 14.33.

(*Z*)-4-decyl-*N*'-hydroxybenzimidamide (8a). General procedure F was used to convert **7a** (0.98 g, 4.03 mmol) to the title product. 90%. R_f = 0.48 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3, 2H), 7.20 (d, *J* = 8.3, 2H), 4.93 (s, 2H), 2.62 (t, *J* = 7.5, 2H), 1.72 – 1.50 (m, 2H), 1.42 – 1.14 (m, 14H), 0.88 (t, *J* = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.94, 145.42, 129.82, 128.91, 126.00, 36.00, 32.13, 31.54, 29.82, 29.72, 29.56, 29.51, 22.92, 14.36.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-4-decylbenzimidamide (9a). General procedure B was used to couple **8a** (150 mg, 0.54 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (60 mg, 0.54 mmol) to yield the title product. 91%. White solid. R_f = 0.32 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1, 2H), 7.19 (d, *J* = 8.1, 2H), 5.31 (s, 2H), 2.61 (t, *J* = 7.7, 2H), 1.78 (dd, *J* = 4.7, 8.3, 2H), 1.66 (dd, *J* = 4.7, 8.3, 2H), 1.58 (m, 2H), 1.24 (m, 14H), 0.86 (t, *J* = 6.2, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.82, 157.95, 146.89,

129.04, 127.88, 126.92, 118.98, 36.02, 32.11, 31.45, 29.80, 29.68, 29.54, 29.43, 22.91, 19.38, 14.36, 12.65.

1-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10a). General procedure G was used to convert **9a** (182 mg, 0.49 mmol) to the title product. 73%. White solid. R_f = 0.43 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2, 2H), 7.27 (d, *J* = 8.1, 2H), 2.65 (t, *J* = 7.5, 2H), 2.01 (s, 4H), 1.63 (m, 2H), 1.25 (m, 18H), 0.88 (t, *J* = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.84, 169.02, 147.23, 129.19, 127.70, 123.48, 117.79, 36.21, 32.15, 31.43, 29.88, 29.71, 29.60, 29.50, 23.33, 22.94, 19.50, 14.38, 9.10.

1-(3-(4-decylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11a). General procedure A was used to convert **10a** (126 mg, 0.36 mmol) to the title product. In this example, the solid was purified via flash chromatography. The hydrochloride salt was prepared by the dropwise addition of 2 M HCl in ether to the purified amidine. The ether was evaporated, reconstituted in ether, and again evacuated to dryness to yield the title product. 66%. Tan solid. R_f = 0.42 (15% MeOH in $CHCl_3$). ^{1}H NMR (500 MHz, DMSO) δ 9.54 (s, 2H), 9.39 (s, 2H), 7.87 (d, *J* = 5.8, 2H), 7.36 (d, *J* = 5.9, 2H), 2.62 (s, 2H), 1.94 (s, 2H), 1.83 (s, 2H), 1.56 (s, 2H), 1.23 (m, 14H), 0.83 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 177.73, 168.18, 166.02, 147.06, 129.70, 127.50, 123.50, 35.50, 31.74, 31.09, 29.43, 29.27, 29.14, 29.08, 22.61, 22.56, 18.67, 14.44. LCMS: t_R = 5.22; *m/z* = 369.2. HRMS *m/z* calcd for $C_{22}H_{33}N_4O$ (M + H), 369.2654; found 369.2644.

4-undecylbenzonitrile (7b). General procedure C was used to couple undecene (2.40 mL, 11.66 mmol) and 4-bromobenzonitrile (1.40 g, 7.70 mmol) to yield the title product. 99%. Colorless oil. R_f = 0.50 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2, 2H), 7.21 (d, *J* = 8.1, 2H), 2.60 (t, *J* = 7.5, 2H), 1.57 (m, 2H), 1.22 (m, 16H), 0.84 (t, *J* = 6.3,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.67, 132.17, 129.35, 119.15, 109.75, 36.28, 32.14, 31.19, 29.86, 29.78, 29.65, 29.58, 29.42, 22.91, 14.30.

(*Z*)-*N*'-hydroxy-4-undecylbenzimidamide (8b). General procedure F was used to convert **7b** (2.00 g, 7.77 mmol) to the title product. 95%. White solid. R_f = 0.51 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2, 2H), 7.19 (d, *J* = 8.2, 2H), 4.93 (s, 2H), 2.61 (t, *J* = 7.5 1H), 1.73 – 1.50 (m, 2H), 1.45 – 1.19 (m, 16H), 0.89 (t, *J* = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.90, 145.36, 129.91, 128.90, 126.01, 36.00, 32.16, 31.55, 29.84, 29.75, 29.59, 29.53, 22.93, 14.37.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-4-undecylbenzimidamide (9b). General procedure B was used to couple **8b** (150 mg, 0.52 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (57 mg, 0.52 mmol) to yield the title product. 82%. White solid. R_f = 0.63 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2, 2H), 7.20 (d, *J* = 8.1, 2H), 5.29 (s, 2H), 2.61 (t, *J* = 7.5, 2H), 1.79 (dd, *J* = 4.6, 8.4, 2H), 1.67 (dd, *J* = 4.8, 8.3, 2H), 1.58 (m, 2H), 1.24 (m, 16H), 0.87 (t, *J* = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.81, 157.94, 146.92, 130.21, 129.06, 127.88, 126.92, 118.99, 36.03, 32.14, 31.46, 29.85, 29.80, 29.69, 29.57, 29.43, 22.92, 19.39, 14.37, 12.66.

1-(3-(4-undecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10b). General procedure G was used to convert **9b** (163 mg, 0.43 mmol) to the title product. 81%. White solid. R_f = 0.64 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3, 2H), 7.27 (d, *J* = 8.3, 2H), 2.65 (t, *J* = 7.5, 2H), 2.02 (d, *J* = 7.9, 4H), 1.63 (m, 2H), 1.28 (m, 16H), 0.88 (t, *J* = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.85, 169.01, 147.24, 129.18, 127.69, 123.51, 117.78, 36.20, 32.15, 31.43, 29.87, 29.71, 29.58, 29.50, 22.93, 20.89, 18.90, 14.37, 9.08.

