Exploring the Structure-Activity-Relationship of the 'B'-ring in Diaryl Ether-Based *pa*FabV Inhibitors

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Abstract: The uncontrolled rise and spread of antimicrobial resistance (AMR) is one of the most severe and immediate threats to global health. Resistant infections are responsible for millions of deaths worldwide annually and current trends indicate that the issue will only aggravate in the future. Meanwhile, commercial drug development is dominated by incremental modifications of existing intellectual property instead of exploring novel therapeutic strategies with lower likelihood of resistance development. FabV is an enoyl-acyl carrier protein reductase (ENR), a crucial component of the universal bacterial fatty acid biosynthetic pathway (FasII), that is found across several critical Gram-negative bacteria. This includes *P. aeruginosa*, an opportunistic pathogen associated with hospital infections. This pathogen co-expresses FabV along with its more frequently occurring isozyme FabI, and is therefore resistant to common FabI inhibitors. This study sought to investigate the rational, iterative design of *pa*FabV inhibitors. A total of 44 compounds, based on the existing diaryl ether scaffold for ENR inhibition, were synthesized and screened in an enzymatic assay. This resulted in a potent inhibitor of FabV, **RGB32**, with an IC_{50} value of 0.59 ± 0.04 µM. The results of this work could serve as an encouraging starting point for further investigation of the therapeutic potential of FabV inhibition.

Introduction

Almost 5 million deaths each year are attributable to antimicrobial resistance (AMR),[1] a staggering number which is poised to continue to rise. If the current trends in the emergence and spread of resistance continue at their current pace, the mortality rate is predicted to double to over 10 million deaths annually by 2050, which would make AMR the leading cause of death worldwide.[1–4] Unfortunately, drug development in this field has slowed significantly over the past 50 years. Since the introduction of ansamycins in 1967 there have been no new biomolecular pathways therapeutically targeted by small molecules, and few major classes of antibiotics have been brought to market altogether.[5,6] The current context thus demands the design and development of innovative molecular scaffolds to combat the growing threat of AMR.

Among the strategic avenues currently under exploration, one with significant potential is disruption of the fatty acid synthase II (FasII) pathway. Fatty acids are essential components of cellular metabolism, especially with regard to membrane formation and maintenance.[7,8] The enzymes that compose the pathway are biorthogonal to the multi-domain complex utilized by mammalian cells, making them ideal drug targets.[7–9] Among these enzymatic targets, one that has garnered significant attention in recent years has been the enoyl-acyl carrier protein (ACP) reductase (ENR), which catalyses the last step in the alkyl chain elongation cycle of FasII. The most widespread ENR isoform is FabI, which has previously been shown to be crucial to bacterial survival.[10] Moreover, in an *E. coli* resistance development model, only two mutation loci were identified, both of which led to decreased

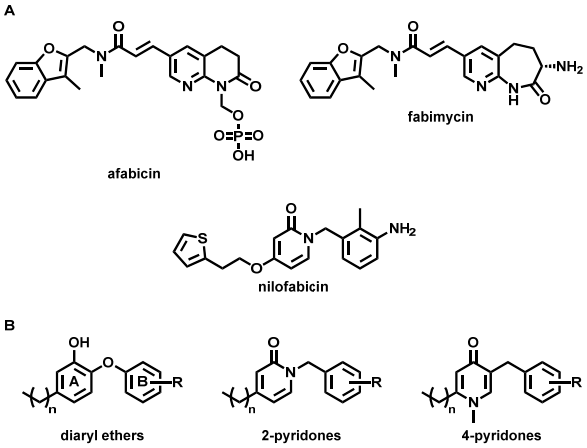


Figure 1 A. FabI inhibitors currently under clinical investigation as drug candidates targeting various infections. **B.** General scaffold of major FabI inhibitor classes tested against FabV, with aryl ring labelling shown on the diaryl ether scaffold.

pathogen growth potential.[11] These characteristics validate ENRs as potential antimicrobial drug development targets and as a result at least three FabI inhibitors are currently undergoing clinical trials (see **Figure 1A**).[12–14]

However, there are some organisms of grave concern that show intrinsic resistance to FabI inhibition, such as *P. aeruginosa.* Carbapenem-resistant *P. aeruginosa* is listed by the WHO as a Priority I pathogen, indicating a high risk of morbidity, spread and resistance to existing therapies.[15] This opportunistic pathogen is commonly acquired during hospital stays and poses a significant threat to patients presenting with comorbidities that can compromise the immune system (*e.g.* cystic

fibrosis, cancer, AIDS, those with internal medical devices, burns, eye injuries and poorly-healing diabetic wounds).[16]

Moreover, *P. aeruginosa* strains have been shown to be unaffected by triclosan, a widespread additive to consumer products, whose antibacterial properties are due in large part to FabI inhibition. This effect is attributed to co-expression of an alternative ENR isoform by *P. aeruginosa* named FabV.[17,18] Encouragingly, FabV knock-out experiments have demonstrated restoration of the antibacterial effect of triclosan against *P. aeruginosa*, which supports the notion that inhibition of FabV by small molecules would resensitize the bacteria to FabI inhibition.[19]

To date, most ENR-inhibitor investigations have focused on FabI, with the most popular strategy being a derivatization of the triclosan motif.[20] These efforts have yielded three general scaffolds, namely the diaryl ethers, the 2-pyridones and the 4-pyridones (see **Figure 1B**). It was also demonstrated that the presence and oxidation state of the cofactor plays a major role in the inhibitory mode of small-molecule ligands.[21] The triclosan derivatization strategy has led to some success, as the candidate drug nilofabicin, a pyridone derivative, recently passed phase II clinical trials.[22] In the case of FabV, work done by Neckles *et al.* has suggested that of these three chemotypes, there is a preference for the diaryl ethers as inhibitors of *Y. pestis* FabV (*yp*FabV), stabilizing the enzyme-NAD^+ interaction via the formation of a ternary complex.[23,24] However, no further investigation into the structure-activity relationship (SAR) of the compounds with the goal of improving their affinity was reported.

The aim of this work was to construct a diverse library of congeners based on the diaryl ether scaffold in order to interrogate their SAR against FabV from *P. aeruginosa* (*pa*FabV).

Results and Discussion

Iterative Library Design & Activity Screening

Previous reports on ENR inhibitors established an ideal length of six carbons for the aliphatic tail of the binder scaffold, while also making clear that substituents on the 'B' ring have a major impact on the enzymatic inhibition efficiency. As such we concentrated our synthetic efforts on that part of the diaryl ether scaffold in this work.

To begin our exploration into *pa*FabV inhibition, we designed and synthesized a first generation of diaryl ether congeners, comprised of a total of 24 compounds (see **Figure 2**). This initial set was meant to identify the types of substituents that have a positive impact on enzymatic inhibition. As a result, most of the compounds in this generation contain mono-substituted rings, with small groups, covering *ortho*-, *meta*-, and *para*-substitution with electron withdrawing (EWG) or donating groups (EDG). Only two compounds, **RGB09** and **RGB10**, are di-substituted, and **RGB11** is the only compound containing a hetero-aromatic system, as the B-ring was modified to a 5-benzofuranyl motif. Of these 24 compounds, 10 have been previously reported in studies of ENR inhibition[25,26], 6 of which were previously assayed against *yp*FabV (**PT04**, **PT10**, **PT12**, **PT15**, **PT70** and **PT113**).[24]

The first generation of diaryl ethers was screened for *pa*FabV inhibition at 10 μM in the presence of both NADH and NAD^+ (assay conditions detailed in the Experimental Protocols section), the results of which are displayed in **Figure 3**. Strikingly, in our assay, the previously reported most potent inhibitor for *yp*FabV, **PT113** (reported IC_{50}: 0.1 μM), only inhibited 51% of *pa*FabV at 10 μM, comparable with the unsubstituted reference **PT04**, despite a >95% sequence identity between *yp*FabV and *pa*FabV.

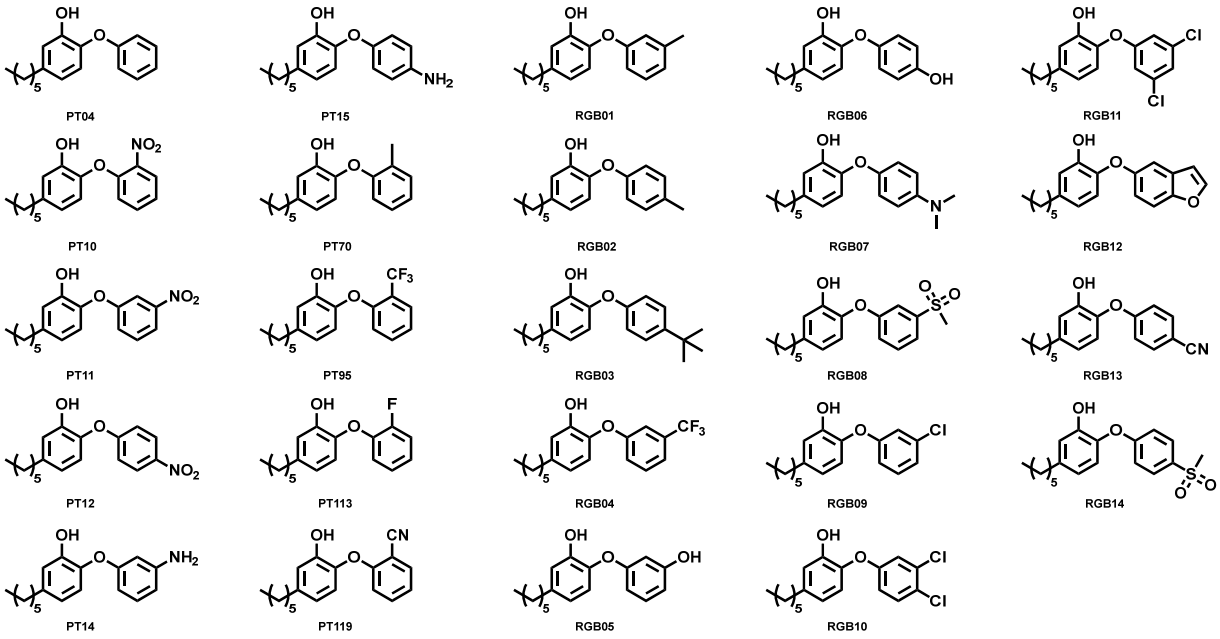


Figure 2 Structure of compounds synthesised in the 1st generation; codes for previously described inhibitors taken from ref. [24]

For all compounds with *paFabV* inhibition of 50% or more at a 10 μM concentration, the IC_{50} was determined. In total, 11 of the 24 tested ethers showed over 50% abrogation of *pa*FabV activity at 10 μM, of which three (**PT04**, **PT12** and **PT113**) had been previously tested against *yp*FabV, and could therefore serve as comparison.

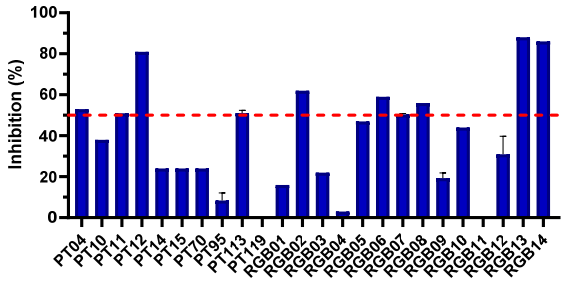
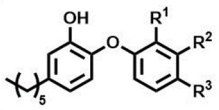


Figure 3 Results of 1st generation of compounds screened against *pa*FabV at fixed concentration of 10 μM inhibitor (n=3) error bars depict standard deviation; red dotted line at 50% inhibition threshold.

Unfortunately, for both **PT04** and **PT113** the IC_{50} could not be determined using our assay conditions, as they failed to show a clear dose-response curve and did not yet reach their maximal effect at 50 μM, the highest concentration assayed. The only compound for which a direct comparison between *yp*FabV and *pa*FabV was possible was **PT12**, which in our assay exhibited an IC_{50} of 2.47 ± 0.44 μM, whereas previously it was reported to inhibit *yp*FabV with an IC_{50} of 0.2 ± 0 μM.

Table 1 Dose-response characterisation of 1st generation compounds.



Code	R^1	R^2	R^3	IC_{50} (μM)[a]
PT04	H	H	H	>10
PT11	H	NO_2	H	2.13 ± 0.46
PT12	H	H	NO_2	2.47 ± 0.44
PT113	F	H	H	>10
RGB02	H	H	Me	2.64 ± 1.60
RGB06	H	H	OH	9.02 ± 3.10
RGB07	H	H	NMe_2	1.99 ± 0.51
RGB08	H	SO_2Me	H	1.78 ± 0.29
RGB13	H	H	CN	0.92 ± 0.12
RGB14	H	H	SO_2Me	1.42 ± 0.09

[a] IC_{50} values determined at 10 nM enzyme concentration (n=3, mean ± standard deviation).

Fortunately, 8 of the other 9 compounds displayed IC_{50} values in the 0.90–3.00 μM range, while **RGB06** demonstrated an IC_{50} of 9.02 ± 3.10 μM (**Table 1** and **Figure S1**). Looking through these values two overall trends appear significant. Firstly, when comparing the position of substituents, potency appears to increase in the order *ortho* < *meta* < *para*, with *o*-substituents larger than F consistently having deleterious effects. Secondly, strong electron-withdrawing groups (EWGs) in the *meta* and especially *para* positions were most conducive to increased efficacy. As a result, compounds **PT12** (*p*-NO_2), **RGB13** (*p*-CN) and **RGB14** (*p*-SO_2Me) were chosen as references for further iterations.

For the second generation of compounds, we hypothesised that the improved binding observed upon addition of EWGs was due to a novel hydrogen bond interaction. We theorise the functional group serves as a hydrogen bond acceptor (HBA), as the IC_{50} trend between **PT12**, **RGB13** and **RGB14** does not follow their relative EWG strength, but may be better aligned with their HBA strength and different geometries. Based on the binding mode of similar molecules to FabV homologues such as FabI, a likely candidate for this interaction is residue Ser155, which also happens to be highly conserved across bacterial species. Since targeting this residue would potentially lead to a broader spectrum inhibitor, we decided to attempt to actively target this putative interaction.

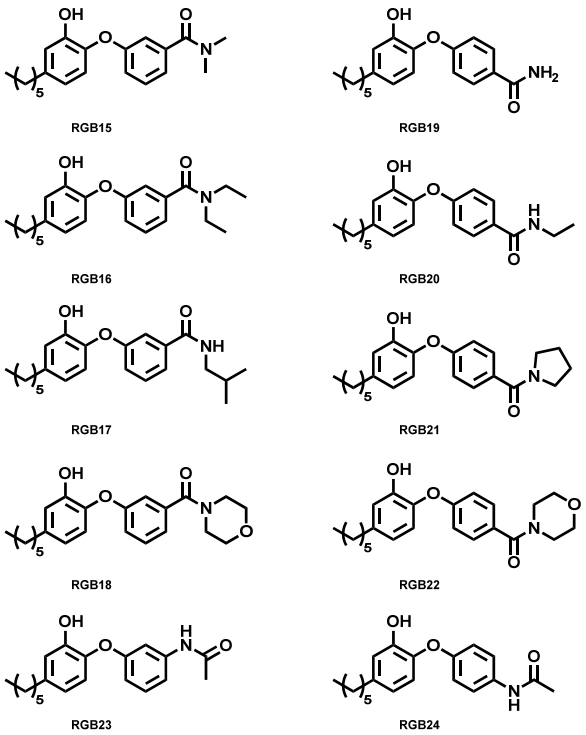


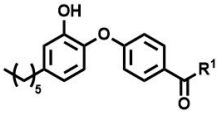
Figure 4 Structure of compounds synthesised in the 2nd generation.

