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Discovery of Novel Small Molecule Dual Inhibitors Targeting Toll-like Receptor 7 and 8

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ABSTRACT: Endosomal Toll-like receptors (TLRs) 7 and 8 recognize viral ssRNAs, a class of imidazoquinoline compounds, 8-oxo-adenosines, 8-aminobenzodiazepines, pyrimidines, and guanosine analogs. Substantial evidence has accrued linking chronic inflammation mediated specifically by TLR7 to the progression of autoimmunity. We identified a new TLR7/8 dual- (**1**) and a TLR8 specific-inhibitor (**2**) based on our previous screen targeting TLR8. Compound **1**, bearing a benzanilide scaffold, was found to inhibit TLR7 and TLR8 at low micromolar concentrations. We envisioned making modifications on the benzanilide scaffold of **1** resulting in a class of highly specific TLR7 inhibitors. Our efforts led to the discovery of a new TLR8 inhibitor (**CU-115**) and identification of a TLR7/8 dual inhibitor (**CU-72**), bearing a distinct diphenyl ether skeleton, with potential for TLR7 selectivity optimization. Given the role of TLR8 in autoimmunity, we also optimized the potency of **2** and developed a new TLR8 inhibitor bearing a 1,3,4-oxadiazole motif.

INTRODUCTION

Nucleic acids (NA) sensors are part of the innate immune system and recognize multiple forms of intracellular self- and non-self RNA and DNA macromolecules. Activation of NA-sensors initiates signal transduction pathways for the upregulation of type I interferon genes (IFNs). The endosomal Toll-like receptors (TLRs) represent a major class of NA sensors that regulate inflammation.[1,2] In humans, four endosomal TLRs (TLR 3, 7, 8 and 9) have been identified. The endosomal TLRs detect viral and endogenous double-stranded RNA (dsRNA; TLR3), single-stranded RNA (ssRNA; TLR7/8), or unmethylated CpG sequences in DNA (TLR9).[1] Of the four-known endosomal TLRs, TLR7 and TLR8 are most similar in sequence and function.[4b] Both TLR7 and TLR8 mount an immune response by detecting and responding to degraded ssRNA products from bacteria and viruses.[3,4] The endosomal TLR NA-sensing pathways modulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IFNs, which leads to the transcription of genes encoding pro-inflammatory cytokines.[1]

Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) are common autoimmune diseases. Substantial evidence has accrued linking chronic inflammation mediated by signaling malfunction of TLR7 to the onset and progression of autoimmune diseases.[5] For example, studies have identified a genetic linkage and observed polymorphisms in TLRs (TLR7, TLR3, and TLR9) associated with SLE.[6] Activation of TLR7 caused by recognition of self-RNAs (e.g. microRNA let-7) and self-ssRNA (released from disrupted cells) has been observed.[7,8,9] TLR7 signaling malfunction is also associated as a contributor to/towards increased tumor necrosis factor alpha (TNF-α) production in autoimmune and autoinflammatory disorders such as SLE.[10] A direct genetic link for TLR8 and autoimmunity remains to be fully established, however, studies have already implicated TLR8 as a contributor in increased TNF-α production of RA.[10,11,12,13] Over-activation of endosomal TLRs, specifically TLR7, leads to increased levels of proinflammatory cytokines linked to inflammatory disorders, which provides a compelling rationale for targeting TLR7. Despite the considerable evidence implicating TLR7 signaling dysregulation in autoimmune diseases, only a few selective small molecule TLR7 inhibitors have been published, which has hindered our understanding of TLR7 signaling and its role in autoimmunity.[14] Few TLR7 inhibitors have entered preclinical development; however, there are currently no clinically available *selective* TLR7 inhibitors.[10]