1-(3-(4-undecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11b). General procedure A was used to convert **10b** (127 mg, 0.35 mmol) to the title product. In this example, the solid was purified via flash chromatography. The hydrochloride salt was prepared by the dropwise addition of 2 M HCl in ether to the purified amidine. The ether was evaporated, reconstituted in ether, and again evacuated to dryness to yield the title product. 32%. Tan solid. R_f = 0.49 (15% MeOH in $CHCl_3$). ^{1}H NMR (500 MHz, DMSO) δ 9.56 (s, 2H), 9.42 (s, 2H), 7.88 (d, *J* = 7.5, 2H), 7.37 (d, *J* = 7.5, 2H), 2.62 (t, *J* = 7.1, 3H), 1.95 (s, 2H), 1.85 (s, 2H), 1.57 (s, 2H), 1.24 (m, 16H), 0.83 (t, *J* = 6.4, 3H). ^{13}C NMR (126 MHz, DMSO) δ 177.72, 168.18, 166.04, 147.05, 129.68, 127.50, 123.50, 35.49, 31.74, 31.08, 29.44, 29.27, 29.16, 29.07, 22.60, 22.55, 18.66, 14.42. LCMS: t_R = 5.22, 6.08; *m/z* = 383.2. HRMS *m/z* calcd for $C_{23}H_{35}N_4O$ (M + H), 383.2811; found 383.2805.

4-dodecylbenzonitrile (7c). General procedure C was used to couple 1-dodecene (3.64 mL, 16.4 mmol) and 4-iodobenzonitrile (2.5 g, 10.9 mmol) to yield the title product. 99%. Colorless oil. R_f = 0.52 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1, 2H), 7.26 (d, *J* = 8.1, 2H), 2.71 – 2.59 (m, 2H), 1.60 (m, 2H), 1.38 – 1.16 (m, 18H), 0.88 (t, *J* = 6.7, 3H).

(*Z*)-*4*-dodecyl-N'-hydroxybenzimidamide (8c). General procedure F was used to convert **7c** (1.17 g, 4.31 mmol) to the title product. 86%. White solid. R_f= 0.52 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.3, 2H), 7.20 (d, *J* = 8.3, 2H), 4.88 (s, 2H), 2.61 (t, *J* = 7.5, 2H), 1.60 (m, 2H), 1.25 (m, 18H), 0.88 (t, *J* = 6.7, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.57, 145.82, 128.78, 128.44, 126.04, 35.81, 31.95, 31.28, 29.71, 29.70, 29.67, 29.63, 29.52, 29.39, 29.34, 22.72, 14.16.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-4-dodecylbenzimidamide (9c). General procedure B was used to couple **8c** (200 mg, 0.66 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (311 mg, 0.60 mmol) to yield the title product. 80%. White solid. R_f = 0.21 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0, 2H), 7.21 (d, *J* = 7.9, 2H), 5.28 (s, 2H), 2.62 (t, *J* = 7.6, 2H), 1.80 (dd, *J* = 4.8, 8.2, 2H), 1.68 (dd, *J* = 4.6, 8.4, 2H), 1.64 – 1.52 (m, 2H), 1.25 (m, 18H), 0.87 (t, *J* = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.81, 157.93, 146.98, 129.09, 127.85, 126.93, 118.99, 36.03, 32.14, 31.47, 29.87, 29.81, 29.69, 29.58, 29.43, 22.92, 19.41, 14.37, 12.65.

1-(3-(4-dodecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10c). General procedure G was used to convert **9c** (190 mg, 0.48 mmol) to the title product. 99%. White solid. R_f = 0.56 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2, 2H), 7.27 (d, *J* = 8.1, 2H), 2.65 (t, *J* = 7.5, 2H), 2.01 (s, 4H), 1.63 (m, 2H), 1.25 (m, 18H), 0.88 (t, *J* = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.83, 169.02, 147.25, 129.19, 127.70, 123.48, 117.80, 36.21, 32.15, 31.45, 29.88, 29.71, 29.60, 29.50, 23.33, 22.94, 20.90, 14.38, 9.10.

1-(3-(4-dodecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride. (11c). General procedure A was used to convert **10c** (190 mg, 0.50 mmol) to the crude amidine. In this example, the solid was purified via flash chromatography. The hydrochloride salt was prepared by the dropwise addition of 2 M HCl in ether to the purified amidine. The ether was evaporated, reconstituted in ether, and again evacuated to dryness to yield the title product. 50%. Yellow solid. R_f = 0.28 (15% MeOH in $CHCl_3$). ^{1}H NMR (500 MHz, DMSO) δ 9.56 (s, 1H), 9.43 (s, 1H), 7.88 (d, J = 7.1, 2H), 7.37 (d, J = 7.2, 2H), 2.62 (m, 2H), 1.96 (s, 2H), 1.84 (s, 2H), 1.57 (s, 2H), 1.24 (m, 18H), 0.83 (t, J = 5.9, 2H). ^{13}C NMR (126 MHz, DMSO) δ 177.73, 168.17, 166.03, 147.04, 129.67, 127.50, 123.51, 35.50, 31.75, 31.09,

29.46, 29.27, 29.17, 29.08, 22.60, 22.56, 18.66, 14.42. LCMS: t_R = 6.65; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O$ (M + H), 397.2967; found 397.2967.

4-tridecylbenzonitrile (7d). General procedure C was used to couple 1-tridecene (1.95 mL, 8.24 mmol) and 4-bromobenzonitrile (1.0 g, 5.49 mmol) to yield the title product. 97%. Clear and colorless oil. R_f = 0.56 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, J = 8.0, 2H), 7.26 (d, J = 8.0, 2H), 2.65 (t, J = 7.7, 2H), 1.71 – 1.51 (m, 2H), 1.41 – 1.17 (m, 20H), 0.87 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.67, 132.15, 129.26, 119.24, 109.54, 36.20, 32.01, 31.06, 29.74, 29.61, 29.49, 29.27, 22.78, 14.20.

(*Z*)-*N*'-hydroxy-4-tridecylbenzimidamide (8d). General procedure F was used to convert **7d** (1.53 g, 5.36 mmol) to the title product. 90%. White solid. R_f = 0.50 (40% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl3) δ 7.54 (d, J = 8.0, 2H), 7.20 (d, J = 8.1, 2H), 4.87 (s, 2H), 2.62 (t, J = 7.7, 2H), 1.71 – 1.51 (m, 2H), 1.39 – 1.16 (m, 20H), 0.88 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.79, 145.27, 129.91, 128.82, 125.85, 35.91, 32.07, 31.46, 29.81, 29.64, 29.50, 29.42, 25.45, 22.84, 14.27, 0.81.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-4-tridecylbenzimidamide (9d). General procedure B was used to couple **8d** (193 mg, 0.61 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (67 mg, 0.61 mmol) to yielr the title product. 82%. White solid. R_f = 0.20 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3, 2H), 7.22 (d, J = 8.2, 2H), 5.24 (s, 2H), 2.56 (t, J = 7.7, 2H), 1.81 (dd, J = 4.6, 8.4, 2H), 1.68 (dd, J = 4.6, 8.4, 2H), 1.65 – 1.52 (m, 2H), 1.39 – 1.17 (m, 20H), 0.87 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.66, 157.78, 146.81, 128.94, 127.76, 126.79, 118.86, 35.90, 32.01, 31.32, 29.75, 29.56, 29.45, 29.30, 22.79, 19.25, 14.22, 12.53.