Given the high hydrogen bond acceptor strength of amides, as well as their potential to add a versatile handle for further substitutions, a series of 8 new benzamide-derived inhibitors were synthesized. Both *m*- and *p*-substituted congeners, with various alkyl groups attached to the nitrogen were synthesized as well as both the *m*- and *p*-isomers of the *N*-phenylacetamide derivative (**Figure 4**). Of these 10 compounds, 3 compounds showed inhibition greater than 50% at a 10 μM concentration (**Figure S2**), and were carried through to an IC_{50} determination (**Table 2** and **Figure S3**). Overall, the same preference for *p*-substitution was observed as previously noted, and the benzamide scaffold was preferred over the phenylacetamide, suggesting that having the putative HBA group closer to the B-ring is ideal.

The most active amide derivative was found to be the primary amide-containing **RGB19**, indicating steric considerations may outweigh the hydrogen bond acceptor strength. Interestingly, small aliphatic rings, as seen for the

N-pyrrolidinyl and *N*-morpholinyl rings, were tolerated. Especially the *N*-morpholinyl derivative **RGB22** was very interesting as the morpholine ring maintains the activity of the primary amide but masks two (weak) hydrogen bond donors as well as removing a potential metabolic liability. While **RGB19** and **RGB22** added interesting functional group versatility to the compound library, no significant improvement in binding potency was observed compared to the first-generation congeners. Thus, **RGB19** and **RGB22** were selected together with **PT12**, **RGB13** and **RGB14** as starting points for a further design iteration.

Table 2 Dose-response characterisation of 2nd generation compounds.



Code	R^1	IC_{50} (μM)[a]
RGB19	NH_2	1.92 ± 0.30
RGB21	*N*-pyrrolidinyl	2.07 ± 0.31
RGB22	*N*-morpholinyl	1.43 ± 0.23

[a] IC_{50} values determined at 10 nM enzyme concentration (n=3, mean ± standard deviation).

Previous work on other ENRs, which share some degree of structural similarity at the active site, revealed that the addition of an *ortho*-substituted fluoride, chloride or nitrile group enhanced their potency as a result of interactions with or replacement of a buried structural water molecule.[27] However, the active site of FabV is likely more sterically encumbered at that location. Thus, we decided to only add a fluoride group at this position for the next iteration of diaryl ethers. Additionally, a small relatively lipophilic cavity adjacent to the p-substituent was expected from an analysis of known FabV crystal structures.[23] In an attempt to populate this putative adjacent pocket, the addition of chlorine as a substituent in the *meta* position was investigated as well.

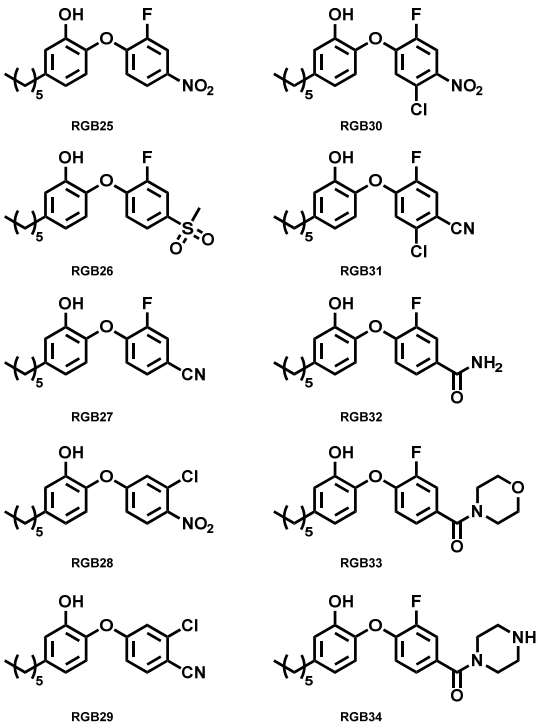


Figure 5 Structure of compounds synthesised in the 3rd generation.

For the third generation, a series of 10 compounds were synthesized, each bearing either a 2-F and/or 5-Cl substitution pattern in addition to one of 5 most potent 4-HBA previously identified (NO_2, CN, SO_2Me, $CONH_2$ or CO-morpholinyl, **Figure 5**). Additionally, replacing the HBA oxygen group of the morpholinyl group with a donor NH group was investigated in **RGB34**.

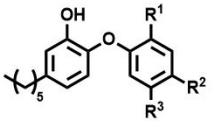
Pleasingly, all of the congeners of this third design iteration exhibited over 50% inhibition (**Figure S4**), giving additional credence to our optimization strategy. The IC_{50} value was the determined for all 10 congeners, with the results presented in **Table 3** and **Figure S5**. The additive approach using the 2-F appeared moderately successful, with potency improving by factors ranging from 1.1 times for **RGB33** to 6.7 times for **RGB25** (when compared to the parent *p*-substituted compound). The only exception was **RGB27**, for which potency decreased by a factor of 1.6 upon introduction of the 2-F pattern. Given this relatively modest improvement in inhibition upon the addition of an *ortho*-fluoride substituent for most congeners, it is unlikely that an additional hydrogen bond interaction with the buried water was achieved. A possible explanation for this observation is that most of these congeners are unable to achieve a simultaneous interaction via the *ortho*- and *para*-substituent, with the linear architecture of the *para*-nitrile exhibiting the lowest tolerability to slight conformation changes. Another potential explanation could be due to a similar effect that was observed when studying the interactions of compounds **PT70** and **PT119** with InhA, another ENR isozyme expressed by *M. tuberculosis*.[25,26] The expanded substituent groups appeared to significantly decrease efficacy as measured by IC_{50} and crystallographic experiments demonstrated clashes with the associated cofactor. However, bacterial experiments showed no loss of bactericidal potency, which was then demonstrated to be due to slow-onset mechanics of enzymatic inhibition associated with significant conformational shifts necessary for optimal binding.[24] Whether a similar mechanism is applicable to FabV inhibition has not been reported and is currently under investigation in our group.

Unfortunately, substitution with 5-Cl was not as successful as the 2-F pattern, both individually (potency improved by 1.7 times for **RGB28** and decreased by 1.9 times for **RGB29**) and in combination (potency improved by 1.4 and 1.1 times for **RGB30** and **RGB31,** respectively).

In addition to the effects of the substituents, a peculiar observation was made, that apart from the IC_{50}, structural features of the B-ring consistently influenced the maximal degree of inhibition as well. Especially the presence of a nitro group (**PT11**, **PT12**, **RGB25**, **RGB28** and **RGB30,** see also **Figures S3** and **S5**), as well the addition of a *meta*-chloride (**RGB29** and **RGB31,** see also **Figure S5**), was associated with clear decreases in the maximal degree of enzyme inhibition. As such, it would appear that **RGB25** is the best performing compound of this optimization campaign when looking at the IC_{50} alone. However, the peculiar influence on the maximal degree of enzyme inhibition, as well as the association of nitro-groups with toxicity[28], led us to abandon these particular scaffold decorations. Instead, compound **RGB32**, with an IC_{50} of

0.59 ± 0.04 μM and a high maximal inhibition, is deemed the most suitable 'B' ring decorated inhibitor of *pa*FabV identified in this study, and is earmarked for further development.

Table 3 Dose-response characterisation of 3rd generation compounds.

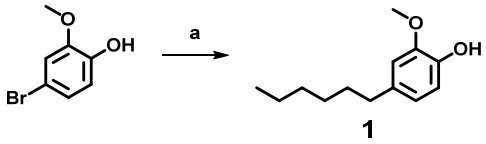


Code	R^1	R^2	R^3	IC_{50} (μM)[a]
RGB25	F	NO_2	H	0.37 ± 0.04
RGB26	F	SO_2Me	H	0.86 ± 0.07
RGB27	F	CN	H	1.45 ± 0.15
RGB28	H	NO_2	Cl	1.43 ± 0.19
RGB29	H	CN	Cl	1.81 ± 0.32
RGB30	F	NO_2	Cl	1.75 ± 0.51
RGB31	F	CN	Cl	0.86 ± 0.11
RGB32	F	$CONH_2$	H	**0.59 ± 0.04**
RGB33	F	CO-morpholinyl	H	1.26 ± 0.11
RGB34	F	CO-piperazinyl	H	3.73 ± 0.61

[a] IC_{50} values determined at 10 nM enzyme concentration (n=3, mean ± standard deviation)

Synthesis

The synthesis of the 2-hydroxy-4-hexyl-diaryl ether scaffold starts from a common phenolic intermediate (**1**). However, the reported method towards this starting material is a three-step synthesis, starting from vanillin and requiring a protection and deprotection step, with an overall yield of 66% over 3 steps.[26]

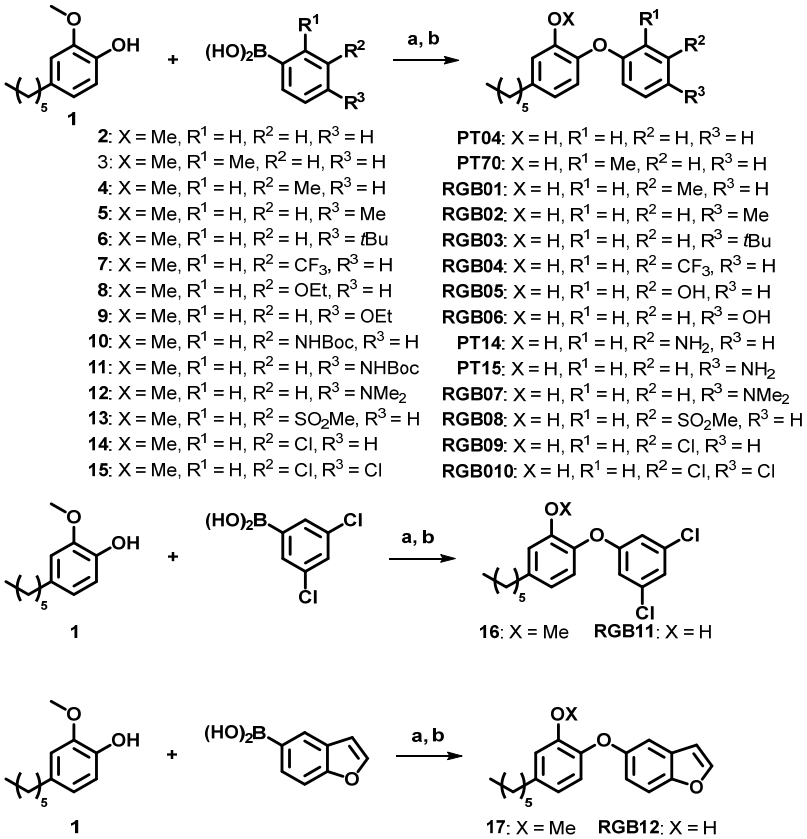


Scheme 1 Synthesis of common intermediate **1**.
a) $nC_6H_{13}MgBr$, $Pd(dppf)Cl_2$, THF, Ar, -78 °C → reflux, 2 h, 80%.

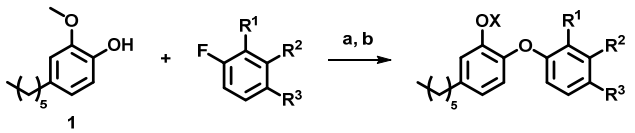
Here, we present an alternative one-step reaction, in which the commercially available 4-bromo-2-methoxy-phenol was efficiently converted to intermediate **1**, via a Kumada coupling reaction with hexylmagnesium bromide in an 80% yield, greatly facilitating our library construction (see **Scheme 1**).

In order to facilitate the span and diversity of our tested compounds we aimed to couple the B-ring portion of the molecule in a single step, ideally in a high-yielding reaction, under mild conditions with high functional group tolerance. As such, we expanded the reaction scope of reactions on intermediate **1** with the Chan-Lam ether coupling.[29,30] A total of 25 commercially available phenylboronic acid derivatives were reacted with **1** by the use of a Cu^{II} catalyst at room temperature over 18 h, giving the desired products in moderate to good yields. (see **Scheme 2** and **4**).

We observed significantly lower yields when the substituent on the boronic acid was a strong electron withdrawing group. For these congeners, an alternative



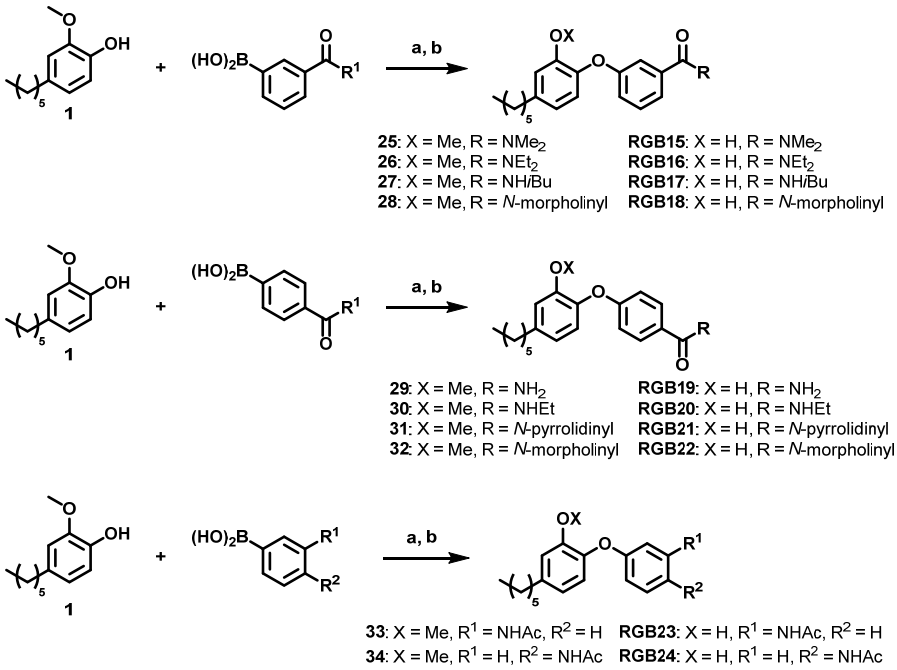
Scheme 2 Synthesis of final compounds via Chan-Lam coupling a) $Cu(OAc)_2$, DCM, 4 Å MS, air, RT, 18 h; b) BBr_3, DCM, Ar,-78 °C → RT, 4.5 h.



18: X = Me, R^1 = NO_2, R^2 = H, R^3 = H
19: X = Me, R^1 = H, R^2 = NO_2, R^3 = H
20: X = Me, R^1 = H, R^2 = H, R^3 = NO_2
21: X = Me, R^1 = CN, R^2 = H, R^3 = H
22: X = Me, R^1 = H, R^2 = H, R^3 = CN
23: X = Me, R^1 = H, R^2 = H, R^3 = SO_2Me
24: X = Me, R^1 = CF_3, R^2 = H, R^3 = H

PT10: X = H, R^1 = NO_2, R^2 = H, R^3 = H
PT11: X = H, R^1 = H, R^2 = NO_2, R^3 = H
PT12: X = H, R^1 = H, R^2 = H, R^3 = NO_2
PT119: X = H, R^1 = CN, R^2 = H, R^3 = H
RGB13: X = H, R^1 = H, R^2 = H, R^3 = CN
RGB14: X = H, R^1 = H, R^2 = H, R^3 = SO_2Me
PT95: X = H, R^1 = CF_3, R^2 = H, R^3 = H

Scheme 3 Synthesis of final compounds via S_NAr a) Cs_2CO_3, DMF, 80 °C, 18 h; b) BBr_3, DCM, Ar, -78 °C → RT, 4.5 h.