Achieving TLR7 inhibition with a high degree of specificity without affecting TLR8 remains a major obstacle for small molecule drug development. This is in part due to the fact that TLR7 and TLR8 are structurally similar and both recognize ssRNA, guanosine analogs, and non-selective imidazoquinoline agonists and inhibitors. Structural studies have aided in the identification of two distinct ligand binding sites for degraded ssRNA products for both TLR7 and TLR8.[3,4] The ligand binding sites for uridine, guanosine, and chemical ligands is conserved between TLR7 and TLR8. Thus, many efforts for the rational design of TLR7 inhibitors have relied on known TLR8 agonists with high binding specificity for TLR8 exclusively. Limitations of side effects in published TLR7 inhibitors include poor TLR selectivity and cellular potency (Figure 1). For example, the small molecule inhibitor hydroxychloroquine targets both TLR7 and TLR9 indirectly by accumulating in the endosome and binding NAs, preventing TLR recognition.[1] The recently reported 3H-imidazoquinolines inhibitors have IC_{50} values in the 25

and 100 μM range.[15, 16] Single-stranded phosphorothioate oligonucleotides have also been reported as TLR7 inhibitors.[17] Other efforts have focused on targeting downstream signaling proteins of endosomal TLRs, such as Interleukin-1 receptor-associated kinase 4 (IRAK4)[-1] A drawback of this approach is that directly targeting the downstream kinase IRAK4 could block the other nine TLR signaling pathways, causing off-target effects.

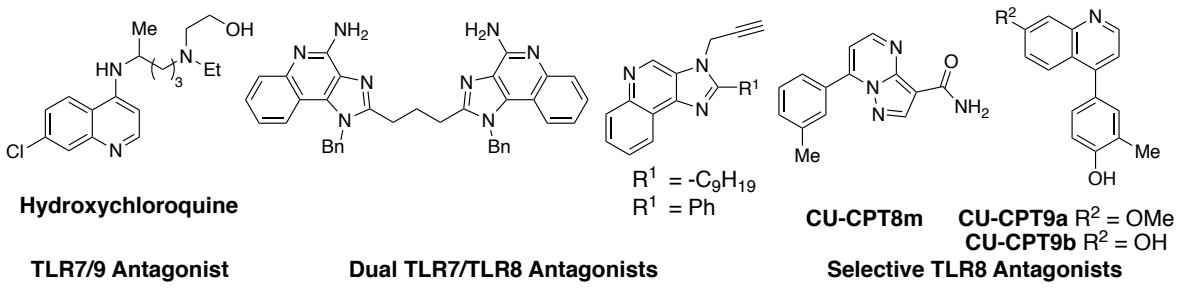


Figure 1. Examples of reported TLR7, TLR7/8, and TLR8 antagonists.

Recently our group overcame TLR7/8 specificity challenges, ultimately developing a new generation of TLR8-specific inhibitors with high selectivity and potency, **CU-CPT8m** (Figure 1).[18] From the screen leading to the identification of **CU-CPT8m**, we serendipitously discovered a small molecule displaying TLR7/8 inhibitory activity and were inspired to use medicinal chemistry and structure-activity relationship studies (SAR) to override the TLR7/8 selectivity to favor TLR7 activity, ultimately enabling the discovery of new selective TLR7 inhibitors through optimization of the TLR7 activity.[4b] Herein, we describe our efforts to develop TLR7, TLR8, and TLR7/8 inhibitors based on two distinct scaffold families and their biophysical characterization and biological evaluation in cellular assays. Our efforts culminated in the discovery of two new TLR8 inhibitors displaying high TLR 8 selectivity at low concentrations and the development of new TLR7/8 inhibitors with potential optimization for TLR7 activity.

RESULTS AND DISCUSSION

High Throughput Screening (HTS) results and validations studies. Hits **1** and **2** were manually identified from an HTS targeting TLR8, see **Error! Reference source not found.**a for chemical structures. The Maybridge Hit Finder library compounds (14, 400 small molecules) follow the Lipinski guidelines for "drug-likeness" and have properties that include: no more than 5 hydrogen bond donors, no more than 10 hydrogen acceptors, a molecular weight less than 500, and an octanol-water partition coefficient (log P) less than 5. The HTS protocol and results using the Maybridge Hit Finder library have been published for the development of the first selective TLR8 inhibitor.[18]