1-(3-(4-tridecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10d). General procedure G was used to convert **9d** (205 mg, 0.50 mmol) to the title product. 88%. White solid. R_f = 0.59 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl3) δ 7.93 (d, J = 8.1, 2H), 7.27 (d, J = 8.1, 2H), 2.56 (t, J = 7.7, 2H), 2.00 (s, 4H), 1.70 – 1.51 (m, 2H), 1.41 – 1.19 (m, 20H), 0.88 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.70, 168.84, 147.05, 129.01, 127.52, 123.35, 117.61, 36.03, 32.00, 31.27, 29.73, 29.65, 29.55, 29.44, 29.34, 22.77, 20.72, 14.20, 8.91.

1-(3-(4-tridecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11d). General procedure A was used to convert **10d** (198 mg, 0.50 mmol) to the title product. 36%. Yellow solid. R_f = 0.23 (15% MeOH in $CHCl_3$). ^{1}H NMR (600 MHz, DMSO) δ 9.56 (s, 2H), 9.44 (s, 2H), 7.88 (d, J = 8.1, 2H), 7.37 (d, J = 8.1, 2H), 2.57 (t, J = 7.6, 2H), 2.03 – 1.78 (m, 4H), 1.70 – 1.48 (m, 2H), 1.36 – 1.12 (m, 20H), 0.84 (t, J = 6.6, 3H). ^{13}C NMR (151 MHz, DMSO) δ 177.09, 167.59, 165.51, 146.43, 129.07, 126.91, 122.93, 34.92, 31.15, 30.47, 28.89, 28.86, 28.82, 28.67, 28.56, 28.48, 21.99, 21.95, 18.12, 13.82. LCMS: t_R = 7.44 *m/z* = 411.3. HRMS *m/z* calcd for $C_{25}H_{39}N_4O$ (M + H), 411.3124; found 411.3119.

3-decylbenzonitrile (7e). General procedure C was used to couple 1-decene (1.6 mL, 8.33 mmol) and 3-bromobenzonitrile (1.0 g, 5.56 mmol) to yield the title product. 99%. Clear and colorless oil. R_f = 0.35 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.30 (m, 4H), 2.62 (t, J = 7.7, 2H), 1.71 – 1.54 (m, 2H), 1.40 – 1.18 (m, 14H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.35, 133.13, 132.04, 129.57, 129.11, 112.34, 35.63, 32.01, 31.22, 29.69, 29.65, 29.52, 29.43, 29.23, 22.80, 14.24.

(*Z*)-3-decyl-*N*'-hydroxybenzimidamide (8e). General procedure F was used to convert **7e** (1.38 g, 5.67 mmol) to the title product. 89%. White solid. R_f = 0.48 (40% EtOAc in hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.41 (m, 2H), 7.37 – 7.19 (m, 2H), 4.97 (s, 2H), 2.57 (t, J = 7.7, 2H), 1.72 – 1.56 (m, 2H), 1.48 – 1.09 (m, 14H), 0.91 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.90, 143.44, 132.44, 130.09, 128.54, 126.05, 123.32, 35.99, 31.99, 31.54, 29.70, 29.60, 29.42, 22.77, 14.20.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-3-decylbenzimidamide (8e). General procedure B was used to couple **8e** (178 mg, 0.64 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (72 mg, 0.64 mmol) to yield the title product. 64%. White solid. R_f = 0.25 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.40 (m, 2H), 7.32 – 7.25 (m, 2H), 5.34 (s, 2H), 2.59 (t, J = 7.7, 2H), 1.77 (dd, J = 4.6, 8.4, 2H), 1.65 (dd, J = 4.8, 8.2, 2H), 1.62 – 1.52 (m, 2H), 1.40 – 1.13 (m, 14H), 0.86 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.66, 157.97, 143.76, 131.45, 130.34, 128.68, 126.89, 124.05, 118.75, 35.82, 31.92, 31.42, 29.62, 29.50, 29.34, 22.71, 19.20, 14.16, 12.45.

1-(3-(3-decylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10e). General procedure G was used to convert **9e** (152 mg, 0.41 mmol) to the title product. 72%. White solid. R_f = 0.63 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.41 – 7.28 (m, 2H), 2.65 (t, J = 7.7, 2H), 2.01 (s, 4H), 1.71 – 1.56 (m, 2H), 1.42 – 1.19 (m, 14H), 0.87 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.78, 168.98, 143.86, 131.81, 128.85, 127.46, 125.85, 124.93, 117.59, 35.87, 31.96, 31.47, 29.65, 29.54, 29.36, 22.75, 20.73, 14.18, 8.91.

1-(3-(3-decylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11e). General procedure A was used to convert **10e** (170 mg, 0.48 mmol) to the title product. 35%. Yellow solid. R_f = 0.31 (15% MeOH in $CHCl_3$). ^{1}H NMR (300 MHz, DMSO) δ 9.57 (s, 2H), 9.43 (s, 2H), 7.89 – 7.72 (m, 2H), 7.54 – 7.36 (m, 2H), 2.66 (t, J = 7.4, 2H), 2.03 – 1.80 (m, 4H), 1.67 – 1.48 (m, 2H), 1.37 – 1.12 (m, 14H), 0.84 (t, J = 6.3, 3H). ^{13}C NMR (151 MHz,

DMSO) δ 177.20, 167.74, 165.58, 143.52, 131.73, 129.19, 126.62, 125.50, 124.43, 34.79, 31.18, 30.86, 28.88, 28.87, 28.72, 28.57, 28.50, 21.99, 18.19, 13.86. LCMS: t_R = 5.44; *m/z* = 369.2. HRMS *m/z* calcd for $C_{22}H_{33}N_4O$ (M + H), 369.2654; found 369.2656.

3-undecylbenzonitrile 7f). General procedure C was used to couple 1-undecene (1.71 mL, 8.33 mmol) and 3-bromobenzonitrile (1.0 g, 5.56 mmol) to yield the title product. 99%. Clear and colorless oil. R_f = 0.38 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.30 (m, 4H), 2.63 (t, J = 7.7, 2H), 1.70 – 1.48 (m, 2H), 1.47 – 1.15 (m, 16H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.35, 133.14, 132.06, 129.57, 129.12, 119.27, 112.35, 35.63, 32.03, 31.23, 29.74, 29.65, 29.53, 29.46, 29.24, 22.81, 14.25.