25: X = Me, R = NMe_2
26: X = Me, R = NEt_2
27: X = Me, R = NH*i*Bu
28: X = Me, R = *N*-morpholinyl

RGB15: X = H, R = NMe_2
RGB16: X = H, R = NEt_2
RGB17: X = H, R = NH*i*Bu
RGB18: X = H, R = *N*-morpholinyl

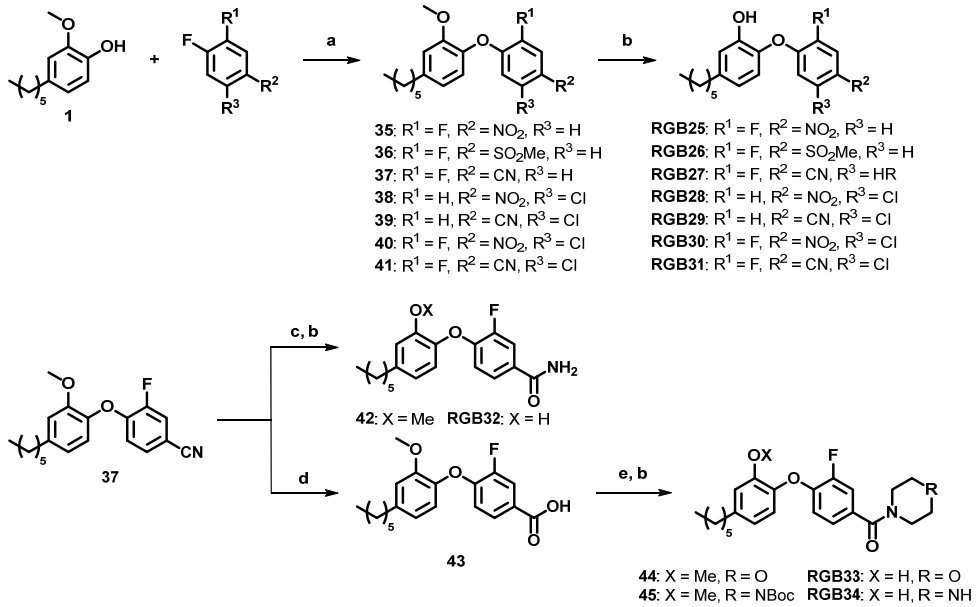
29: X = Me, R = NH_2
30: X = Me, R = NHEt
31: X = Me, R = *N*-pyrrolidinyl
32: X = Me, R = *N*-morpholinyl

RGB19: X = H, R = NH_2
RGB20: X = H, R = NHEt
RGB21: X = H, R = *N*-pyrrolidinyl
RGB22: X = H, R = *N*-morpholinyl

33: X = Me, R^1 = NHAc, R^2 = H
34: X = Me, R^1 = H, R^2 = NHAc

RGB23: X = H, R^1 = NHAc, R^2 = H
RGB24: X = H, R^1 = H, R^2 = NHAc

Scheme 4 Synthesis of amide derivatised final compounds a) $Cu(OAc)_2$, DCM, 4 Å MS, air, RT, 18 h; b) BBr_3, DCM, Ar, -78 °C → RT, 4.5 h.



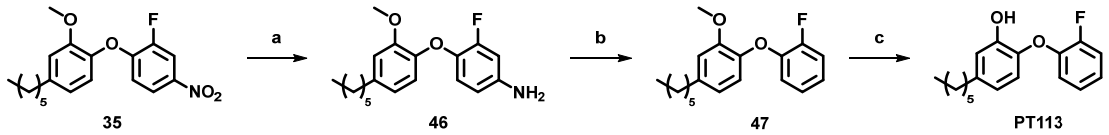
35: R^1 = F, R^2 = NO_2, R^3 = H
36: R^1 = F, R^2 = SO_2Me, R^3 = H
37: R^1 = F, R^2 = CN, R^3 = H
38: R^1 = H, R^2 = NO_2, R^3 = Cl
39: R^1 = H, R^2 = CN, R^3 = Cl
40: R^1 = F, R^2 = NO_2, R^3 = Cl
41: R^1 = F, R^2 = CN, R^3 = Cl

RGB25: R^1 = F, R^2 = NO_2, R^3 = H
RGB26: R^1 = F, R^2 = SO_2Me, R^3 = H
RGB27: R^1 = F, R^2 = CN, R^3 = HR
RGB28: R^1 = H, R^2 = NO_2, R^3 = Cl
RGB29: R^1 = H, R^2 = CN, R^3 = Cl
RGB30: R^1 = F, R^2 = NO_2, R^3 = Cl
RGB31: R^1 = F, R^2 = CN, R^3 = Cl

42: X = Me **RGB32**: X = H

44: X = Me, R = O **RGB33**: X = H, R = O
45: X = Me, R = NBoc **RGB34**: X = H, R = NH

Scheme 5 Synthesis of multi-substituted final compounds a) Cs_2CO_3, DMF, 80 °C, 18 h; b) BBr_3, DCM, Ar, -78 °C → RT, 4.5 h; c) NaOH (10 mol%), EtOH/H_2O (7:3), 80 °C, 18 h; d) KOH, EtOH/H_2O (1:1), 100 °C, 18 h; e) morpholine (for 44) or 1-Boc-piperazine (for 45), HATU, DIPEA, DMF, 0 °C → RT, 2 h.



Scheme 6 Synthesis of reference compound **PT113** a) Zn, HCl, EtOH/H_2O (10:1), 0 °C → RT, 1 h; b) $NaNO_2$, H_2SO_4, Zn, EtOH/H_2O (10:1), 0 °C → reflux, 3 h c) BBr_3, DCM, Ar, -78 °C → RT, 4.5 h.

nucleophilic aromatic substitution route was employed, yielding 15 diaryl ether derivatives in good to excellent yields (see **Scheme 3** and **5**).

While the necessary reagents to obtain some 2-F substituted amides in one step were unavailable, the (partial) hydrolysis of the nitrile of intermediate **37** served as a facile handle for further decorations. For compound **42**, the primary amide motif was obtained subjecting the nitrile group of **37** to partial hydrolysis under mildly basic conditions with moderate heating, resulting in the desired product in a 71% yield. A complete hydrolysis of the same intermediate to carboxylic acid **43** was enabled by increasing the pH of the mixture as well as the reaction time. Further amide bond formation resulted in compounds **44** (56%) and **45** (72%) (see **Scheme 5**).

The synthesis of reference compound **PT113**, proceeded via a literature procedure, starting from intermediate **35**.[26] Briefly, the nitro group was reduced to an aniline (**46**), followed by a diazotation and elimination of nitrogen, resulting in **47** (**Scheme 6**).

For all congeners a final demethylation of their methoxyaryl ethers using BBr_3 was carried out in good to excellent yields, to reveal the phenolic oxygen of the A-ring.

Conclusion

In total, 44 diaryl ether-based inhibitors were synthesized, all bearing a six-carbon chain on the A-ring while variations were explored on the B-ring. All compounds were tested against *pa*FabV in an absorbance-based enzymatic assay at a fixed concentration of 10 µM. The 24 compounds causing at least a 50% reduction in enzymatic activity at this fixed concentration were investigated further for their dose-dependent effect and IC_{50} values.

Our iterative library building approach allowed us to form hypotheses regarding the binding mode of our compounds which were then tested in subsequent generations. The most significant and consistent trend observed across this study was that substituting the 4-position of the B-ring with a good HBA group led to a stark increase in inhibitory activity. Based on previously reported crystal structures of FabV homologues bound to closely related molecules, we theorise that this effect is the result of direct or water-mediated hydrogen bonding to Ser155, a residue that is also highly conserved across various bacterial species.

Another strategy was F-substitution at the 2-position of the B-ring. We saw a moderate increase in binding upon combining the *o*-F pattern with the most potent single substitutions identified, such as *p*-NO_2, *p*-SO_2Me and *p*-$CONH_2$. However, the underwhelming performance observed suggests that if this interaction is accessible, it is not significant or compatible with *para* substitutions, at least in the current scaffold. As activities were slightly enhanced *o*-F likely only has an electronic effect by contributing to the overall polarization of the aromatic ring. Similar attempts to increase lipophilic interactions by introducing a 5-Cl group to the B-ring also proved largely unsuccessful.

In the closely related FabI isozyme, expanding the 2-substituent of the B-ring to a nitrile group, allows for significant interactions with the co-factor as well as the peptide backbone by replacing a structural water molecule.[27] Importantly, our results with FabV clearly indicate a diametrically opposed effect, *i.e.* a total annulment of compound activity when any group larger than fluorine was introduced in the *ortho* position. We attribute this observation largely due to a different binding pocket architecture in FabV leading to steric clashes.

We utilised an iterative approach, based upon enzymatic inhibition studies and augmented by structural information and computational simulations, which yielded our most potent inhibitor of *pa*FabV, **RGB32**, with an IC_{50} of 0.59 ± 0.04 µM. Given the very high sequence identity with *yp*FabV, especially at the active site, it is unlikely that activity differences between **PT12** observed here and in the previous report by Neckles *et al.* are the result of subtle differences in protein sequences. This discrepancy is more likely a result of significant differences in the assay conditions. As such we believe **RGB32** may be the most potent inhibitor of FabV reported to date, combining both potency and high maximal inhibition.

The results of this work could serve as an encouraging starting point for future exploration of the therapeutic potential of ENR inhibition and the development of the next generation of Gram-negative antimicrobials.

Experimental Protocols

Chemistry: general materials and instrumentation

Chemicals and solvents utilised in synthesis were acquired from commercial suppliers (BLDpharm, Fluorochem, TCI, Sigma-Aldrich, Fisher Scientific) and used without further purification. Reaction progression was assessed by thin layer chromatography (TLC) using commercial pre-coated aluminium foils (silica gel matrix 60 F254, Sigma-Aldrich, St. Louis, Missouri, USA), visualised by UV light at 254 nm. The ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on a Bruker UltraShield Avance 300 or 600 MHz machine (Brüker, Fällanden, Switzerland) in deuterated solvents. The chemical shifts (δ) are reported as parts per million (ppm) with respect to the tetramethylsilane (TMS) internal standard. High resolution mass spectrometry (HRMS) was performed on a quadrupole time-of-flight system (Q-Tof 2, Micromass, Manchester, UK) by the use of electrospray ionisation (ESI) techniques. For all

previously published compounds, characterisation data is in good accordance with reported values. Flash chromatography was performed on a Pure C-815 Flash medium pressure liquid chromatography (MPLC) system (Buchi, Flawil, Switzerland) utilising commercial silica cartridges (Buchi, Flawil, Switzerland & Phenomenex, Torrance, California, USA).

General method for coupling of aryl boronic acids (A)
To a stirred solution of the appropriate aryl boronic acid (1.4 eq.) dissolved in DCM (~34 mM) were added copper acetate (1.0 eq.) and the phenol intermediate **1** (1.0 eq.), as well as 4 Å molecular sieves (0.3 g). The flask was left open to air and the reaction was stirred overnight at RT. The mixture was then filtered through celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford the desired coupled product.

General method for aromatic nucleophilic substitution (B)
To a stirred solution of the appropriate fluorobenzene derivative (1-1.2 eq.) dissolved in dry DMF (~0.24 M) were added cesium carbonate (2.0 eq.) and the phenol intermediate **1** (1.0 eq.) under an inert atmosphere. The reaction was then heated at 80 °C overnight. Once complete conversion was confirmed on TLC, the mixture was diluted with water (15 mL), extracted with EtOAc (3 × 5 mL) and the combined organic fractions were subsequently washed with water (15 mL) and brine (15 mL). The organic phase is then dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture is then purified by flash chromatography, yielding the desired substituted product.

General method for demethylation (C)
The methylated substrate is dissolved in dry DCM (~50 mM) under an inert atmosphere. The solution is then cooled to -78 °C followed by the dropwise addition of BBr_3 (1 M in DCM, 5.0 eq.) under stirring. The mixture is kept at -78 °C for an additional 1.5 h after the addition is complete, after which cooling is removed and the mixture is allowed to reach RT and react for an additional 3 h. Once complete conversion is confirmed on TLC, the reaction is quenched with MeOH at -78 °C. The solvent is then removed under reduced pressure and the residue is resuspended in water (15 mL). The suspension is then extracted with DCM (3 × 5 mL) and the combined organic fractions were subsequently washed with water (15 mL) and brine (15 mL). The organic phase is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture is purified by flash chromatography, yielding the desired phenol.

4-Hexyl-2-methoxyphenol (1)
Under an inert atmosphere, hexylmagnesium bromide (15 mL, 1.0 M in THF, 15 mmol, 3.0 eq.) was added dropwise to a stirred mixture of 4-bromo-2-methoxyphenol (1.02 g, 5 mmol, 1.0 eq.) and $Pd(dppf)Cl_2$ (0.037 g, 0.5 mmol, 0.1 eq.) in dry THF (5 mL) at -78 °C. Upon complete addition the reaction was stirred for an additional 10 min before cooling was removed. The mixture was allowed to come up to RT before heating to reflux. After 2 h, TLC showed complete conversion and heating was stopped. The mixture was allowed to cool to RT, after which further it was quenched with 0.5 N HCl until pH = 2 in an ice bath. The crude mixture is then extracted with diethyl ether (3 × 30 mL) and the combined organic fractions were washed with water (30 mL) and brine (30 mL). The organic layer is then dried on Na_2SO_4, filtered and concentrated *in vacuo*. The crude product is then purified by flash chromatography (EtOAc/heptane, 5%) to give **1** as a clear oil (0.83 g, 80%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (d, *J* = 8.4 Hz, 1H), 6.69-6.64 (m, 2H), 5.45 (s, 1H), 3.87 (s, 3H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.62-1.54 (m, 2H), 1.35-1.26 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.3, 143.5, 135.0, 120.9, 114.1, 111.0, 55.8, 35.7, 31.8, 31.8, 29.0, 22.7, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M]^+$ calc. for $C_{13}H_{20}O_2$: 208.1463, found: 208.1440.

4-hexyl-2-methoxy-1-(2-tolyloxy)benzene (3)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with *o*-tolylboronic acid (0.14 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-5% EtOAc in heptane over 15 min) afforded the desired product (49 mg, 23%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.1 Hz, 1H), 6.97 (t, *J* = 7.1 Hz, 1H), 6.80 (s, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.68 (s, 2H), 3.85 (s, 3H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 1.69-1.57 (m, 2H), 1.41-1.27 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 150.5, 143.9, 138.9, 131.1, 128.6, 126.8, 122.8, 120.6, 119.1, 117.3, 113.0, 56.1, 35.8, 31.8, 31.6, 29.0, 22.6, 16.2, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{26}O_2$: 299.2005, found: 299.2000.

4-hexyl-2-methoxy-1-(3-tolyloxy)benzene (4)
Common intermediate **1** (0.26 g, 1.25 mmol) was reacted with *m*-tolylboronic acid (0.24 g, 1.79 mmol) according to general method **A**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (155 mg, 42%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.85–6.68 (m, 1H), 3.82 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 3H), 1.64 (t, *J* = 7.1 Hz, 2H), 1.40-1.28 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 151.3, 142.9, 140.0, 139.7, 129.3, 123.1, 121.1, 120.8, 117.7, 114.0, 113.2, 56.1, 36.0, 31.9, 31.7, 29.2, 22.7, 21.5, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{26}O_2$: 299.2005, found: 299.2009.

4-hexyl-2-methoxy-1-(4-tolyloxy)benzene (5)
Common intermediate **1** (0.20 g, 1.25 mmol) was reacted with *p*-tolylboronic acid (0.19 g, 1.37 mmol) according to general method **A**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (141 mg, 48%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 3H), 6.80 (d, *J* = 1.3 Hz, 1H), 6.70 (dd, *J* = 1.3, 3.3 Hz, 1H), 3.83 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 3H), 1.62 (t, *J* = 7.1 Hz, 2H), 1.39-1.24 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 151.0, 143.3, 140.0, 131.7, 130.0, 120.7, 120.4, 117.1, 113.0, 56.0, 35.8, 31.7, 31.6, 29.0, 22.6, 20.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{26}O_2$: 299.2005, found: 299.2006.

1-(4-(*tert*-butyl)phenoxy)-4-hexyl-2-methoxybenzene (6)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (4-(*tert*-butyl)phenyl)boronic acid (0.183 g, 1.03 mmol) according to general method **A**. Flash chromatography (1% EtOAc in heptane) afforded the desired product (126 mg, 51%) as a clear oil.
^{1}H NMR (600 MHz, CDCl3): δ = 7.29 (d, *J* = 8.7 Hz, 2H), 6.88-6.85 (m, 3H), 6.81 (s, 1H), 6.72 (d, *J* = 4.0 Hz, 1H), 3.84 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.66–1.59 (m, 2H), 1.38–1.31 (m, 6H), 1.30 (s, 9H), 0.90 (t, *J* = 6.6 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.8, 151.1, 144.9, 143.0, 139.6, 126.2, 120.7, 120.6, 116.4, 112.9, 56.0, 35.8, 34.2, 31.7, 31.5, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{23}H_{32}O_2$: 341.2475, found: 341.2479.