For this project, hit **1** and **2** were purchased from Maybridge and first re-tested for potency validation, cell toxicity, and TLR specificity. Both compounds inhibited TLR7 and TLR8 signaling in a dose-dependent manner to down regulate TLR7- and TLR8-induced secreted embryonic alkaline phosphatase (SEAP) levels with IC_{50} values of 2.88 ±0.25 μM (TLR7) and 1.64 ±0.40 μM (TLR8) for **1** and IC_{50}= 1.40 ±0.06 μM (TLR8) for **2**, (see Figure S1 and Figure S2), and were nontoxic, (see Figure S4). In humans, there are a total of 10 TLRs and some share

adapter proteins and downstream signaling pathways. As such, a high degree of TLR specificity is necessary and important for therapeutic applications. The specificity tests for **1** and **2** using stably transfected human embryonic kidney (HEK 293-Blue) cells individually overexpressing each human TLR indicated no obvious inhibition of other TLRs, (**Error! Reference source not found.**b), except for TLR9 pathway at 1.5 μM for **1**. Interestingly, compound **1** was the only inhibitor that down-regulated TLR7-induced SEAP levels at 1.5 μM. Although **1** lacked specificity at 3 and 5 μM, we continued to pursue SAR since **1** displayed more activity at 1.5 μM in TLR7 cell line compared to TLR8 and TLR9. Compounds **1** and **2** both contained a diaryl ether linkage and the aromatic tricyclic ring core scaffold, indicating those motifs are important for target selectivity. Differences such as the amide functional group and the 1,3,5-oxadiazole motif suggested those motifs could be modified to modulate TLR7/8 selectivity for SAR. Compounds **1** and **2** represent two different scaffold families that are still capable of maintaining high inhibitory activity and selectivity toward TLR8, which presents the opportunity to discover a new binding mode or identify inhibitors with altered and/or more suitable pharmacokinetic or pharmacodynamic properties for drug development. Because of the clinical relevance of TLR7 and TLR8 in autoimmunity, we conducted SAR studies for both **1** and **2** and primarily focused on **1** owing to the significant potential for discovering a much needed TLR7-selective inhibitor.

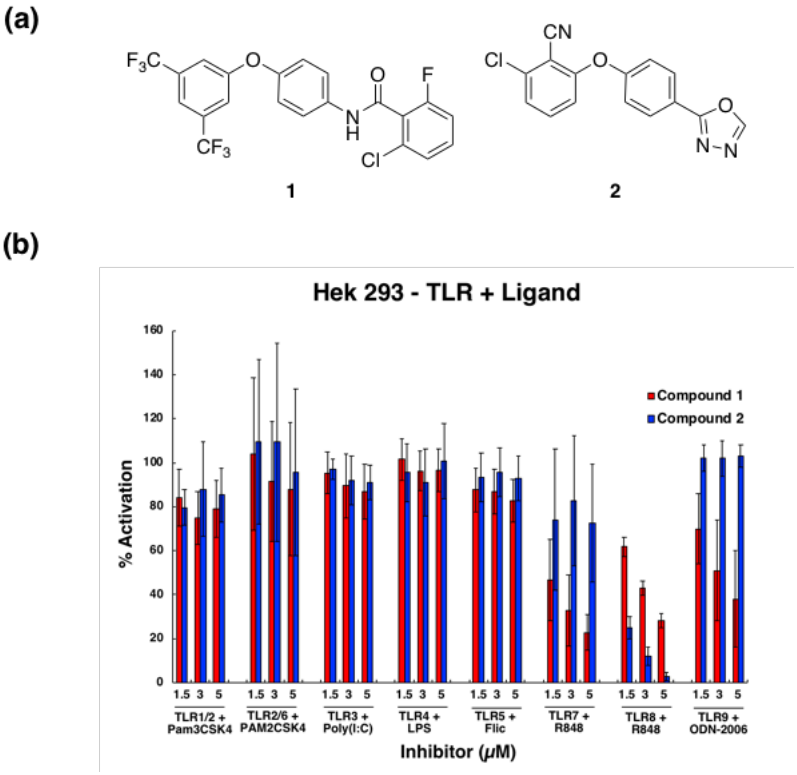
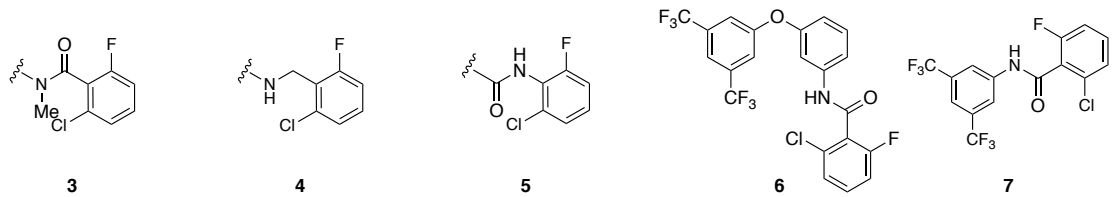