(*Z*)-*N*'-hydroxy-3-undecylbenzimidamide (8f). General procedure F was used to convert **7f** (1.41 g, 5.5 mmol) to the title product. 90%. White solid. R_f = 0.49 (40% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7, 2H), 7.35 – 7.20 (m, 2H), 4.92 (s, 2H), 2.57 (t, J = 7.7, 2H), 1.72 – 1.51 (m, 2H), 1.44 – 1.06 (m, 16H), 0.88 (d, J = 6.9, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.90, 143.56, 132.49, 130.21, 128.63, 126.05, 123.32, 36.04, 32.05, 31.59, 29.73, 29.65, 29.46, 22.82, 14.25.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-3-undecylbenzimidamide (9f). General procedure B was used to couple **8f** (192 mg, 0.66 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (73 mg, 0.66 mmol) to yield the title product. 64%. White solid. R_f = 0.24 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.46 – 7.39 (m, 1H), 7.29 – 7.22 (m, 2H), 5.38 (s, 2H), 2.49 (t, J = 7.7, 2H), 1.80 – 1.69 (m, 2H), 1.68 – 1.47 (m, 5H), 1.38 – 1.01 (m, 16H), 0.85 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.61, 157.94, 143.64, 131.34, 130.28, 128.58, 126.82, 124.00, 118.67, 35.75, 31.88, 31.36, 29.55, 29.44, 29.29, 22.65, 19.12, 14.10, 12.38.

1-(3-(3-undecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10f). General procedure G was used to convert **9f** (163 mg, 0.43 mmol) to the title product. 75%. White solid. R_f = 0.56 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.41 – 7.28 (m, 2H), 2.66 (t, J = 7.7, 2H), 2.02 (s, 4H), 1.74 – 1.58 (m, 2H), 1.48 – 1.17 (m, 16H), 0.88 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.79, 169.02, 143.91, 131.85, 128.89, 127.51, 125.87, 124.96, 117.63, 35.91, 32.00, 31.51, 29.71, 29.57, 29.39, 22.78, 20.75, 14.21, 8.94.

1-(3-(3-undecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11f). General procedure A was used to convert **10f** (181 mg, 0.50 mmol) to the title product. 48%. Yellow solid. R_f = 0.35 (15% MeOH in $CHCl_3$). ^{1}H NMR (600 MHz, DMSO) δ 9.59 (s, 2H), 9.49 (s, 2H), 7.86 – 7.76 (m, 2H), 7.51 – 7.41 (m, 2H), 2.67 (t, J = 7.5, 2H), 2.04 – 1.96 (m, 2H), 1.90 – 1.84 (m, 2H), 1.65 – 1.53 (m, 2H), 1.36 – 1.18 (m, 16H), 0.85 (t, J = 6.9, 3H). ^{13}C NMR (151 MHz, DMSO) δ 177.23, 167.77, 165.60, 143.55, 131.74, 129.20, 126.64, 125.52, 124.45, 34.81, 31.21, 30.88, 28.94, 28.90, 28.75, 28.62, 28.53, 22.03, 22.02, 18.20, 13.88. LCMS: t_R = 5.72; *m/z* = 383.2. HRMS *m/z* calcd for $C_{23}H_{35}N_4O$ (M + H), 383.2811; found 383.2813.

3-dodecylbenzonitrile (7g). General Procedure C was used to couple 1-dodecene (1.83 mL, 8.24 mmol) and 3-bromobenzonitrile (1.0 g, 5.49 mmol) to yield the title product. 98%. Clear and colorless oil. R_f = 0.40 (5% EtoAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.32 (m, 2H), 2.63 (t, J = 6.0, 7.5, 2H), 1.73 – 1.48 (m, 2H), 1.41 – 1.13 (m, 18H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.42, 133.21, 132.14, 129.64, 129.18, 119.34, 112.41, 77.65, 77.23, 76.81, 35.72, 32.12, 31.31, 29.84, 29.73, 29.62, 29.55, 29.32, 22.90, 14.34.

3-dodecyl-*N*'-hydroxybenzimidamide (8g). General Procedure F was used to convert **7g** (1.4 g, 5.16 mmol) to the title product. 25%. White solid. R_f = 0.60 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 2H), 7.35 – 7.19 (m, 2H), 4.92 (s, 2H), 2.62 (t, J = 7.5, 2H), 1.71 – 1.55 (m, 2H), 1.44 – 1.20 (m, 18H), 0.89 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.97, 143.63, 132.56, 130.27, 128.69, 126.12, 123.39, 36.12, 32.11, 31.66, 29.87, 29.71, 29.55, 22.89, 14.33.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-3-dodecylbenzimidamide (9g). General Procedure B was used to couple **8g** (438 mg, 1.43 mmol) and 1-cyano-1-cyclpropanecarboxylic acid (159 mg, 1.43 mmol) to yield the title product. 25%. White solid. R_f = 0.25 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.43 (m, 2H), 7.38 – 7.27 (m, 2H), 5.25 (s, 2H), 2.62 (t, J = 7.5, 2H), 1.82 (dd, J = 3.1, 6.5, 2H), 1.69 (dd, J = 4.6, 8.4, 2H), 1.66 – 1.53 (m, 2H), 1.41 – 1.14 (m, 18H), 0.87 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.88, 158.08, 144.06, 131.71, 130.54, 128.92, 127.07, 124.21, 118.94, 36.01, 32.11, 31.60, 29.85, 29.77, 29.67, 29.51, 22.88, 19.38, 14.32, 12.62.

1-(3-(3-dodecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10g). General Procedure G was used to convert **9g** (100 mg, 0.25 mmol) to the title product. 69%. R_f = 0.64 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.81 (m, 2H), 7.45 – 7.29 (m, 2H), 2.83 – 2.46 (m, 2H), 2.03 (s, 4H), 1.64 (bs, 2H), 1.41 – 1.19 (m, 18H), 0.88 (t, J = 6.5, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.21, 169.36, 144.15, 132.18, 131.97, 129.09, 127.65, 125.11, 117.74, 36.02, 34.95, 33.36, 32.93, 32.65, 32.38, 32.11, 31.62, 29.85, 29.68, 29.54, 27.76, 27.06, 25.91, 24.53, 24.24, 22.88, 20.85, 20.03, 18.76, 14.32, 9.05.

1-(3-(3-dodecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11g). General procedure A was used to convert **10g** (66 mg, 0.17 mmol) to the

title product. In this example, the solid was purified via flash chromatography (15 % MeOH in $CHCl_3$). The hydrochloride salt was prepared by the dropwise addition of 2 M HCl in ether to the purified amidine. The ether was evaporated, reconstituted in ether, and again evacuated to dryness to yield the title product. Yellow solid. 19%. ^{1}H NMR (600 MHz, DMSO) δ 9.54 (s, 2H), 9.41 (s, 2H), 7.88 – 7.74 (m, 2H), 7.52 – 7.39 (m, 2H), 2.66 (s, 2H), 1.97 (s, 2H), 1.86 (s, 2H), 1.58 (s, 2H), 1.41 – 1.09 (m, 18H), 0.84 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 177.79, 168.30, 166.11, 144.09, 132.31, 129.77, 127.19, 126.06, 125.01, 35.38, 31.77, 31.46, 29.51, 29.50, 29.48, 29.46, 29.31, 29.18, 29.10, 22.58, 18.77, 14.45. LCMS: t_R = 5.44; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O_2$ (M + H), 397.2967; found 397.2963.