4-hexyl-2-methoxy-1-(3-(trifluoromethyl)phenoxy)benzene (7)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-(trifluoromethyl)phenyl)boronic acid (0.196 g, 1.03 mmol) according to general method **A**. Flash chromatography (1% EtOAc in heptane) afforded the desired product (126 mg, 51%) as a clear oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.15 (s, 1H), 7.05 (q, *J* = 3.5 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.77 (q, *J* = 3.3 Hz, 1H), 3.79 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.68-1.61 (m, 2H), 1.39-1.30 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.7, 151.3, 141.4, 141.1, 131.9 (q, *J* = 31.4 Hz), 129.9, 123.9 (q, *J* = 272.5 Hz), 121.6, 121.0, 119.5, 118.6, 113.3, 113.2, 55.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (565 MHz, $CDCl_3$): δ = -62.7 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M]^+$ calc. for $C_{20}H_{23}O_2F_3$: 352.1650, found: 352.1644.

1-(3-ethoxyphenoxy)-4-hexyl-2-methoxybenzene (8)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-ethoxyphenyl)boronic acid (0.17 g, 1.03 mmol) according to general method **A**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (107 mg, 45%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 8.5 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 1.3 Hz, 1H), 6.73 (dd, *J* = 1.4, 3.2 Hz, 1H), 6.56 (t, *J* = 4.4 Hz, 1H), 6.53-6.46 (m, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 1.63 (q, *J* = 7.2 Hz, 2H), 1.45-1.28 (m, 9H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 159.6, 151.2, 142.4, 140.1, 129.8, 121.3, 120.7, 113.0, 109.0, 108.3, 103.5, 63.4, 56.0, 35.9, 31.7, 31.5, 29.0, 22.6, 14.8, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{28}O_3$: 329.2111, found: 329.2116.

1-(4-ethoxyphenoxy)-4-hexyl-2-methoxybenzene (9)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (4-ethoxyphenyl)boronic acid (0.17 g, 1.03 mmol) according to general method **A**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (88 mg, 37%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 4.5 Hz, 2H), 6.86-6.74 (m, 4H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.61 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.37-1.28 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 151.4, 150.6, 144.3, 138.9, 120.6, 119.3, 118.9, 115.3, 112.9, 63.9, 56.0, 35.8, 31.7, 31.6, 29.0, 22.6, 14.9, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{28}O_3$: 329.2111, found: 329.2116.

***tert*-butyl(3-(4-hexyl-2-methoxyphenoxy)phenyl) carbamate (10)**
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-((*tert*-butoxycarbonyl)amino)phenyl)boronic acid (0.24 g, 1.03 mmol) according to general method **A**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (104 mg, 36%) as a white solid.
^{1}H NMR (300 MHz, CD_3OD): δ = 7.11 (t, *J* = 8.0 Hz, 1H), 7.05-6.95 (m, 2H), 6.94-6.84 (m, 2H), 6.76 (dd, *J* = 1.4, 8.1 Hz, 1H), 6.43 (dd, *J* = 1.4, 8.0 Hz, 1H), 3.76 (s, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.75–1.58 (m, 2H), 1.48 (s, 9H), 1.41-1.31 (s, 6H), 0.91 (t, *J* = 9.0 Hz, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 159.2, 153.7, 151.5, 142.1, 140.4, 140.3, 128.9, 121.4, 120.6, 113.2, 111.9, 109.9, 106.6, 79.5, 55.0, 35.4, 31.5, 31.4, 28.7, 27.3, 22.3, 13.0 ppm;
HRMS (ESI$^+$) *m/z* $[M+Na]^+$ calc. for $C_{24}H_{33}NO_4$: 422.2302, found: 422.2302.

***tert*-butyl (4-(4-hexyl-2-methoxyphenoxy)phenyl) carbamate (11)**
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (4-((*tert*-butoxycarbonyl)amino)phenyl)boronic acid (0.24 g, 1.03 mmol) according to general method **A**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (85 mg, 30%) as a white solid.
^{1}H NMR (300 MHz, CD_3OD): δ = 7.27 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 1.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 3H), 3.76 (s, 3H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.65 (t, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.40-1.31 (m, 6H), 0.93 (s, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 154.1, 151.3, 142.9, 140.0, 133.4, 120.7, 120.5, 120.1, 116.3, 113.1, 79.3, 55.0, 35.3, 31.5, 31.4, 29.6, 28.7, 27.3, 22.3, 13.0 ppm;
HRMS (ESI$^+$) *m/z* $[M+Na]^+$ calc. for $C_{24}H_{33}NO_4$: 422.2302, found: 422.2294.

4-(4-hexyl-2-methoxyphenoxy)-*N*,*N*-dimethylaniline (12)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (4-(dimethylamino)phenyl)boronic acid (0.17 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-10% EtOAc in heptane over 50 min) afforded the desired product (40 mg, 17%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 1.4 Hz, 1H), 6.75-6.68 (m, 3H), 6.64 (dd, *J* = 1.3, 8.1 Hz, 1H), 3.87 (s, 3H), 2.90 (s, 6H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.72-1.51 (m, 2H), 1.38-1.25 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2, 148.7, 147.1, 145.1, 138.2, 121.8, 120.4, 119.4, 118.4, 114., 113.1, 112.7, 56.0, 41.4, 35.8, 31.8, 31.6, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{29}NO_2$: 328.2271, found: 328.2270.

4-hexyl-2-methoxy-1-(3-(methylsulfonyl)phenoxy)benzene (13)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-(methylsulfonyl)phenyl)boronic acid (0.21 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-20% EtOAc in heptane over 20 min) afforded the desired product (98 mg, 38%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.50-7.40 (m, 2H), 7.16 (dd, *J* = 1.3, 8.1 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 1.75-1.58 (m, 2H), 1.43-1.27 (m, 6H), 0.91 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 151.2, 141.7, 141.5, 140.9, 130.5, 121.8, 121.5, 121.1, 120.5, 114.7, 113.2, 55.8, 44.4, 35.9, 31.7, 31.5, 29.1, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{26}O_4S$: 363.1624, found: 363.1616.

1-(3-chlorophenoxy)-4-hexyl-2-methoxybenzene (14)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-chlorophenyl)boronic acid (0.17 g, 1.08 mmol) according to general method **A**. Flash chromatography (0-12% EtOAc in heptane over 20 min) afforded the desired product (168 mg, 73%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 8.1 Hz, 1H), 7.00-6.85 (m, 3H), 6.83-6.71 (m, 3H), 3.79 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 1.63 (qu, *J* = 7.2 Hz, 2H), 1.40-1.27 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 151.3, 141.6, 140.9, 134.8, 130.2, 122.1, 121.7, 120.9, 116.7, 114.8, 113.1, 55.9, 35.9, 31.7, 31.5, 29.1, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H+MeCN]^+$ calc. for $C_{19}H_{23}ClO_2$: 360.1730, found: 360.1696.

1,2-dichloro-4-(4-hexyl-2-methoxyphenoxy)benzene (15)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3,4-dichlorophenyl)boronic acid (0.20 g, 1.03 mmol) according to general method **A**. Flash chromatography (1% EtOAc in heptane) afforded the desired product (91 mg, 36%) as a clear oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.9 Hz, 1H), 6.96 (d, *J* = 2.8 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.78–6.75 (m, 2H), 3.79 (s, 3H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.67–1.60 (m, 2H), 1.37–1.31 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.7, 151.2, 141.3, 141.2, 132.8, 130.6, 125.1, 121.7, 120.9, 118.1, 116.0, 113.1, 55.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{22}Cl_2O_2$: 353.1069, found: 353.0959.

1-(3,5-dichlorophenoxy)-4-hexyl-2-methoxybenzene (16)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3,5-dichlorophenyl)boronic acid (0.20 g, 1.03 mmol) according to general method **A**. Flash chromatography (1% EtOAc in heptane) afforded the desired product (97 mg, 38%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.84–6.75 (m, 4H), 3.80 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.66 (t, *J* = 7.1 Hz, 2H), 1.42-1.25 (m, 6H), 0.91 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 151.3, 141.6, 140.7, 135.3, 122.1, 122.0, 121.0, 115.0, 113.2, 55.9, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{22}Cl_2O_2$: 353.1069, found: 353.0938.

5-(4-hexyl-2-methoxyphenoxy)benzofuran (17)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with benzofuran-5-ylboronic acid (0.17 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-8% EtOAc in heptane over 30 min) afforded the desired product (154 mg, 66%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.00 (dd, *J* = 2.5, 8.9 Hz, 1H), 6.86-6.78 (m, 2H), 6.73–6.65 (m, 2H), 3.85 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.64 (t, *J* = 7.1 Hz, 2H), 1.42-1.26 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 151.0, 150.8, 145.9, 144.2, 139.3, 128.1, 120.6, 119.9, 115.4, 113.0, 111.8, 109.1, 106.8, 56.0, 35.8, 31.7, 31.6, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{24}O_3$: 325.1798, found: 325.1808.

4-hexyl-2-methoxy-1-(2-nitrophenoxy)benzene (18)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-fluoro-2-nitrobenzene (0.11 g, 0.72 mmol) according to general method **B**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (176 mg, 74%) as an off-white solid.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 1.7, 8.2 Hz, 1H), 7.41 (dt, *J* = 1.7, 7.9 Hz, 1H), 7.09 (dt, *J* = 1.3, 7.7 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.83–6.81 (m, 2H), 6.78 (dd, *J* = 1.9, 8.1 Hz, 1H), 3.78 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.67–1.60 (m, 2H), 1.37–1.30 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.1, 151.0, 141.6, 141.0, 139.8, 133.9, 125.6, 121.7, 121.0, 117.8, 113.3, 56.0, 35.8, 31.7, 31.5, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{23}NO_4$: 330.1698, found: 330.1704.

4-hexyl-2-methoxy-1-(3-nitrophenoxy)benzene (19)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-fluoro-3-nitrobenzene (0.11 g, 0.72 mmol) according to general method **B**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (126 mg, 53%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.29-7.21 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.84 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.75-1.58 (m, 2H), 1.44-1.28 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 151.2, 149.2, 141.7, 140.7, 129.9, 122.5, 122.0, 121.1, 116.7, 113.2, 110.8, 55.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+Na]^+$ calc. for $C_{19}H_{23}NO_4$: 352.1519, found: 352.1516.

4-hexyl-2-methoxy-1-(4-nitrophenoxy)benzene (20)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-fluoro-4-nitrobenzene (0.11 g, 0.72 mmol) according to general method **B**. Flash chromatography (0-10% EtOAc in heptane over 20 min) afforded the desired product (210 mg, 89%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 9.2 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.85 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 3.77 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.66 (t, *J* = 7.1 Hz, 2H), 1.44-1.24 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 151.2, 142.1, 140.3, 127.9, 125.8, 122.2, 121.1, 115.7, 113.2, 55.8, 36.0, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{23}NO_4$: 330.1698, found: 330.1696.

2-(4-hexyl-2-methoxyphenoxy)benzonitrile (21)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 2-fluorobenzonitrile (0.09 g, 0.72 mmol) according to general method **B**. Flash chromatography (0-20% EtOAc in heptane over 25 min) afforded the desired product (212 mg, 95%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.39 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.08-6.96 (m, 2H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.64 (t, *J* = 7.3 Hz, 2H), 1.41-1.27 (s, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 151.3, 141.8, 140.7, 133.9, 133.5, 122.2, 121.8, 121.0, 116.3, 115.0, 113.5, 102.2, 56.0, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{23}NO_2$: 310.1801, found: 310.1802.

4-(4-hexyl-2-methoxyphenoxy)benzonitrile (22)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 4-fluorobenzonitrile (0.09 g, 0.72 mmol) according to general method **B**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (157 mg, 71%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 2H), 7.00-6.88 (m, 3H), 6.83 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.74–1.57 (m, 2H), 1.44-1.27 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 151.3, 141.9, 140.3, 133.9, 122.2, 121.1, 119.1, 116.4, 113.1, 105.0, 55.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{23}NO_2$: 310.1801, found: 310.1802.

4-hexyl-2-methoxy-1-(4-(methylsulfonyl)phenoxy)benzene (23)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-fluoro-4-(methylsulfonyl)benzene (0.13 g, 0.72 mmol) according to general method **B**. Flash chromatography (0-20% EtOAc in heptane over 30 min) afforded the desired product (183 mg, 70%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.8 Hz, 2H), 7.04-6.94 (m, 3H), 6.84 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.77

(s, 3H), 3.03 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.66 (t, *J* = 7.0 Hz, 2H), 1.43-1.26 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 151.3, 141.9, 140.4, 133.2, 129.5, 122.2, 121.1, 116.2, 113.2, 55.8, 44.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{26}O_4S$: 363.1622, found: 363.1622.

4-hexyl-2-methoxy-1-(2-(trifluoromethyl)phenoxy)benzene (24)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-fluoro-2-(trifluoromethyl)benzene (0.12 g, 0.72 mmol) according to general method **B**. Flash chromatography (0-7% EtOAc in heptane over 20 min) afforded the desired product (67 mg, 26%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 1.4 Hz, 1H), 6.76 (dd, *J* = 1.6, 8.1 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 1.64 (t, *J* = 7.1 Hz, 2H), 1.39-1.28 (m, 6H), 0.91 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 151.4, 141.7, 141.1, 132.9, 126.9 (q, *J* = 4.9 Hz), 125.5, 121.9, 121.3, 121.0, 119.4 (d, *J* = 31.6 Hz), 116.2, 113.7, 56.2, 35.9, 32.0, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -61.9 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{23}F_3O_2$: 353.1723, found: 353.1728.

3-(4-hexyl-2-methoxyphenoxy)-*N*,*N*-dimethylbenzamide (25)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-(dimethylcarbamoyl)phenyl)boronic acid (0.21 g,1.03 mmol) according to general method **A**. Flash chromatography (0-45% EtOAc in heptane over 35 min) afforded the desired product (199 mg, 78%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.00–6.88 (m, 3H), 6.80 (s, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 3.80 (s, 3H), 3.06 (s, 3H), 2.96 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.63 (qu, *J* = 7.3 Hz, 2H), 1.39-1.27 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 158.3, 151.2, 142.0, 140.5, 137.6, 129.6, 121.4, 120.9, 120.6, 117.8, 115.2, 113.0, 55.9, 39.5, 35.9, 35.3, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{22}H_{29}NO_3$: 356.2220, found: 356.1.

***N*,*N*-diethyl-3-(4-hexyl-2-methoxyphenoxy)benzamide (26)**
Common intermediate **1** (0.10 g, 0.48 mmol) was reacted with (3-(diethylcarbamoyl)phenyl)boronic acid (0.16 g, 0.72 mmol) according to general method **A**. Flash chromatography (0-45% EtOAc in heptane over 35 min) afforded the desired product (199 mg, 78%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 8.3 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.96 (dd, *J* = 2.2, 8.3 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 1.3 Hz, 1H), 6.80 (s, 1H), 6.74 (dd, *J* = 1.5, 8.1 Hz, 1H), 3.80 (s, 3H), 3.47 (bs, 2H), 3.25 (bs, 2H), 2.60 (t, *J* = 7.7 Hz, 2H), 1.69-1.57 (m, 2H), 1.40-1.27 (m, 6H), 1.19 (bs, 3H), 1.05 (bs, 3H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 158.4, 151.2, 142.0, 140.5, 138.5, 129.7, 121.4, 120.9, 120.0, 117.5, 114.4, 113.0, 55.9, 43.2, 39.2, 35.9, 31.7, 31.5, 9.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{33}NO_3$: 384.2533, found: 384.0.