3-tridecylbenzonitrile (7h). General procedure C was used to couple 1-tridecene (1.95 mL, 8.24 mmol) and 3-bromobenzonitrile (1.0 g, 5.49 mmol) to yield the title product. 97%. Clear and colorless oil. R_f = 0.55 (5% EtOAcin hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.29 (m, 4H), 2.58 (t, J = 7.7, 2H), 1.69 – 1.52 (m, 2H), 1.51 – 1.11 (m, 20H), 0.87 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.35, 133.13, 132.05, 129.56, 129.10, 119.25, 112.34, 35.63, 32.04, 31.22, 29.77, 29.65, 29.53, 29.48, 29.24, 22.82, 14.24.

(*Z*)-*N*'-hydroxy-3-tridecylbenzimidamide (8h). General procedure F was used to convert **7h** (1.53 g, 5.36 mmol) to the title product. 90%. White solid. R_f = 0.56 (40% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.35 – 7.19 (m, 2H), 4.89 (s, 2H), 2.54 (t, J = 7.7, 2H), 1.75 – 1.49 (m, 2H), 1.46 – 1.04 (m, 20H), 0.88 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.98, 143.63, 132.51, 130.26, 128.66, 126.03, 123.29, 36.06, 32.06, 31.60, 29.81, 29.65, 29.47, 22.83, 14.26.

(*Z*)-*N*'-((1-cyanocyclopropanecarbonyl)oxy)-3-tridecylbenzimidamide (9h). General procedure B was used to couple **8h** (193 mg, 0.61 mmol) and 1-cyano-1-cyclopropanecarboxylic

acid (67 mg, .61 mmol) to yield the title product. 79%. White solid. R_f = 0.24 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.43 (m, 2H), 7.38 – 7.28 (m, 2H), 5.26 (s, 2H), 2.61 (t, J = 7.7, 2H), 1.81 (dd, J = 3.1, 6.6, 2H), 1.69 (dd, J = 2.9, 6.7, 2H), 1.65 – 1.51 (m, 2H), 1.25 (s, 20H), 0.87 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.68, 158.00, 143.96, 131.61, 130.46, 128.83, 126.98, 124.12, 118.86, 35.93, 32.03, 31.52, 29.77, 29.69, 29.59, 29.47, 22.80, 19.30, 14.25, 12.53.

1-(3-(3-tridecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarbonitrile (10h). General procedure G was used to convert **9h** (196 mg, 0.48 mmol) to the title product. 86%. White solid. R_f = 0.65 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.79 (m, 2H), 7.41 – 7.27 (m, 2H), 2.65 (t, J = 7.7, 2H), 2.01 (m, 4H), 1.71 – 1.56 (m, 2H), 1.44 – 1.16 (m, 20H), 0.88 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.78, 168.99, 143.89, 131.82, 128.86, 127.48, 125.87, 124.95, 117.61, 35.89, 32.00, 31.49, 29.74, 29.57, 29.43, 29.38, 22.77, 20.73, 14.20, 8.93.

1-(3-(3-tridecylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropanecarboximidamide hydrochloride (11h). General procedure A was used to convert **10h** (192 mg, 0.49 mmol) to the title product. 54%. Yellow solid. R_f = 0.27 (15% MeOH in $CHCl_3$) ^{1}H NMR (600 MHz, DMSO) δ 9.55 (s, 2H), 9.46 (s, 2H), 7.88 – 7.69 (m, 2H), 7.56 – 7.32 (m, 2H), 2.57 (t, J = 7.7, 2H), 2.05 – 1.80 (m, 4H), 1.66 – 1.48 (m, 2H), 1.38 – 1.11 (m, 20H), 0.83 (t, J = 6.7, 3H). ^{13}C NMR (151 MHz, DMSO) δ 176.93, 167.47, 165.31, 143.25, 131.51, 129.00, 126.37, 125.24, 124.20, 34.59, 30.96, 30.62, 28.67, 28.49, 28.36, 28.28, 21.77, 18.05, 13.68. LCMS: t_R = 7.44; *m/z* = 411.3. HRMS *m/z* calcd for $C_{25}H_{39}N_4O$ (M + H), 411.3124; found 411.3112.

***N*-(1-cyanocyclopropyl)-3-dodecylbenzamide (12).** General procedure L was used to convert 3-dodecylbenzoic acid (7.34 mmol) to the corresponding acyl chloride. After standard

work-up procedures, the acyl chloride was coupled to 1-amino-1-cyclopropylcarbonitrile hydrochloride (1.0 g, 3.0 mmol) using general procedure M. 76%. White solid. R_f = 0.48 (30% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.34 (m, 2H), 6.78 (m,), 2.68 – 2.56 (m, 2H), 1.68 – 1.50 (m, 4H), 1.41 – 1.11 (m, 20H), 0.88 (t, J = 5.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.43, 143.92, 132.72, 129.04, 128.72, 127.59, 124.55, 120.28, 35.91, 32.06, 31.51, 29.78, 29.47, 22.84, 21.01, 20.41, 17.05, 14.26.

***N*-(1-carbamimidoylcyclopropyl)-3-dodecylbenzamide hydrochloride (13).** General procedure A was used to convert **12** (2.15 mmol) to the title product. 9%. Yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 9.10 (s, 1H), 8.75 (s, 2H), 8.54 (s, 2H), 7.75 – 7.62 (m, 2H), 7.40 – 7.33 (m, 3H), 2.54 (t, J = 7.6, 2H), 1.66 (dd, J = 5.7, 7.4, 2H), 1.62 – 1.50 (m, 2H), 1.38 (dd, J = 5.8, 7.7, 2H), 1.35 – 1.16 (m, 18H), 0.83 (t, J = 6.7, 3H). ^{13}C NMR (126 MHz, DMSO) δ 172.14, 167.98, 144.33, 132.98, 129.56, 128.84, 127.88, 124.97, 35.97, 32.20, 31.58, 29.98, 29.76, 23.04, 21.41, 20.72, 18.01, 14.45. LCMS: t_R = 5.44; *m/z* = 372.3. HRMS *m/z* calcd for $C_{23}H_{38}N_3O$ (M + H), 372.3015; found 372.3017.

2-(3-(4-dodecylphenyl)-1,2,4-oxadiazol-5-yl)acetonitrile (14).

General procedure B was used to couple **8a** (200 mg, 0.66 mmol) and cyanoacetic acid (51 mg, 0.60 mmol) to yield the oxadiazole product. 27%. White solid. R_f = 0.50 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2, 2H), 7.30 (d, *J* = 8.2, 2H), 4.12 (s, 2H), 2.64 (t, *J* = 7.6, 2H), 1.63 (m, 2H), 1.28 (m, 18H), 0.87 (t, *J* = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.33, 168.94, 147.50, 129.30, 127.71, 123.23, 115.45, 67.39, 36.22, 32.15, 31.44, 29.89, 29.81, 29.71, 29.60, 29.51, 22.94, 17.38, 14.37.

2-(3-(4-dodecylphenyl)-1,2,4-oxadiazol-5-yl)acetimidamide hydrochloride (15).

General procedure A was used to convert **14** (61 mg, 0.16 mmol) to the title product. In this example, the solid was purified via flash chromatography. The hydrochloride salt was prepared by the dropwise addition of 2 M HCl in ether to the purified amidine. The ether was evaporated, reconstituted in ether, and again evacuated to dryness to yield the title product. 40%. Tan solid. R_f = 0.25 (15% MeOH in $CHCl_3$). ^{1}H NMR (500 MHz, DMSO) δ 9.47 (s, 2H), 9.15 (s, 2H), 7.90 (s, 2H), 7.37 (s, 2H), 4.38 (s, 2H), 2.63 (s, 2H), 1.57 (s, 2H), 1.21 (s, 18H), 0.82 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.81, 168.25, 163.97, 147.06, 129.72, 127.48, 123.56, 35.50, 31.75, 31.09, 30.63, 29.46, 29.27, 29.16, 29.08, 22.56, 14.43. LCMS: t_R = 6.46; *m/z* = 371.54. HRMS *m/z* calcd for $C_{22}H_{35}N_4O$ (M + H), 371.2811; found 371.2814.

***Z*)-ethyl 1-(*N*'-hydroxycarbamimidoyl)cyclopropanecarboxylate (16).** Sodium hydroxide (0.33 g, 8.26 mmol) and hydroxylamine hydrochloride (0.55 g, 7.91 mmol) were stirred in EtOH (7.19 mL, 1 M) at room temperature for 2 h. The mixture was filtered through a fine frit and ethyl 1-cyano-1-cyclorpropanecarboxylate (1.0 g, 7.19 mmol) was added and the reaction heated to 50 °C overnight. The mixture was then cooled to room temperature, evaporated to a white solid, and immediately purified by flash chromatography. 46%. White solid. R_f = 0.37 (75% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 2H), 4.11 (q, 7.1, 2H), 1.37 (dd, J = 4.2, 7.2, 2H), 1.29 (dd, J = 4.0, 7.1, 2H), 1.20 (t, J = 7.1, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.40, 152.34, 61.41, 25.02, 15.65, 14.11.

(*Z*)-ethyl 1-(*N*'-((4-dodecylbenzoyl)oxy)carbamimidoyl)cyclopropanecarboxylate (17a). General procedure B was used to couple **16** (0.23 g, 1.35 mmol) and 4-dodecylbenzoic acid (0.39 g, 1.35 mmol) to yield the title product. 54%. White solid. R_f = 0.27 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2, 2H), 7.17 (d, J = 8.2, 2H), 5.61 (s, 2H), 4.08 (q, J = 7.1, 2H), 2.40 (t, J = 7.7, 2H), 1.60 – 1.44 (m, 6H), 1.28 – 1.18 (m, 21H), 0.82 (t, J = 6.6, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.76, 163.88, 157.45, 148.49, 129.38, 128.41, 126.86, 61.39, 35.92, 31.83, 31.05, 29.56, 29.49, 29.38, 29.27, 29.19, 28.67, 24.83, 22.60, 16.60, 14.03, 13.99.

ethyl 1-(5-(4-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxylate (18a). General procedure G was used to convert **17a** (325 mg, 0.73 mmol) to the title product. 84%. R_f = 0.56 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2, 2H), 7.26 (d, J = 8.2, 2H), 4.16 (q, J = 7.1, 2H), 2.62 (t, J = 7.7, 2H), 1.68 (dd, J = 4.3, 7.6, 2H), 1.64 – 1.54 (m, 2H), 1.50 (dd, J = 4.3, 7.6, 2H), 1.36 – 1.12 (m, 21H), 0.82 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.61, 170.94, 169.68, 148.39, 129.09, 128.07, 121.61, 61.58, 36.04, 31.91, 31.09, 29.63, 29.56, 29.45, 29.35, 29.22, 22.68, 21.27, 16.65, 14.09.

1-(5-(4-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxylic acid (19a). To a mixture of **18a** (261 mg, 0.61 mmol) and LiOH (3.0 equiv) were added THF (2 mL), ^{t}BuOH (2 mL), and H_2O (2 mL). The mixture was stirred at room temperature for 4 h. The mixture was diluted with EtOAc (100 mL) and washed with 1 M HCl (3 x 10 mL). The organic layer was washed with brine, dried over $MgSO_4$, evaporated to a white solid and carried on crude.

1-(5-(4-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarbonitrile (20a). Crude acid, **19a** (244 mg, 0.61 mmol) was dissolved in CH_2Cl_2 (0.3 M) at 0 °C and treated with TEA (3.0 equiv) and then isobutyl chloroformate (1.1 equiv). The mixture turned turbid after the addition and was allowed to warm to room temperature. After 1 h at room temperature, the mixture was treated with 2 M NH_3 in MeOH (2.0 equiv) and allowed to stir 8 h. The mixture was then evaporated and taken on crude. The crude amide (168 mg, 0.42 mmol) was dissolved in DMF (0.1 M) and 2,4,6-collidine (8 equiv) at 0 °C and then treated with cyanuric chloride (3.15 equiv) and allowed to warm to room temperature. The reaction turned a deep red color and was allowed to stir for 12 h. The mixture was then extracted with EtOAc (20 x volume of DMF) and washed

3 x with saturated $NaHCO_3$ (10 x the volume of DMF), 3 x with 1 M HCl (10 x the volume of DMF), and once with brine (10 x the volume of DMF). The organic layer was then dried with $MgSO_4$, evaporated to a yellow oil and immediately purified with flash chromatography to yield the title compound. 31% (over 3 steps). R_f = 0.34 (15% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3, 2H), 7.31 (d, J = 8.4, 2H), 2.67 (t, J = 7.7, 2H), 1.84 (s, 4H), 1.70 – 1.56 (m, 2H), 1.43 – 1.19 (m, 18H), 0.87 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.78, 168.09, 149.17, 129.32, 128.30, 121.03, 119.08, 36.18, 32.00, 31.15, 29.73, 29.64, 29.53, 29.45, 29.31, 22.78, 18.29, 14.22, 7.87.