3-(4-hexyl-2-methoxyphenoxy)-*N*-isobutylbenzamide (27)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-(isobutylcarbamoyl)phenyl)boronic acid (0.23 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-40% EtOAc in heptane over 25 min) afforded the desired product (109 mg, 39%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 3H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.11 (bs, 1H), 3.80 (s, 3H), 3.26 (t, *J* = 6.3 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 2H), 1.87 (sept, *J* = 6.6 Hz, 1H), 1.70-1.54 (m, 3H), 1.44-1.24 (m, 6H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.94-0.86 (m, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 158.7, 151.2, 141.8, 140.7, 136.6, 129.6, 121.4, 120.9, 120.3, 119.3, 115.2, 113.1, 55.9, 47.3, 35.9, 31.7, 31.5, 29.0, 28.6, 22.6, 20.2, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{33}NO_3$: 384.2533, found: 384.2530.

(3-(4-hexyl-2-methoxyphenoxy)phenyl)(morpholino)methanone (28)
Common intermediate **1** (0.08 g, 0.36 mmol) was reacted with (3-(morpholine-4-carbonyl)phenyl)boronic acid (0.13 g, 0.54 mmol) according to general method **A**. Flash chromatography (0-80% EtOAc in heptane over 15 min) afforded the desired product (108 mg, 75%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.82 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.77-3.26 (m, 8H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.66 (t, *J* = 6.8 Hz, 2H), 1.44-1.24 (m, 6H), 0.89 (t, *J* = 6.0 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 158.5, 151.2, 141.7, 140.8, 136.5, 129.8, 121.5, 120.9, 120.6, 118.0, 115.1, 113.0, 66.9, 55.8, 48.2, 42.5, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{31}NO_4$: 398.2326, found: 398.2325.

4-(4-hexyl-2-methoxyphenoxy)benzamide (29)
Common intermediate **1** (0.150 g, 0.72 mmol) was reacted with (4-carbamoylphenyl)boronic acid (0.170 g, 1.03 mmol) according to general method **A**. DMSO (12 mL) was added to aid in solubilising the boronic acid. After celite filtration, an additional aqueous workup was performed to remove DMSO. The solvent was evaporated and the crude was diluted with 1 × 20 mL sat. $NaHCO_3$. The mixture was extracted with DCM (3 × 15 mL) and the combined organic layers were washed with 1 × 20 mL water, followed by 1 × 20 mL brine. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed solvent *in vacuo*. Flash chromatography (0-70% EtOAc in heptane over 25 min) afforded the desired product (35 mg, 15%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.9 Hz, 2H), 6.94 (t, *J* = 9.9 Hz, 3H), 6.79 (t, *J* = 9.6 Hz, 2H), 5.89 (bs, 2H), 3.78 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.67-1.53 (m, 2H), 1.46-1.20 (m, 6H), 1.02-0.80 (m, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 161.8, 151.3, 141.2, 129.2, 126.7, 122.0, 120.9, 115.9, 113.1, 55.9, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{25}NO_3$: 328.1907, found: 328.1907.

***N*-ethyl-4-(4-hexyl-2-methoxyphenoxy)benzamide (30)**
Common intermediate **1** (0.13 g, 0.62 mmol) was reacted with (4-(ethylcarbamoyl)phenyl)boronic acid (0.17 g, 0.89 mmol) according to general method **A**. Flash chromatography (0-50% EtOAc in heptane over 25 min) afforded the desired product (42 mg, 19%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.7 Hz, 2H), 6.92 (t, *J* = 9.1 Hz, 3H), 6.82 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.98 (bs, 1H), 3.78 (s, 3H), 3.48 (qu, *J* = 6.8 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.65 (t, *J* = 7.0 Hz, 2H), 1.43-1.28 (m, 6H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 161.1, 151.3, 141.4, 141.0, 128.5, 128.3, 121.8, 120.9, 116.0, 113.1, 55.9, 35.9, 34.9, 31.7, 31.5, 29.0, 22.6, 15.0, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{22}H_{29}NO_3$: 356.2220, found: 356.1.

(4-(4-hexyl-2-methoxyphenoxy)phenyl)(pyrrolidin-1-yl)methanone (31)
Common intermediate **1** (0.08 g, 0.36 mmol) was reacted with (4-(pyrrolidine-1-carbonyl)phenyl)boronic acid (0.12 g, 0.52 mmol) according to general method **A**. Flash chromatography (0-80% EtOAc in heptane over 30 min) afforded the desired product (88 mg, 64%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.6 Hz, 2H), 6.96-6.85 (m, 3H), 6.82 (s, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.79 (s, 3H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.01–1.78 (m, 4H), 1.63 (qu, *J* = 7.3 Hz, 2H), 1.40-1.27 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 159.8, 151.3, 141.6, 140.8, 129.0, 121.7, 120.8, 115.8, 113.1, 55.9, 49.8, 46.3, 35.9, 31.7, 31.5, 29.0, 26.5, 24.5, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{31}NO_3$: 382.2377, found: 382.0.

(4-(4-hexyl-2-methoxyphenoxy)phenyl)(morpholino) methanone (32)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (4-(morpholine-4-carbonyl)phenyl)boronic acid (0.25 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-85% EtOAc in heptane over 15 min) afforded the desired product (195 mg, 69%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 9.2 Hz, 2H), 6.92 (t, *J* = 7.8 Hz, 3H), 6.83 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.76-3.51 (m, 8H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.64 (qu, *J* = 7.4 Hz, 2H), 1.44-1.28 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 160.0, 151.4, 141.4, 141.0, 129.0, 128.5, 121.8, 120.9, 116.1, 113.1, 66.9, 55.9, 48.1, 43.4, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{31}NO_4$: 398.2326, found: 398.2321.

***N*-(3-(4-hexyl-2-methoxyphenoxy)phenyl)acetamide (33)**
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with (3-acetamidophenyl)boronic acid (0.18 g, 1.03 mmol) according to general method **A**. Flash chromatography (0-60% EtOAc in heptane over 30 min) afforded the desired product (106 mg, 43%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.12 (m, 2H), 7.03 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.81 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.13 (s, 3H), 1.69-1.54 (m, 2H), 1.44-1.23 (m, 6H), 0.89 (s, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 158.9, 151.2, 142.2, 140.3, 139.0, 129.8, 121.4, 120.8, 113.6, 113.1, 112.5, 108.2, 56.0, 35.9, 31.7, 31.5, 29.0, 24.6, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{27}NO_3$: 342.2064, found: 342.2068.

***N*-(4-(4-hexyl-2-methoxyphenoxy)phenyl)acetamide (34)**
Common intermediate **1** (0.300 g, 1.44 mmol) was reacted with (4-acetamidophenyl)boronic acid (0.37 g, 2.06 mmol) according to general method **A**. Flash chromatography (2% MeOH in DCM) followed by recrystallisation in an EtOAc/heptane mixture afforded the desired product (67 mg, 14%) as a white solid.
^{1}H NMR (300 MHz, CD_3OD): δ = 7.40 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 1.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.81-6.71 (m, 3H), 3.75 (s, 3H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.09 (s, 3H), 1.64 (qu, *J* = 7.7 Hz, 2H), 1.45-1.25 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 170.0, 155.2, 151.4, 142.5, 140.3, 132.7, 121.4, 121.0, 120.6, 116.0, 113.1, 54.9, 35.4, 31.5, 31.4, 28.7, 22.3, 22.2, 13.0 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{27}NO_3$: 342.2064, found: 342.2060.

2-fluoro-1-(4-hexyl-2-methoxyphenoxy)-4-nitrobenzene (35)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1,2-difluoro-4-nitrobenzene (0.14 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-17% EtOAc in heptane over 15 min) afforded the desired product (189 mg, 76%) as a light-yellow solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 2.6, 10.5 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.73 (t, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.66 (t, *J* = 7.0 Hz, 2H), 1.42-1.27 (s, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 152.3 (d, *J* = 10.7 Hz), 150.9, 149.4, 142.4, 141.7 (d, *J* = 6.7), 140.0, 121.9, 121.1, 120.4 (d, *J* = 2.9), 115.7, 113.2, 112.7 (d, *J* = 22.8 Hz), 55.8, 35.9, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -130.1 (s) ppm;
HRMS (ESI$^-$) *m/z* $[M]^-$ calc. for $C_{19}H_{22}FNO_4$: 347.1533, found: 347.1515.

2-fluoro-1-(4-hexyl-2-methoxyphenoxy)-4-(methylsulfonyl) benzene (36)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1,2-difluoro-4-(methylsulfonyl)benzene (0.17 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-30% EtOAc in heptane over 15 min) afforded the desired product (194 mg, 71%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 1.9, 9.8 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.87-6.74 (m, 3H), 3.78 (s, 3H), 3.05 (s, 3H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.64 (qu, *J* = 7.5 Hz, 2H), 1.43-1.27 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 151.0, 142.2, 140.1, 133.7 (d, *J* = 5.1 Hz), 124.2 (d, *J* = 3.1 Hz), 121.8, 121.0, 116.8, 116.3, 116.0, 113.2, 55.8, 44.7, 35.9, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -130.4 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{25}FO_4S$: 381.1530, found: 381.1518.

3-fluoro-4-(4-hexyl-2-methoxyphenoxy)benzonitrile (37)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 3,4-difluorobenzonitrile (0.12 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-12% EtOAc in heptane over 15 min) afforded the desired product (233 mg, 98%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 1.7, 10.3 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.72 (t, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.65 (t, *J* = 7.1 Hz, 2H), 1.43-1.27 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 150.9, 150.7 (d, *J* = 10.5 Hz), 150.0, 142.2, 140.1, 129.2 (d, *J* = 3.5 Hz), 121.8, 121.0, 120.2 (d, *J* = 21.1 Hz), 117.9, 117.2, 113.2, 105.2 (d, *J* = 8.1 Hz), 55.8, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -131.0 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{22}FNO_2$: 328.1707, found: 328.1708.

2-chloro-4-(4-hexyl-2-methoxyphenoxy)-1-nitrobenzene (38)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 2-chloro-4-fluoro-1-nitrobenzene (0.15 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-17% EtOAc in heptane over 15 min) afforded the desired product (241 mg, 92%) as a yellow solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.1 Hz, 1H), 7.02-6.93 (m, 2H), 6.88-6.77 (m, 3H), 3.78 (s, 3H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.65 (qu, *J* = 9.1 Hz, 2H), 1.44-1.27 (m, 6H), 0.90 (t, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 151.1, 142.5, 141.4, 139.8, 129.5, 127.8, 122.2, 121.1, 118.4, 114.4, 113.2, 55.8, 36.0, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M\text{-}Me]^+$ calc. for $C_{19}H_{22}ClNO_4$: 348.1003, found: 348.1353.

2-chloro-4-(4-hexyl-2-methoxyphenoxy)benzonitrile (39)
Common intermediate **1** (0.07 g, 0.31 mmol) was reacted with 2-chloro-4-fluorobenzonitrile (0.05 g, 0.35 mmol) according to general method **B**. Flash chromatography (0-17% EtOAc in heptane over 15 min) afforded the desired product (102 mg, 95%) as an off-white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.7 Hz, 1H), 7.00-6.92 (m, 2H), 6.87-7.77 (m, 3H), 3.77 (s, 3H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.66 (t, *J* = 6.9 Hz, 2H), 1.44-1.27 (m, 6H), 0.90 (t, *J* = 6.1 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 151.1, 142.4, 139.7, 138.2, 135.0, 122.2, 121.1, 117.2, 116.3, 114.8, 113.2, 105.9, 55.8, 36.0, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{22}ClNO_2$: 344.1411, found: 344.1409.

1-chloro-4-fluoro-5-(4-hexyl-2-methoxyphenoxy)-2-nitro benzene (40)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 1-chloro-4,5-difluoro-2-nitrobenzene (0.17 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-13% EtOAc in heptane over 15 min) afforded the desired product (204 mg, 74%) as an off-white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 10.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.88-6.79 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.66 (qu, *J* = 7.6 Hz, 2H), 1.45-1.28 (m, 7H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 150.7, 147.8, 142.9, 139.5, 124.1, 121.9, 121.2, 118.5, 115.1, 114.8, 113.3, 55.8, 36.0, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -131.7 (s) ppm;
HRMS (ESI$^-$) *m/z* $[M\text{-}MeO+H]^-$ calc. for $C_{19}H_{21}ClFNO_4$: 351.1032, found: 351.1163.

2-chloro-5-fluoro-4-(4-hexyl-2-methoxyphenoxy)benzonitrile (41)
Common intermediate **1** (0.15 g, 0.72 mmol) was reacted with 2-chloro-4,5-difluorobenzonitrile (0.15 g, 0.86 mmol) according to general method **B**. Flash chromatography (0-14% EtOAc in heptane over 15 min) afforded the desired product (224 mg, 86%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 9.7 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.87-6.79 (m, 2H), 6.71 (d, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.65 (qu, *J* = 7.4, 2H), 1.45-1.27 (m, 6H), 0.90 (t, *J* = 6.1 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 151.2 (d, *J* = 11.3 Hz), 150.8, 148.6, 142.8, 139.4, 133.2 (d, *J* = 3.7 Hz), 121.9, 121.2, 121.1, 120.9, 117.6, 115.3, 113.3, 105.6 (*J* = 7.8 Hz), 55.8, 36.0, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -133.1 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{21}ClFNO_2$: 362.1318, found: 362.1313.

3-fluoro-4-(4-hexyl-2-methoxyphenoxy)benzamide (42)
Compound **37** (0.08 g, 0.23 mmol, 1.0 eq.) was added to a vial containing 0.5 mL of a 0.2% w/v solution of NaOH in EtOH/H_2O (7:3). The vial was loosely stoppered and the mixture was heated to 80 °C under stirring overnight. Full conversion was confirmed by TLC, at which point the reaction was allowed to cool to RT and the solution was diluted with 5 mL EtOAc. The mixture was then washed with 1 × 5 mL sat. $NaHCO_3$. The aqueous layer was subsequently extracted 2 × 5 mL EtOAc. The combined organic fractions were then washed 1 × 10 mL water and 1 × 10 mL brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (0-75% EtOAc in heptane over 7 min) afforded the desired product (56 mg, 71%) as a white solid
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 11.2 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.87-6.71 (m, 3H), 5.81 (bs, 2H), 3.79 (s, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.68 (qu, *J* = 7.4 Hz, 2H), 1.42-1.26 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 150.9, 150.5, 149.4, 141.4, 141.2, 123.6, 121.2, 120.9, 117.0, 116.2, 116.0, 113.2, 55.9, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.4 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{24}FNO_3$: 346.1813, found: 346.1804.

3-fluoro-4-(4-hexyl-2-methoxyphenoxy)benzoic acid (43)
To 3 mL of an EtOH/H_2O (1:1) mixture were added KOH (0.171 g, 3.05 mmol, 10.0 eq.) and compound **37** (0.100 g, 0.31 mmol, 1.0 eq.). The solution was stirred under reflux at 100 °C overnight. Full conversion of the starting material was confirmed on TLC and the solution was allowed to cool to RT. The mixture was then quenched with a 2 M HCl solution until pH 1. The resulting suspension was extracted with EtOAc (3 × 5 mL), after which the combined organic fractions were washed with 1 × 10 mL water and 1 × 10 mL brine. The organic layer is then dried over Na_2SO_4 and filtered, after which the solvent is removed *in vacuo*. This yielded the desired product (90 mg, 85%) as a white solid without the need for further purification.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 11.1 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.85–6.68 (m, 3H), 3.78 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.64 (qu, *J* = 6.8 Hz, 2H), 1.43-1.27 (m, 6H), 0.90 (s, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 153.5, 151.3 (d, *J* = 10.7 Hz), 151.0, 150.2, 141.7, 140.7, 127.0, 123.3 (d, *J* = 6.3 Hz), 121.3 (d, *J* = 46.8 Hz), 118.4 (d, *J* = 19.7 Hz), 116.4, 113.2, 55.9, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -133.0 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{23}FO_4$: 347.1653, found: 347.1649.