1-(5-(4-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboximidamide hydrochloride (21a). General procedure A was used to convert **20a** (71 mg, 0.19 mmol) to the title product. 20%. Yellow solid. R_f = 0.42 (15% MeOH in $CHCl_3$). ^{1}H NMR (600 MHz, DMSO) δ 9.27 (s, 4H), 7.77 (d, J = 8.2, 2H), 7.28 (d, J = 8.2, 2H), 2.58 (t, J = 7.6, 2H), 1.86 – 1.44 (m, 6H), 1.41 – 0.95 (m, 18H), 0.83 (t, J = 6.6, 2H). ^{13}C NMR (151 MHz, DMSO) δ 175.28, 169.33, 166.96, 148.58, 129.38, 127.74, 124.37, 34.97, 31.10, 30.30, 28.82, 28.61, 28.51, 28.40, 21.90, 20.93, 15.87, 13.81. LCMS: t_R = 5.15; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O$ (M + HCl), 397.2967; found 397.2949.

***Z*)-ethyl 1-(*N*'-((3-dodecylbenzoyl)oxy)carbamimidoyl)cyclopropanecarboxylate (17b).** General procedure C was used to couple amidoxime **16** (1.4 mmol) to 3-dodecylbenzoic acid (1.4 mmol) to yield the title product. 72%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89-7.77 (m, 2H), 7.45-7.31 (m, 2H), 5.59 (s, 2H), 4.18 (q, *J* = 3Hz, 2H), 2.65 (t, *J* = 3Hz, 2H), 1.65-1.60 (m, 2H), 1.34-1.21 (m, 18H), 0.88 (t, 3H). ^{13}C NMR (125 MHz, DMSO) δ 167.35, 159.52, 153.20, 138.91, 128.61, 124.99, 124.91, 123.81, 122.17, 57.03, 31.27, 27.41, 26.89, 25.15, 25.07, 24.98, 24.84, 24.78, 20.23, 18.18, 12.49, 9.59.

Ethyl 1-(5-(3-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxylate (18b). General procedure G was used to convert **17b** (1.01 mmol) to the title product. 89%. White solid. R_f = 0.51 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.90 (m, 2H), 7.45-7.37 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.68 (t, 2H), 1.70-1.60 (m, 2H), 1.37-1.18 (m, 25H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.97, 171.19, 169.95, 144.29, 133.17, 129.18, 128.22, 125.63, 124.22, 61.86, 35.97, 32.13, 31.59, 29.86, 29.78, 29.69, 29.57, 29.47, 22.90, 21.47, 16.87, 14.33.

1-(5-(3-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboxylic acid (19b). To a solution of **17b** (0.90 mmol) in 1.65 mL each of MeOH, THF, and H_2O were added LiOH (2.7 mmol). This mixture was allowed to stir 15 h at room temperature. The mixture was then taken up in 100 mL EtOAc, washed with three 10 mL portions of 1 M HCl, one portion of brine (10 mL), and then dried over Na_2SO_4. 92%. White solid.

1-(5-(3-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarbonitrile (20b). To a solution of **19b** (0.83 mmol) in DCM (1.66 mL) was added *i*-butylchloroformate (0.91 mmol) and TEA (0.35 mL). After this solution stirred 1 h, NH_3 in MeOH (1.25 mL) were added dropwise, and the mixture stirred and additional 15 h at rt. The solvent was then evaporated and the crude product purified by flash chromatography (silica gel, 20% EtOAc in Hexanes). 76%. White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.96-7.89 (m, 2H), 7.47-7.39 (m, 2H), 2.69 (t, *J* = 4.5 Hz, 2H), 1.69-1.62 (m, 2H), 1.38-1.21 (m, 22H), 0.88 (t, *J* = 7.1 Hz, 3H). To an ice-cold stirring solution of 2,4,6-collidine (5.03 mmol) and cyanuric chloride (1.98 mmol) in DMF (6.3 mL) was added the 1,2,4-oxadiazole amide (0.63 mmol). This mixture was allowed to warm to room temperature and stirred for 15 h. At this time, the reaction was slowly quenched with a saturated $NaHCO_3$ solution and then extracted with three portions of 25 mL EtOAc. The combined organic

layers were then washed with three 10 mL portions of 1 N HCl and one 10 mL portion of brine, and then dried over Na_2SO_4. 66%. White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.87 (m, 2H), 7.47-7.38 (m, 2H), 2.74-2.64 (m, 2H), 1.70-1.60 (m, 2H), 1.37-1.16 (m 22H), 0.88 (t, *J* = 6.7 Hz, 3H).

1-(5-(3-dodecylphenyl)-1,2,4-oxadiazol-3-yl)cyclopropanecarboximidamide hydrochloride (21b). General procedure A was used convert nitrile **20b** (0.42 mmol) to the title product. Additional purification through flash chromatography was required (silica gel, 15% MeOH in $CHCl_3$). 13%. Yellow solid. ^{1}H NMR (600 MHz, DMSO) δ 9.32 (s, 2H), 9.11 (s, 2H), 7.94-7.90 (m, 2H), 7.60-7.54 (m, 2H), 2.52 (t, *J* = 1.8 Hz, 2H), 1.64-1.56 (m, 2H), 1.33-1.18 (m, 22H), 0.86 (t, *J* = 9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 176.08, 170.09, 168.54, 167.40, 166.01, 144.60, 134.16, 130.11, 127.97, 125.83, 123.35, 65.39, 35.19, 31.76, 31.34, 29.48, 29.47, 22.57, 21.69, 16.44, 15.65, 14.44. LCMS: t_R = 5.15; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O$ (M + HCl), 397.2967; found 397.2957.

methyl 4-dodecylbenzoate (22a). General procedure I was used to convert 4-dodecylbenzoic acid (1.2 g, 4.13 mmol) to the title product. 95%. Clear and colorless oil. R_f = 0.45 (5% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 8.1, 2H), 7.23 (d, J = 8.1, 2H), 3.89 (s, 3H), 2.61 (t, J = 7.7, 2H), 1.67 – 1.55 (m, 2H), 1.37 – 1.17 (m, 18H), 0.88 (t, J = 7.0, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.31,148.62, 129.73, 128.54, 127.75, 60.68, 36.14, 32.05, 31.25, 29.76, 29.68, 29.58, 29.47, 29.37, 29.33, 22.81, 14.23.

4-dodecylbenzohydrazide (23a). General procedure J was used to convert **22a** (1.2 g, 3.94 mmol) to the title product. 42%. White solid. R_f = 0.31 (75% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2, 2H), 7.22 (d, J = 8.3, 2H), 4.92 (s, 2H), 2.62 (t, J = 7.7, 2H), 1.66 – 1.54 (m, 2H), 1.37 – 1.17 (m, 18H), 0.86 (t, J = 6.6, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 168.92, 147.51, 130.12, 129.74, 128.86, 127.00, 36.00, 32.04, 31.73, 31.32, 29.77, 29.70, 29.59, 29.48, 29.38, 22.79, 14.24.