(3-fluoro-4-(4-hexyl-2-methoxyphenoxy)phenyl)(morpholino)methanone (44)
A solution of **43** (0.04 g, 0.12 mmol, 1.0 eq.) in dry DMF (0.5 mL) under argon was cooled to at 0 °C. To this was added HATU (0.048 g, 0.13 mmol, 1.1 eq.) and DIPEA (60 µL, 0.35 mmol, 3.0 eq.) and the resulting solution was stirred for 30 min while allowed to come up to RT. Subsequently morpholine (0.01 g, 0.13 mmol, 1.1 eq.) was added and allowed to react for 2 h at RT. Full conversion was confirmed on TLC, at which point the reaction was diluted with 5 mL water. The resulting suspension was extracted 3 × 5 mL DCM, after which the combined organic fractions were washed with 1 × 10 mL water and 1 × 10 mL brine. The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (0-55% EtOAc in heptane over 15 min) affords the desired product (27 mg, 56%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 12.0 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.88-6.70 (m, 3H), 3.80 (s, 3H), 3.77-3.52 (m, 8H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.63 (qu, *J* = 6.9 Hz, 2H), 1.43-1.27 (m, 6H), 0.89 (s, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 153.9, 150.9, 150.6, 147.5 (d, *J* = 10.9 Hz), 141.5, 141.1, 129.4 (d, *J* = 5.3 Hz), 123.6 (d, *J* = 3.6 Hz), 120.8, 117.7, 116.1 (d, *J* = 19.7 Hz), 113.1, 66.8, 55.9, 35.9, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.2 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{24}H_{30}FNO_4$: 416.2231, found: 416.2231.

***tert*-butyl 4-(3-fluoro-4-(4-hexyl-2-methoxyphenoxy) benzoyl)piperazine-1-carboxylate (45)**
A solution of **43** (0.04 g, 0.12 mmol, 1.0 eq.) in dry DMF (0.5 mL) under argon was cooled to at 0 °C. To this was added

HATU (0.05 g, 0.13 mmol, 1.1 eq.) and DIPEA (60 µL, 0.35 mmol, 3.0 eq.) and the resulting solution was stirred for 30 min while allowed to come up to RT. Subsequently *tert*-butyl piperazine-1-carboxylate (0.02 g, 0.13 mmol, 1.1 eq.) was added and allowed to react for 2 h at RT. Full conversion was confirmed on TLC, at which point the reaction was diluted with 5 mL water. The resulting suspension was extracted 3 × 5 mL DCM, after which the combined organic fractions were washed with 1 × 10 mL water and 1 × 10 mL brine. The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (0-40% EtOAc in heptane over 15 min) affords the desired product (43 mg, 72%) as an off-white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 10.6 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.85-6.70 (m, 3H), 3.80 (s, 3H), 3.67-3.38 (m, 8H), 2.61 (t, *J* = 6.9 Hz, 2H), 1.70-1.56 (m, 2H), 1.47 (s, 9H), 1.41-1.27 (m, 6H), 0.89 (s, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 154.5, 153.9, 150.9, 150.5, 147.6 (d, *J* = 10.8 Hz), 141.4, 141.1, 129.5 (d, *J* = 5.1 Hz), 123.6 (d, *J* = 3.4 Hz), 120.9 (d, *J* = 6.8 Hz), 117.6, 116.1 (d, *J* = 19.6 Hz), 113.1, 80.4, 55.9, 47.2, 43.7, 35.9, 31.7, 31.5, 29.0, 28.4, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.2 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{29}H_{39}FN_2O_5$: 515.2916, found: 515.2914.

3-fluoro-4-(4-hexyl-2-methoxyphenoxy)aniline (46)
Procedure adapted from Pan *et al*.[26] To a stirred solution of **35** (0.09 g, 0.27 mmol, 1.0 eq.) in EtOH (5 mL) kept at 0 °C conc. HCl (0.5 mL) was added dropwise. The solution is stirred under cooling for 5 min, meanwhile white precipitation was observed. Zinc powder (0.42 g, 6.39 mmol, 23.7 eq.) is slowly added to the mixture and the reaction was allowed to come up to RT. After 1 h, TLC indicated complete conversion and the reaction is quenched with Et_3N. The solvent is then removed under reduced pressure and the residue redissolved in 5 mL DCM. The suspension is then washed with 1 × 5 mL sat. $NaHCO_3$, followed by 1 × 5 mL water and 1 × 5 mL brine. The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (0-35% EtOAc in heptane over 15 min) affords the desired product (75 mg, 87%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83 (t, *J* = 8.8 Hz, 1H), 6.77 (s, 1H), 6.63 (s, 2H), 6.47 (dd, *J* = 2.3, 12.2 Hz, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.63 (bs, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.59 (qu, *J* = 6.8 Hz, 2H), 1.41-1.20 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 153.0, 149.4, 145.3, 143.7 (d, *J* = 9.2 Hz), 138.1, 135.6 (d, *J* = 12.1 Hz), 122.7, 120.3, 116.3, 112.8, 110.7 (d, *J* = 2.0 Hz), 103.8 (d, *J* = 21.4 Hz), 56.1, 35.7, 31.7, 31.6, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -130.1 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{24}FNO_2$: 318.1864, found: 318.1863.

1-(2-fluorophenoxy)-4-hexyl-2-methoxybenzene (47)
Procedure adapted from Pan *et al*.[26] To a stirred solution of **46** (0.07 g, 0.22 mmol, 1.0 eq.) in EtOH (2.5 mL) kept at 0 °C conc. H_2SO_4 (0.25 mL) was added dropwise. A solution of $NaNO_2$ (0.03 g, 0.44 mmol, 2.0 eq.) in water (0.25 mL) is very slowly added over 30 min at 0 °C under strong stirring. The mixture is then allowed to come up to RT and a portion of zinc powder (0.14 mg, 2.20 mmol, 10.0 eq.) is added. The reaction is refluxed for 30 min, the remaining zinc powder is added (0.18 g, 2.69 mmol, 12.2 eq.) and the reflux is continued for an additional 2.5 h. Full conversion is then confirmed by TLC, at which point heating is stopped and the mixture is allowed to cool to RT. The solids were then filtered off and the filtrate is concentrated under reduced pressure. The resulting aqueous suspension is then neutralized with sat. $NaHCO_3$ until pH 8 and extracted 2 × 5 mL EtOAc. The combined organic fractions were washed with 1 × 10 mL water, 1 × 10 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (0-24% EtOAc in heptane over 20 min) affords the desired product (31 mg, 46%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.08 (m, 1H), 7.04-6.96 (m, 2H), 6.91–6.79 (m, 3H), 6.70 (dd, *J* = 1.3, 8.1 Hz, 1H), 3.84 (s, 3H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.63 (qu, *J* = 7.0 Hz, 2H), 1.42-1.26 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 151.7, 150.5, 145.3 (d, *J* = 11.0 Hz), 143.0, 140.0, 124.3 (d, *J* = 3.4 Hz), 123.3 (d, *J* = 6.6 Hz), 120.6, 119.3 (d, *J* = 16.5 Hz), 116.7 (d, *J* = 18.2 Hz), 113.1, 56.0, 35.8, 31.7, 31.5, 29.0, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.9 (s) ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{23}FO_2$: 303.1755, found: 303.1748.

5-hexyl-2-phenoxyphenol (PT04)
Compound **2** (0.11 g, 0.39 mmol) was demethylated *via* general method **C**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (90 mg, 86%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 7.9 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.65 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.46 (s, 1H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.61 (t, *J* = 7.1 Hz, 2H), 1.40-1.23 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 147.3, 141.0, 140.1, 129.8, 123.3, 120.5, 119.0, 117.6, 116.0, 35.5, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{22}O_2$: 269.1547, found: 269.1553.

5-hexyl-2-(2-tolyloxy)phenol (PT70)
Compound **3** (0.05 g, 0.16 mmol) was demethylated *via* general method **C**. Flash chromatography (0-15% EtOAc in heptane over 7 min) afforded the desired product (22 mg, 47%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 6.4 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.88-6.81 (m, 2H), 6.60 (s, 2H), 5.55 (s, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 2.28 (s, 3H), 1.59 (t, *J* = 6.5 Hz, 3H), 1.38-1.23 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 146.5, 141.9, 139.1, 131.5, 129.1, 127.2, 123.9, 120.3, 118.1, 117.0, 115.8, 35.5, 31.7, 31.4, 29.0, 22.6, 16.1, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{24}O_2$: 283.1703, found: 283.1706.

5-hexyl-2-(3-tolyloxy)phenol (RGB01)
Compound **4** (0.15 g, 0.50 mmol) was demethylated *via* general method **C**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (46 mg, 45%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 3H), 6.64 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.47 (s, 1H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.32 (s, 3H), 1.59 (qu, *J* = 7.2 Hz, 2H), 1.38-1.23 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 147.3, 141.1, 140.1, 140.0, 129.5, 124.1, 120.5, 119.0, 118.2, 116.0, 114.6, 35.5, 31.8, 31.4, 29.0, 22.6, 21.4, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{24}O_2$: 285.1849, found: 285.1838.

5-hexyl-2-(4-tolyloxy)phenol (RGB02)
Compound **5** (0.13 g, 0.45 mmol) was demethylated *via* general method **C**. Flash chromatography (2% EtOAc in heptane) afforded the desired product (87 mg, 68%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 1.6 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.63 (dd, *J* = 1.6, 8.2 Hz, 1H), 5.49 (s, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.32 (s, 3H), 1.61 (t, *J* = 7.2 Hz, 2H), 1.38-1.23 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 147.1, 141.6, 139.7, 132.9, 130.3, 120.4, 118.4, 117.8, 115.9, 35.5, 31.7, 31.4, 29.0, 22.6, 20.7, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{24}O_2$: 285.1849, found: 285.1833.

2-(4-(*tert*-butyl)phenoxy)-5-hexylphenol (RGB03)
Compound **6** (0.13 g, 0.37 mmol) was demethylated *via* general method **C**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (110 mg, 91%) as a brown oil.
^{1}H NMR (600 MHz, CD_3OD): δ =7.30 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.61 (dd, *J* = 2.1, 8.2 Hz, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.60 (qu, *J* = 7.5 Hz, 2H), 1.35–1.31 (m, 6H), 1.29 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, CD_3OD): δ = 157.4, 149.8, 146.1, 143.1, 141.0, 127.3, 121.6, 121.0, 117.9, 117.6, 36.4, 35.0, 32.9, 32.7, 31.9, 30.0, 23.7, 14.4 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{22}H_{30}O_2$: 327.2318, found: 327.2316.

5-hexyl-2-(3-(trifluoromethyl)phenoxy)phenol (RGB04)
Compound **7** (0.11 g, 0.31 mmol) was demethylated *via* general method **C**. Flash chromatography (0-18% EtOAc in heptane over 20 min) afforded the desired product (59 mg, 56%) as a clear oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.26 (s, 1H), 7.15 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.84-6.81 (m, 1H), 6.70 (dd, *J* = 2.0, 8.2 Hz, 1H), 5.35 (s, 1H), 2.57 (t, *J* = 7.8 Hz, 2H), 1.61 (qu, *J* = 7.5 Hz, 2H), 1.37–1.29 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.6, 147.3, 141.1, 140.0, 132.3 (q, *J* = 32.7 Hz), 130.4, 120.9, 120.4, 119.8 (q, *J* = 3.9 Hz), 119.4, 119.3, 116.5, 114.3 (q, *J* = 3.7 Hz), 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.7 (s) ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{21}F_3O_2$: 337.1421, found: 337.1414.

5-hexyl-2-(3-hydroxyphenoxy)phenol (RGB05)
Compound **8** (0.11 g, 0.33 mmol) was demethylated *via* general method **C**. Flash chromatography (40% EtOAc in DCM, 2% TFA) afforded the desired product (87 mg, 91%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 2.1, 8.2 Hz, 1H), 6.58 (ddd, *J* = 0.8, 2.4, 8.2 Hz, 1H), 6.55 (ddd, *J* = 0.7, 2.3, 8.0 Hz, 1H), 6.48 (t, *J* = 2.3 Hz, 1H), 5.39 (s, 1H), 4.77 (s, 1H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.60 (qu, *J* = 7.6 Hz, 2H), 1.36–1.28 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.6, 156.8, 147.3, 140.5, 140.4, 130.5, 120.6, 119.6, 116.1, 110.2, 109.7, 104.6, 35.5, 31.7, 31.4, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+Na]^+$ calc. for $C_{18}H_{22}O_3$: 309.1461, found: 309.1460.

5-hexyl-2-(4-hydroxyphenoxy)phenol (RGB06)
Compound **9** (0.08 g, 0.25 mmol) was demethylated *via* general method **C**. Flash chromatography (20% EtOAc in heptane) afforded the desired product (55 mg, 71%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.52 (s, 1H), 4.58 (s, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.59 (qu, *J* = 6.3 Hz, 2H), 1.40-1.24 (m, 6H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6, 150.5, 146.7, 142.3, 139.3, 120.3, 119.6, 117.5, 116.3, 115.8, 35.4, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{22}O_3$: 285.1496, found: 285.1501.

2-(3-aminophenoxy)-5-hexylphenol (PT14)
Compound **10** (0.10 g, 0.26 mmol) was demethylated *via* general method **C**. Flash chromatography (30% EtOAc in heptane, 2% Et_3N) afforded the desired product (63 mg, 85%) as a white solid.
^{1}H NMR (300 MHz, CD_3OD): δ = 6.98 (t, *J* = 8.0 Hz, 1H), 6.81-6.71 (m, 2H), 6.61 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.37 (d, *J* = 7.9 Hz, 1H), 6.29 (t, *J* = 2.0 Hz, 1H), 6.24 (dd, *J* = 1.9, 8.1 Hz, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.59 (qu, *J* = 7.0 Hz, 2H), 1.40-1.24 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 159.3, 148.9, 148.4, 141.5, 139.6, 129.4, 120.5, 119.5, 116.4, 109.3, 106.4, 103.8, 35.0, 31.5, 31.3, 28.6, 22.3, 13.0 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{18}H_{23}NO_2$: 286.1801, found: 286.1805.

2-(4-aminophenoxy)-5-hexylphenol (PT15)
Compound **11** (0.09 g, 0.21 mmol) was demethylated *via* general method **C**. Recrystallization from DCM afforded the HBr salt of the product (72 mg, 92%) as a white solid.
^{1}H NMR (300 MHz, CD_3OD): δ = 7.27 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 1.5 Hz, 1H), 6.68 (dd, *J* = 1.6, 8.1 Hz, 1H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.61 (qu, *J* = 7.0 Hz, 2H), 1.47-1.27 (m, 6H), 0.91 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 158.5, 148.8, 141.0, 140.3, 125.1, 123.3, 121.3, 119.8, 117.1, 116.8, 35.1, 31.5, 31.2, 28.6, 22.3, 13.0 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{18}H_{23}NO_2$: 286.1801, found: 286.1805.

2-(4-(dimethylamino)phenoxy)-5-hexylphenol (RGB07)
Compound **12** (0.03 g, 0.09 mmol) was demethylated *via* general method **C**. Flash chromatography (0-10% EtOAc in heptane over 50 min) afforded the desired product (25 mg, 84%) as a brown oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 9.0 Hz, 2H), 6.84 (s, 1H), 6.77-6.63 (m, 3H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.67 (s, 1H), 2.91 (s, 6H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.59 (t, *J* = 6.8 Hz, 2H), 1.38-1.23 (m, 6H), 0.88 (t, *J* = 6.2 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 146.6, 143.1, 138.6, 120.1, 119.7, 116.8, 115.6, 114.0, 41.3, 35.4, 31.8, 31.5, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{27}NO_2$: 314.2114, found: 314.2112.

5-hexyl-2-(3-(methylsulfonyl)phenoxy)phenol (RGB08)
Compound **13** (0.10 g, 0.26 mmol) was demethylated *via* general method **C**. The desired product (79 mg, 87%) was obtained as a white solid after aqueous workup without the need for further purification.
^{1}H NMR (300 MHz, CD_3OD): δ = 7.60–7.47 (m, 2H), 7.39 (s, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.71 (qu, *J* = 1.5, 8.1 Hz, 1H), 3.08 (s, 3H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.63 (qu, *J* = 7.0 Hz, 2H), 1.41-1.26 (m, 6H), 0.91 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, CD_3OD): δ = 160.6, 150.2, 143.2, 142.8, 141.1, 131.7, 123.0, 122.3, 121.4, 121.3, 118.4, 115.5, 44.3, 36.5, 32.9, 32.6, 30.0, 23.7, 14.4 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{24}O_4S$: 349.1468, found: 349.1470.