***N*'-(1-cyanocyclopropanecarbonyl)-4-dodecylbenzohydrazide (24a).** General procedure B was used to couple **23a** (250 mg, 0.82 mmol) and 1-cyano-1-cyclopropanecarboxylic acid (91 mg, 0.82 mmol) to yield the title product. 71%. White solid. R_f = 0.57 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3, 2H), 7.19 (d, J = 8.3, 2H), 2.55 (t, J = 7.7, 2H), 1.68 (dd, J = 4.6, 8.3, 2H), 1.64 – 1.48 (m, 4H), 1.41 – 1.18 (m, 18H), 0.87 (t, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.68, 164.69, 148.31, 128.83, 128.44, 127.60, 118.89, 36.02, 32.02, 31.25, 29.76, 29.57, 29.45, 29.39, 22.79, 18.56, 14.23, 12.64.

1-(5-(4-dodecylphenyl)-1,3,4-oxadiazol-2-yl)cyclopropanecarbonitrile (25a). General procedure K was used to convert **24a** (230 mg, 0.58 mmol) to the title product. 75%. White solid. R_f = 0.46 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.3, 2H), 7.29 (d, J = 8.3, 2H), 2.64 (t, J = 7.7, 2H), 1.93 (s, 4H), 1.73 – 1.50 (m, 2H), 1.48 – 1.16 (m, 18H), 0.85 (t, J = 6.2, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.64, 162.07, 147.79, 129.21, 126.96, 120.53, 117.91, 36.03, 31.95, 31.14, 29.67, 29.60, 29.49, 29.38, 29.27, 22.72, 19.17, 14.16, 7.14.

1-(5-(4-dodecylphenyl)-1,3,4-oxadiazol-2-yl)cyclopropanecarboximidamide hydrochloride (26a). General procedure A was used to convert **25a** (164 mg, 0.43 mmol) to the title product. 46%. Tan solid. R_f = 0.36 (15% MeOH in $CHCl_3$). ^{1}H NMR (600 MHz, DMSO) δ 9.39 (d, J = 11.1, 4H), 7.91 (d, J = 7.5, 2H), 7.42 (d, J = 7.6, 2H), 2.66 (t, J = 7.1, 2H), 1.96 – 1.81 (m, 4H), 1.64 – 1.54 (m, 2H), 1.33 – 1.19 (m, 18H), 0.85 (t, J = 6.7, 3H). ^{13}C NMR (151 MHz, DMSO) δ 166.68, 164.11, 163.69, 146.93, 129.22, 126.53, 120.55, 34.97, 31.20, 30.51,

28.94, 28.91, 28.88, 28.72, 28.62, 28.50, 22.01, 20.26, 16.81, 13.88. LCMS: t_R = 4.86; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O$ (M + HCl), 397.2967; found 397.2956.

Methyl 3-dodecylbenzoate (22b). Acetyl chloride (15.5 mmol) was added dropwise over 10 minutes to ice-cold MeOH (12 mL), and this solution was allowed to stir 5 min. 3-dodecylbenzoic acid (5.2 mmol) was then added to the solution in one portion. This solution was heated to reflux with stirring for 2 h. At this point solid $NaHCO_3$ was added to neutralize the solution, which was then filtered through a fine fritted funnel. The solvent was evaporated from the filtrate to yield the title product. 96%. Amber oil. R_f = 0.87 (15% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.80 (m, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 3.91 (s, 3H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.32 – 1.14 (m, 18H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.33, 143.23, 133.08, 130.08, 129.51, 128.25, 126.93, 52.02, 35.78, 31.96, 31.42, 29.70 , 29.68 , 29.67 , 29.60 , 29.51 , 29.39 , 29.28 , 22.73, 14.14.

3-dodecylbenzohydrazide (23b). General procedure J was used to convert **22b** (5.0 mmol) to the title product. 58%. White solid. R_f = 0.62 (10% MeOH in $CHCl_3$). ^{1}H NMR (300 MHz, DMSO) δ 9.69 (bs, 1H), 7.66 – 7.59 (m, 2H), 7.33-7.26 (m, 2H), 2.52-2.45 (m, 2H), 1.97 (s, 2H), 1.25-1.10 (m, 18H), 0.82 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 166.46, 142.93, 133.72, 131.46, 128.62, 127.35, 124.73, 35.49, 31.77, 31.30, 29.51, 29.48, 29.46, 29.33, 29.19, 29.10, 22.58, 14.44.

***N*'-(1-cyanocyclopropanecarbonyl)-3-dodecylbenzohydrazide (24b).** General procedure B was used to couple **23b** (2.86 mmol) to 1-cyano-1-cyclopropanecarboxylic acid (2.86 mmol). 56%. White solid. R_f = 0.52 (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.88-8.78 (bs, 1H), 8.34-8.30 (s, 1H), 7.65-7.57 (m, 2H), 7.42-7.35 (m, 2H), 2.71-2.59 (m, 2H), 1.85-1.74 (m, 2H), 1.29-1.22 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.34,

163.83, 143.95, 132.90, 130.99, 128.73, 127.39, 124.49, 118.80, 35.81, 31.94, 31.37, 29.69, 29.67, 29.66, 29.59, 29.49, 29.37, 29.30, 22.71, 19.90, 18.50, 14.15, 12.54.

1-(5-(3-dodecylphenyl)-1,3,4-oxadiazol-2-yl)cyclopropanecarbonitrile (25b). General procedure K was used to convert **24b (**1.6 mmol) to the title product. R_f = 0.51 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2H), 7.48-7.32 (m, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.34-1.22 (m, 18H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.98, 165.98, 144.44, 132.62, 129.28, 127.08, 124.56, 123.17, 118.13, 36.02, 32.14, 31.62, 29.88, 29.81, 29.70, 29.59, 29.50, 22.93, 19.45, 14.36, 7.31.

1-(5-(3-dodecylphenyl)-1,3,4-oxadiazol-2-yl)cyclopropanecarboximidamide hydrochloride (26b). General procedure A was used to convert **25b** (0.92 mmol) to the title product. 42%. Yellow solid. ^{1}H NMR (600 MHz, DMSO) δ 9.31 (s, 2H), 9.16 (s, 2H), 7.82 (dd, *J* = 6.8, 1.4 Hz, 2H), 7.55-7.46 (m, 2H), 2.69 (t, *J* = 3 Hz, 2H), 1.64-1.58 (m, 2H), 1.32-1.2 (m, 18H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (600 MHz, DMSO) δ 166.45, 164.20, 163.98, 143.80, 64.89, 40.06 , 34.80, 31.26, 30.86, 28.99, 28.98, 28.97, 28.96, 28.88, 28.67, 28.57, 22.07, 20.43, 16.73, 15.15, 13.93. LCMS: t_R = 5.15; *m/z* = 397.3. HRMS *m/z* calcd for $C_{24}H_{37}N_4O$ (M + HCl), 397.2967; found 397.2957.

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