2-(3-chlorophenoxy)-5-hexylphenol (RGB09)
Compound **14** (0.10 g, 0.31 mmol) was demethylated *via* general method **C**. Flash chromatography (0-13% EtOAc in heptane over 20 min) afforded the desired product (72 mg, 75%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 6.94-6.85 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.34 (s, 1H), 2.56 (t, *J* = 7.7 Hz, 3H), 1.62 (t, *J* = 6.8 Hz, 2H), 1.41-1.24 (m, 6H), 0.89 (t, *J* = 5.9 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 147.3, 140.9, 140.2, 135.2, 130.6, 123.4, 120.8, 119.5, 117.7, 116.4, 115.5, 35.5, 31.7, 31.3, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{21}ClO_2$: 303.1157, found: 303.1162.

2-(3,4-dichlorophenoxy)-5-hexylphenol (RGB10)
Compound **15** (0.09 g, 0.26 mmol) was demethylated *via* general method **C**. Flash chromatography (0-72% EtOAc in heptane over 20 min) afforded the desired product (63 mg, 72%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.90–6.79 (m, 3H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.32 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.61 (t, *J* = 7.3 Hz, 2H), 1.43-1.26 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 147.2, 141.2, 140.0, 133.3, 131.1, 126.6, 120.9, 119.5, 119.2, 116.8, 116.6, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{20}Cl_2O_2$: 337.0767, found: 337.0761.

2-(3,5-dichlorophenoxy)-5-hexylphenol (RGB11)
Compound **16** (0.10 g, 0.27 mmol) was demethylated *via* general method **C**. Flash chromatography (0-50% EtOAc in heptane over 25 min) afforded the desired product (67 mg, 73%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.08 (t, *J* = 1.8 Hz, 1H), 6.90-6.86 (m, 3H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.71 (dd, *J* = 2.1, 8.2 Hz, 1H), 5.24 (s, 1H), 2.57 (t, *J* = 7.8 Hz, 2H), 1.61 (qu, *J* = 7.6 Hz, 2H), 1.37–1.29 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm;
^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.6, 147.2, 141.6, 139.4, 135.7, 123.4, 121.0, 120.0, 116.7, 115.8, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{18}H_{20}Cl_2O_2$: 339.0913, found: 339.0740.

2-(benzofuran-5-yloxy)-5-hexylphenol (RGB12)
Compound **17** (0.15 g, 0.47 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 20 min) afforded the desired product (17 mg, 12%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 6.78-6.66 (m, 2H), 6.62 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.59 (s, 1H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.60 (qu, *J* = 6.4 Hz, 2H), 1.40-1.24 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 151.4, 146.9, 146.3, 142.4, 139.5, 128.3, 120.4, 117.9, 115.9, 115.7, 112.2, 109.8, 106.8, 35.5, 31.7, 31.4, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{20}H_{22}O_3$: 309.1496, found: 309.1500.

5-hexyl-2-(2-nitrophenoxy)phenol (PT10)
Compound **18** (0.17 g, 0.50 mmol) was demethylated *via* general method **C**. Flash chromatography (5% EtOAc in heptane) afforded the desired product (66 mg, 42%) as an off-white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.48 (dt, *J* = 1.2, 8.5 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 1H), 6.71 (dd, *J* = 1.6, 8.2 Hz, 1H), 6.20 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.61 (qu, *J* = 7.1 Hz, 2H), 1.41-1.21 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.8, 147.7, 142.1, 140.6, 139.7, 134.3, 125.7, 123.1, 120.7, 120.5, 118.5, 117.2, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{18}H_{21}NO_4$: 316.1543, found: 316.1544.

5-hexyl-2-(3-nitrophenoxy)phenol (PT11)
Compound **19** (0.12 g, 0.35 mmol) was demethylated *via* general method **C**. The desired product (79 mg, 72%) was obtained as a brown oil after aqueous workup without the need for further purification.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 2.1 Hz, 1H), 7.48 (t, *J* = 8.2 Hz, 1H), 7.32 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.72 (dd, *J* = 1.6, 8.2 Hz, 1H), 5.27 (s, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 7.2 Hz, 2H), 1.43-1.22 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 149.3, 147.3, 141.7, 139.6, 130.4, 123.1, 121.2, 119.8, 117.9, 116.9, 112.0, 35.5, 31.7, 31.3, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+Na]^+$ calc. for $C_{18}H_{21}NO_4$: 338.1363, found: 338.1365.

5-hexyl-2-(4-nitrophenoxy)phenol (PT12)
Compound **20** (0.20 g, 0.59 mmol) was demethylated *via* general method **C**. Flash chromatography (0-17% EtOAc in heptane over 20 min) afforded the desired product (146 mg, 79%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.95-6.84 (m, 2H), 6.75 (dd, *J* = 1.5, 8.2 Hz, 1H), 5.27 (s, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.63 (t, *J* = 6.8 Hz, 2H), 1.42-1.23 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 147.4, 143.0, 142.2, 139.0, 126.0, 121.2, 120.6, 117.0, 116.6, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{18}H_{21}NO_4$: 316.1543, found: 316.1551.

2-(4-hexyl-2-hydroxyphenoxy)benzonitrile (PT119)
Compound **21** (0.10 g, 0.32 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 7 min) afforded the desired product (50 mg, 52%) as a yellow solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.47 (dt, *J* = 1.1, 8.5 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.86 (t, *J* = 7.4 Hz, 2H), 6.72 (dd, *J* = 1.3, 8.2 Hz, 1H), 5.48 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.61 (qu, *J* = 7.1 Hz, 2H), 1.42-1.23 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 147.4, 142.0, 139.3, 134.4, 133.9, 123.0, 121.0, 120.2, 117.1, 115.8, 103.1, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{21}NO_2$: 294.1499, found: 294.1495.

4-(4-hexyl-2-hydroxyphenoxy)benzonitrile (RGB13)
Compound **22** (0.13 g, 0.42 mmol) was demethylated *via* general method **C**. Flash chromatography (0-50% EtOAc in heptane over 20 min) afforded the desired product (77 mg, 62%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.94-6.82 (m, 2H), 6.73 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.33 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.67-1.55 (m, 2H), 1.42-1.24 (m, 6H), 0.90 ppm (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 147.5, 142.0, 139.0, 134.2, 121.1, 120.5, 118.7, 117.2, 116.9, 106.2, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;

HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{21}NO_2$: 296.1645, found: 296.1648.

5-hexyl-2-(4-(methylsulfonyl)phenoxy)phenol (RGB14)
Compound **23** (0.17 g, 0.47 mmol) was demethylated *via* general method **C**. Flash chromatography (0-63% EtOAc in heptane over 20 min) afforded the desired product (80 mg, 49%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.97-6.83 (m, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.35 (s, 1H), 3.04 (s, 3H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 6.4 Hz, 2H), 1.41-1.25 (m, 6H), 0.90 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 147.5, 142.0, 139.1, 134.5, 129.8, 121.1, 120.5, 117.1, 116.9, 44.8, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{24}O_4S$: 347.1322, found: 347.1312.

5-hexyl-2-(2-(trifluoromethyl)phenoxy)phenol (PT95)
Compound **24** (0.07 g, 0.19 mmol) was demethylated *via* general method **C**. Flash chromatography (0-17% EtOAc in heptane over 7 min) afforded the desired product (19 mg, 30%) as a clear oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.96–6.83 (m, 3H), 6.70 (dd, *J* = 1.4, 8.1 Hz, 1H), 5.41 (s, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 6.0 Hz, 2H), 1.41-1.24 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 147.4, 141.2, 140.0, 133.4, 127.3 (q, *J* = 4.8 Hz), 125.3, 122.7, 121.7, 120.7, 120.2, 119.8, 117.1, 116.6, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
^{19}F NMR (282 MHz, $CDCl_3$): δ = -61.8 (s) ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{21}F_3O_2$: 337.1421, found: 337.1425.

3-(4-hexyl-2-hydroxyphenoxy)-*N*,*N*-dimethylbenzamide (RGB15)
Compound **25** (0.20 g, 0.56 mmol) was demethylated *via* general method **C**. Flash chromatography (0-60% EtOAc in heptane over 25 min) afforded the desired product (111 mg, 58%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.06-6.96 (m, 2H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 1.7, 8.2 Hz, 1H), 5.60 (s, 1H), 3.07 (s, 3H), 2.97 (s, 3H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 6.6 Hz, 2H), 1.40-1.24 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 157.4, 147.4, 140.7, 140.4, 138.0, 129.9, 121.6, 120.7, 119.5, 118.3, 116.4, 116.0, 39.5, 35.5, 35.3, 31.7, 31.3, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{27}NO_3$: 342.2064, found: 342.2064.

***N*,*N*-diethyl-3-(4-hexyl-2-hydroxyphenoxy)benzamide (RGB16)**
Compound **26** (0.02 g, 0.05 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 40 min) afforded the desired product (8 mg, 48%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.04-6.96 (m, 2H), 6.87 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 1.5, 8.2 Hz, 1H), 5.58 (bs, 1H), 3.49 (bs, 2H), 3.26 (bs, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.61 (t, *J* = 6.8 Hz, 2H), 1.38-1.26 (m, 6H), 1.19 (bs, 3H), 1.06 (bs, 3H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 157.4, 147.4, 140.6, 140.4, 138.9, 130.0, 21.0, 120.7, 119.5, 117.9, 116.4, 115.2, 43.3, 39.3, 35.5, 31.7, 31.3, 29.7, 28.9, 22.6, 14.1, 12.8 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{23}H_{31}NO_3$: 370.2377, found: 370.2375.

3-(4-hexyl-2-hydroxyphenoxy)-*N*-isobutylbenzamide (RGB17)
Compound **27** (0.11 g, 0.28 mmol) was demethylated *via* general method **C**. Flash chromatography (0-40% EtOAc in heptane over 25 min) afforded the desired product (78 mg, 76%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.30 (m, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.99 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.87 (s, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.66 (s, 1H), 6.60 (bs, 1H), 6.48 (t, *J* = 5.5 Hz, 1H), 3.19 (t, *J* = 6.4 Hz, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.84 (sept, *J* = 6.7 Hz, 1H), 1.58 (qu, *J* = 6.8 Hz, 2H), 1.40-1.21 (m, 6H), 1.00-0.78 (m, 9H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 157.8, 147.7, 140.6, 140.5, 136.5, 129.8, 121.1, 120.5, 119.8, 119.7, 116.8, 116.1, 47.5, 35.5, 31.7, 31.4, 29.0, 28.5, 22.6, 20.2, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{23}H_{31}NO_3$: 368.2231, found: 368.2238.

(3-(4-hexyl-2-hydroxyphenoxy)phenyl)(morpholino)methanone (RGB18)
Compound **28** (0.08 g, 0.19 mmol) was demethylated *via* general method **C**. Flash chromatography (0-88% EtOAc in heptane over 15 min) afforded the desired product (24 mg, 33%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.6 Hz, 1H), 7.15-6.93 (m, 3H), 6.88-6.78 (m, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 1H), 3.84-3.29 (m, 8H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.60 (qu, *J* = 6.3 Hz, 2H), 1.41-1.21 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 157.8, 147.6, 140.9, 140.2, 136.8, 130.1, 121.4, 120.6, 119.9, 118.4, 116.6, 115.8, 66.8, 48.1, 42.5, 35.5, 31.7, 31.3, 29.0, 22.6, 14.1 ppm;
HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{23}H_{29}NO_4$: 382.2024, found: 382.2049.

4-(4-hexyl-2-hydroxyphenoxy)benzamide (RGB19)
Compound **29** (0.04 g, 0.11 mmol) was demethylated *via* general method **C**. Flash chromatography (0-85% EtOAc in heptane over 7 min) afforded the desired product (26 mg, 78%) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.90 (s, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.22-5.57 (m, 3H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.61 (qu, *J* = 6.8 Hz, 2H), 1.42-1.21 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 160.8, 147.6, 141.3, 139.8, 129.4, 127.6, 120.8, 120.2, 116.6, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{19}H_{23}NO_3$: 314.1751, found: 314.1747.

***N*-ethyl-4-(4-hexyl-2-hydroxyphenoxy)benzamide (RGB20)**
Compound **30** (0.04 g, 0.12 mmol) was demethylated *via* general method **C**. Flash chromatography (0-65% EtOAc in heptane over 20 min) afforded the desired product (26 mg, 42%) as an off-white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.5 Hz, 2H), 7.00-6.87 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.20-6.02 (m, 2H), 3.47 (qu, *J* = 6.8, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 6.5 Hz, 2H), 1.42-1.25 (m, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 6.2 Hz, 3H) ppm;
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.2, 147.7, 141.1, 140.0, 129.0, 128.7, 120.6, 120.1, 116.7, 35.5, 35.0, 31.7, 31.3, 29.0, 22.6, 14.9, 14.1 ppm;
HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{21}H_{27}NO_3$: 342.2064, found: 342.2054.

(4-(4-hexyl-2-hydroxyphenoxy)phenyl)(pyrrolidin-1-yl)methanone (RGB21)

Compound **31** (0.09 g, 0.23 mmol) was demethylated *via* general method **C**. Flash chromatography (0-65% EtOAc in heptane over 25 min) afforded the desired product (40 mg, 47%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.68 (dd, *J* = 1.6, 8.2 Hz, 1H), 5.50 (s, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.04–1.81 (m, 4H), 1.64 (d, *J* = 6.2 Hz, 2H), 1.42-1.23 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3, 159.1, 147.9, 140.8, 140.2, 131.1, 129.2, 120.4, 120.2, 116.7, 116.4, 49.8, 46.4, 35.5, 31.7, 31.3, 29.0, 26.5, 24.4, 22.6, 14.1 ppm;

HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{23}H_{29}NO_3$: 368.2220, found: 368.2218.

(4-(4-hexyl-2-hydroxyphenoxy)phenyl)(morpholino)methanone (RGB22)

Compound **32** (0.10 g, 0.25 mmol) was demethylated *via* general method **C**. Flash chromatography (0-85% EtOAc in heptane over 15 min) afforded the desired product (48 mg, 50%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.89-6.79 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.40 (bs, 1H), 3.84-3.46 (m, 8H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.60 (qu, *J* = 7.4 Hz, 2H), 1.40-1.22 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 159.2, 147.8, 141.0, 140.0, 129.2, 129.1, 120.5, 120.3, 116.78, 116.7, 77.5, 77.1, 76.7, 66.9, 48.3, 42.8, 35.5, 31.7, 31.3, 29.0, 22.6, 14.1 ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{23}H_{29}NO_4$: 382.2024, found: 382.2016.

***N*-(3-(4-hexyl-2-hydroxyphenoxy)phenyl)acetamide (RGB23)**

Compound **33** (0.05 g, 0.16 mmol) was demethylated *via* general method **C**. Flash chromatography (0-45% EtOAc in heptane over 7 min) afforded the desired product (16 mg, 31%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 7.24-7.16 (m, 4H), 6.86 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.75-6.61 (m, 2H), 5.68 (bs, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.13 (s, 3H), 1.61 (qu, *J* = 6.7 Hz, 2H), 1.40-1.24 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 157.8, 147.4, 140.6, 140.4, 139.2, 130.1, 120.6, 119.4, 116.3, 114.5, 113.0, 109.2, 35.5, 31.7, 31.6, 29.0, 24.6, 22.6, 14.1 ppm;

HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{20}H_{25}NO_3$: 328.1907, found: 328.1895.

***N*-(4-(4-hexyl-2-hydroxyphenoxy)phenyl)acetamide (RGB24)**

Compound **34** (0.05 g, 0.15 mmol) was demethylated *via* general method **C**. Flash chromatography (0-50% EtOAc in heptane over 7 min) afforded the desired product (26 mg, 54%) as a red solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 6.93 (s, 1H), 6.87 (d, *J* = 9.8 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.93 (bs, 1H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H), 1.59 (qu, *J* = 7.2 Hz, 2H), 1.40-1.21 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 153.8, 147.2, 141.3, 140.1, 133.1, 122.0, 120.5, 118.8, 118.0, 116.2, 35.5, 31.7, 31.4, 29.0, 24.2, 22.6, 14.1ppm;

HRMS (ESI$^-$) *m/z* $[M-C_2H_5NO]^-$ calc. for $C_{20}H_{25}NO_3$: 268.1469, found: 268.9617.

2-(2-fluoro-4-nitrophenoxy)-5-hexylphenol (RGB25)

Compound **35** (0.08 g, 0.22 mmol) was demethylated *via* general method **C**. Flash chromatography (0-15% EtOAc in heptane over 7 min) afforded the desired product (49 mg, 66%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 2.4, 10.2 Hz, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 6.96 (t, *J* = 8.6 Hz, 1H), 6.92-6.84 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.49 (s, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.61 (qu, *J* = 7.3 Hz, 2H), 1.44-1.21 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 151.1 (d, *J* = 10.0), 150.0, 147.0, 142.6 (d, *J* = 6.8 Hz), 142.4, 139.0, 121.3, 120.6 (d, *J* = 3.0 Hz), 120.0, 117.3, 117.0, 113.0 (d, *J* = 22.7 Hz), 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -130.1 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{20}FNO_4$: 332.1303, found: 332.1308.

2-(2-fluoro-4-(methylsulfonyl)phenoxy)-5-hexylphenol (RGB26)

Compound **36** (0.05 g, 0.13 mmol) was demethylated *via* general method **C**. Flash chromatography (0-37% EtOAc in heptane over 7 min) afforded the desired product (44 mg, 92%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 9.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 8.1 Hz, 1H), 6.94-6.81 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 5.78 (bs, 1H), 3.05 (s, 3H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.60 (qu, *J* = 6.6 Hz, 2H), 1.41-1.21 (m, 6H), 0.89 (t, *J* = 5.7 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 150.7, 150.2 (d, *J* = 10.5 Hz), 147.2, 142.1, 139.1, 134.8 (d, *J* = 4.9 Hz), 124.4 (d, *J* = 3.4 Hz), 121.1, 120.0, 118.1, 117.2, 116.5 (d, *J* = 20.9 Hz), 44.6, 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -129.0 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-F-2H]^-$ calc. for $C_{19}H_{23}FO_4S$: 345.1160, found: 345.1145.

3-fluoro-4-(4-hexyl-2-hydroxyphenoxy)benzonitrile (RGB27)

Compound **37** (0.10 g, 0.31 mmol) was demethylated *via* general method **C**. Flash chromatography (0-17% EtOAc in heptane over 7 min) afforded the desired product (68 mg, 71%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 1.0, 10.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.97-6.83 (m, 3H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.71 (bs, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.62 (qu, *J* = 6.7 Hz, 2H), 1.43-1.22 (m, 6H), 0.89 (t, *J* = 6.4 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 150.6, 149.8 (d, *J* = 10.5 Hz), 147.2, 142.1, 139.0, 129.5 (d, *J* = 3.5 Hz), 121.1, 120.6 (d, *J* = 21.1 Hz), 120.0, 118.3, 117.5, 117.2, 106.3 (d, *J* = 8.0 Hz), 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -129.8 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{20}FNO_2$: 312.1405, found: 312.1405.

2-(3-chloro-4-nitrophenoxy)-5-hexylphenol (RGB28)

Compound **38** (0.08 g, 0.21 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 7 min) afforded the desired product (65 mg, 90%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.1 Hz, 1H), 7.10 (d, *J* = 1.9 Hz, 1H), 6.96 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.93-6.86 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.16 (bs, 1H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.64 (qu, *J* = 6.8 Hz, 2H), 1.42-1.25 (m, 6H), 0.89 (t, *J* = 5.9 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 147.2, 142.6, 142.3, 138.6, 129.7, 128.0, 121.4, 120.7, 119.3, 117.2, 115.1, 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{20}ClNO_4$: 348.1008, found: 348.1002.

2-chloro-4-(4-hexyl-2-hydroxyphenoxy)benzonitrile (RGB29)

Compound **39** (0.05 g, 0.15 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 15 min) afforded the desired product (27 mg, 56%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.6 Hz, 1H), 7.08 (s, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.92-6.85 (m, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.13 (bs, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 1.63 (qu, *J* = 6.8 Hz, 2H), 1.43-1.24 (m, 6H), 0.89 (t, *J* = 6.2 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 147.3, 142.5, 138.6, 138.5, 135.3, 121.4, 120.7, 117.9, 115.9, 115.5, 107.2, 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{19}H_{20}ClNO_2$: 328.1110, found: 328.1110.

2-(5-chloro-2-fluoro-4-nitrophenoxy)-5-hexylphenol (RGB30)

Compound **40** (0.10 g, 0.26 mmol) was demethylated *via* general method **C**. Flash chromatography (0-17% EtOAc in heptane over 15 min) afforded the desired product (62 mg, 64%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 9.8 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.95-6.87 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.21 (bs, 1H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.63 (qu, *J* = 8.8 Hz, 2H), 1.42-1.24 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8, 149.6 (d, *J* = 11.4 Hz), 148.4, 146.9, 142.8, 138.5, 124.4 (d, *J* = 3.8 Hz), 121.5, 120.1, 119.7, 117.5, 115.2 (d, *J* = 23.9 Hz), 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -13.5 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-F-2H]^-$ calc. for $C_{18}H_{19}ClFNO_4$: 346.0846, found: 346.0874.

2-chloro-5-fluoro-4-(4-hexyl-2-hydroxyphenoxy)benzonitrile (RGB31)

Compound **41** (0.10 g, 0.28 mmol) was demethylated *via* general method **C**. Flash chromatography (0-20% EtOAc in heptane over 15 min) afforded the desired product (34 mg, 35%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 9.7 Hz, 1H), 6.98-6.85 (m, 3H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.22 (bs, 1H), 2.59 (t, *J* = 7.6 Hz, 3H), 1.62 (qu, *J* = 7.6 Hz, 2H), 1.43-1.24 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 142.8, 138.4, 133.6, 133.5, 121.7, 121.5, 121.4, 120.1, 118.6, 117.4, 114.9, 107.1, 35.5, 31.7, 31.2, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.0 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-F-2H]^-$ calc. for $C_{19}H_{19}ClFNO_2$: 346.1015, found: 346.0995.

3-fluoro-4-(4-hexyl-2-hydroxyphenoxy)benzamide (RGB32)

Compound **42** (0.04 g, 0.11 mmol) was demethylated *via* general method **C**. Flash chromatography (0-85% EtOAc in heptane over 7 min) afforded the desired product (26 mg, 78%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 10.9 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 8.1 Hz, 1H), 6.89 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.20-5.51 (m, 3H), 2.57 (t, *J* = 7.3 Hz, 2H), 1.69-1.51 (m, 2H), 1.40-1.20 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 147.0, 146.4, 141.3, 140.1, 123.8, 123.7, 120.8, 118.9, 118.4, 116.8, 116.7, 116.5, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -131.2 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-F-2H]^-$ calc. for $C_{19}H_{22}FNO_3$: 310.1443, found: 310.1450.

(3-fluoro-4-(4-hexyl-2-hydroxyphenoxy)phenyl)(morpholino)methanone (RGB33)

Compound **44** (0.03 g, 0.06 mmol) was demethylated *via* general method **C**. Flash chromatography (0-60% EtOAc in heptane over 7 min) afforded the desired product (19 mg, 73%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 8.2 Hz, 1H), 6.88 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 3.85-3.45 (m, 8H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.59 (t, *J* = 7.3 Hz, 2H), 1.40-1.20 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 154.5, 151.2, 147.0, 146.3 (d, *J* = 11.3 Hz), 141.0, 140.4, 130.7 (d, *J* = 5.5 Hz), 123.8 (d, *J* = 3.8 Hz), 120.6, 118.8 (d, *J* = 16.8 Hz), 116.7, 116.5 (d, *J* = 19.7 Hz), 66.8, 35.5, 31.7, 31.3, 29.7, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -131.1 (s) ppm;

HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{23}H_{28}FNO_4$: 402.2075, found: 402.2073.

(3-fluoro-4-(4-hexyl-2-hydroxyphenoxy)phenyl)(piperazin-1-yl)methanone (RGB34)

Compound **45** (0.04 g, 0.08 mmol) was demethylated *via* general method **C**. Flash chromatography (0-10% MeOH in DCM, 1% Et_3N over 20 min) afforded the desired product (10 mg, 30%) as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 11.1 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.96-6.81 (m, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 3.92-3.30 (m, 6H), 3.00-2.73 (m, 4H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.59 (qu, *J* = 7.4 Hz, 2H), 1.40-1.21 (s, 6H), 0.88 (t, *J* = 5.7 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 154.3, 151.0, 147.4, 146.3 (d, *J* = 10.7 Hz), 141.1, 140.4, 131.0 (d, *J* = 7.0 Hz), 123.7, 120.5, 118.9 (d, *J* = 32.8 Hz), 117.1, 116.3 (d, *J* = 19.7 Hz), 45.9, 35.5, 31.7, 31.3, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -131.7 (s) ppm;

HRMS (ESI$^+$) *m/z* $[M+H]^+$ calc. for $C_{23}H_{29}FN_2O_3$: 401.2235, found: 401.2233.

2-(2-fluorophenoxy)-5-hexylphenol (PT113)

Compound **47** (0.03 g, 0.10 mmol) was demethylated *via* general method **C**. Flash chromatography (0-10% EtOAc in heptane over 7 min) afforded the desired product (22 mg, 77%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.00 (m, 4H), 6.86 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 5.56 (s, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 1.60 (qu, *J* = 7.0 Hz, 2H), 1.40-1.21 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 152.1, 146.5, 144.1 (d, *J* = 10.7 Hz), 141.5, 140.0, 124.7, 124.6, 120.4, 117.3, 117.1 (d, *J* = 18.2 Hz), 116.2, 35.4, 31.7, 31.4, 28.9, 22.6, 14.1 ppm;

^{19}F NMR (282 MHz, $CDCl_3$): δ = -132.1 (s) ppm;

HRMS (ESI$^-$) *m/z* $[M-H]^-$ calc. for $C_{18}H_{21}FO_2$: 287.1452, found: 287.1447.

Cloning, expression & purification of *pa*FabV

The *fabV* gene (1197 bp) was amplified from purified genomic DNA of *P. aeruginosa* PAO1 (DSM 22644) by the use of primers whose sequence is listed in **Table S1** (obtained from Integrated DNA Technologies). To facilitate directional ligation into the pET28aplasmid, *Nde*I and *Bam*HI restriction sites were introduced on the forward and reverse primers respectively. Amplification was achieved by polymerase chain reaction (PCR) and the product was purified using the GeneJET Gel Extraction kit (Thermo Scientific). The purified product was then digested with *Nde*I and *Bam*HI and ligated with appropriately linearized pET28a plasmid by the use of T4 DNA ligase (Thermo Scientific), following manufacturer's instructions. Chemically competent *E. coli* One Shot TOP10 cells (Life Technologies) were then transformed with the

ligation mixture and transformants were selected on lysogeny broth (LB) plates supplemented with kanamycin (50 µg/mL). The plasmids were then extracted and purified from resistant colonies by the GeneJET Plasmid Miniprep kit (Thermo Scientific) and their sequence was confirmed through Sanger-sequencing (GATC, Eurofins Genomics). The correct constructs were then used to transform into chemically competent *E. coli* BL21 cells. These were inoculated into LB broth (4 mL) complemented with kanamycin (50 µg/mL) and incubated overnight at 37°C while shaking (150 rpm). This preculture was then inoculated into 1 L of the same LB/kantamycin mixture and incubated at 37 °C until an optical density at 600 nm (OD_{600}) of 0.5 was achieved. Isopropyl β-D-1-thiogalactopyranoside (IPTG) was added to a final concentration of 0.5 mM to induce expression and the cultures were incubated overnight at 16 °C on a rotary shaker (150 rpm). The cells were then collected by centrifugation (4,600 rpm, 45 min, 4°C) and the pellets were resuspended in 10 mL of a binding buffer (20 mM Tris-HCl (pH 8.0), 500 mM NaCl, 10% glycerol, 20 mM imidazole). To the suspended cells was added 1 mL of hen egg white lysozyme (20 mg/mL) as well as 250 µl of Pefabloc (100 mM, Sigma-Aldrich). The cells were subjected to two freeze-thaw cycles (2 hours at -80°C followed by 30 minutes at RT) and then stored at -80°C overnight. After thawing, 10 µL of DNaseI was added to the cells, which were then lysed by pulsed sonication for 8 × 30 s while cooled on ice (Vibra-Cell Ultrasonic Liquid Processor; Sonics & Materials, Inc). The lysate was centrifuged (26,000 rpm, 10 min, 4 °C) and the resulting supernatant was filtered to remove cellular debris and applied to a 1 mL HiTrap HP affinity column (GE Healthcare) that was previously equilibrated with binding buffer. Non-specifically bound proteins were removed by applying 15 mL of binding buffer. The His_6-tagged FabV protein was eluted by applying an elution buffer (20 mM Tris-HCl (pH 8.0), 500 mM NaCl, 10% glycerol, 300 mM imidazole). All collected fractions were then analysed by SDS-PAGE and those containing the pure His_6-tagged protein were combined and concentrated. The protein was then transferred to a storage buffer (20 mM Tris-HCl (pH 8.0), 500 mM NaCl, 10% glycerol) by the use of Amicon Ultra centrifugal filters (10 kDa cut-off, EMD Millipore) and then flash-frozen in liquid nitrogen for storage at -80 °C.

Fixed concentration screening & dose-response assays

Inhibitors were screened at 10 µM using a Greiner Bio-One 384-well polystyrene non-binding flat bottom microplate (Fisher Scientific, Waltham, Massachusetts, USA) by addition of 2 µL of a dimethyl sulfoxide (DMSO) solution of the desired compound to 193 µL of a mixture containing 10 nM enzyme, 150 µM NADH, 200 µM NAD^+, 0.1 mg/mL bovine serum albumin (BSA) and 0.01% Triton X-100 in a phosphate buffer (77.4 mM $Na_2HPO_4{\cdot}7H_2O$, 22.6 mM $NaH_2PO_4{\cdot}H_2O$, 150 mM NaCl, 1 mM $EDTA{\cdot}2H_2O$, 8% glycerol in milliQ water, pH adjusted to 7.8). The reaction is allowed to incubate for 3 minutes before 5 µL of a *trans*-2-dodecenoyl-CoA solution in DMSO is added to a final concentration of 100 µM. The reaction is followed by monitoring NADH to NAD^+ oxidation at 340 nm. The measurement was performed on a SPECTROstar Nano (BMG Labtech, Ortenberg, Germany) at 25 °C and initial velocities were determined by taking slope of the measurements over the first 120 s. The percent inhibition (Inh%) was calculated as in **Eq. 1** where S_i is the slope of the absorbance in the presence of the compound S_0 is the slope obtained using a blank DMSO control.

$$\boldsymbol{Eq.1}\ Inh\% = 1 - \left(\frac{S_i}{S_0} \times 100\%\right)$$

To obtain the dose-response curves the same protocol was followed while varying the concentration of inhibitor added, maintaining the same quantity of DMSO. The IC_{50} values were determined by fitting the data to four-parameter, variable-slope non-linear regression model, the resulting curve being constrained from the bottom (fixed at 0% inhibition when no inhibitor present) and from the top (maximum predicted inhibition must be below 100%). The model was created using GraphPad Prism version 10.1.0 (Boston, USA).

Supporting Information

A separate file is provided containing additional graphs of fixed-concentration inhibitor screening, dose-response curves of selected compounds as well as the primer sequences used during gene cloning experiments

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