Figure 2. (a) Chemical structures of **1** and **2**. (b) HEK 293 cells expressing human toll-like receptor (hTLR) gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were incubated with **1** or **2** for 16 h. At 1.5, 3 and 5 μM **1** does not inhibit not modulate the NF-κB inhibition induced by LPS, R848, Poly(I:C), in HEK-293 TLR4, TLR3, TLR7, and TLR9 cells. Compound **1** modulates the TLR9 pathway at ~ 3–5 μM and only exhibits partially selectivity at low concentrations. At 1.5, 3 and 5 μM **2** does not modulate the NF-κB inhibition

induced by LPS, Pam2CSK4, Pam3CSK4, Flic, R848, and Poly(I:C) in HEK-293 TLR1/2, TLR2/6, TLR3, TLR4, and TLR7 cells and **2** displays selectivity for TLR8. The data were normalized as [(raw data – untreated cells)/(ligand + solvent control – untreated cells)]. Ligand + solvent is 100% activation, and untreated cells are 0% activation. The result of one representative biological replicate for three independent days is plotted with the error bars representing the standard deviation of three technical replicates for one independent biological replicate.

Preliminary SAR studies for 1. Initially, five analogs were designed to identify key structural motifs contributing to TLR7/8 dual inhibitory activity, see (Figure 3). Benzanilide and 1,3,4-oxadiazole motifs are common structural elements found in biologically active molecules and both 1,3,4- and 1,2,4-oxadiazoles are known amide bioisosteres.[19] The presence of the -NH, an H-bond donor, between the B- and A-ring is a notable difference between **1** and **2** thus revealing some SAR information for modulating TLR7/8 activity.

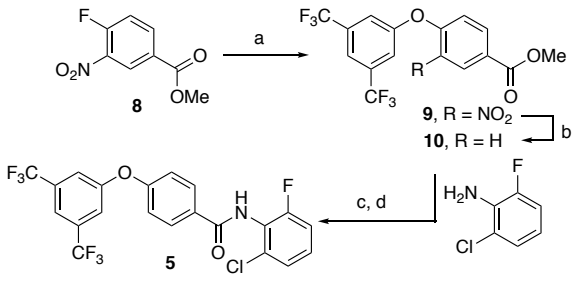


3	**4**	**5**	**6**	**7**
3° Methylated amide	**2° Alkyl amine**	**Reverse amide**	**1,3-disubstituted B ring**	**Removed aryl ether**
0% TLR7 inhibition	IC_{50} > 50 μM TLR7	0% TLR7 inhibition	0% TLR7 inhibition	0% TLR7 inhibition
TLR8 IC_{50} = 2.9 (±0.8) μM	IC_{50} > 50 μMTLR8	TLR8 IC_{50} = 1.4 (±0.1) μM	TLR8 IC_{50}= 7.10 (±1.78) μM	0% TLR8 inhibition

Figure 3. Preliminary SAR results for 1.

We synthesized the tertiary benzanilide (**3**), the corresponding secondary alkyl amine (**4**) and reverse amide (**5**), (Figure 3). The tertiary amide **3** was synthesized by alkylation of **1** with methyl iodide, and reductive amination of 2-chloro-6-fluorobenzaldehyde with 4-[3,5-bis(trifluoromethyl)phenoxy aniline provided **4** in 88% yield. The synthesis of **5** began with S_NAr of methyl 4-fluoro-3-nitrobenzoate, **8**, to afford intermediate **9**. Reduction of the nitro group gave compound **10**, which was then converted to the corresponding benzoyl chloride, 4-[3,5-bis(trifluoromethyl)phenoxy] benzoyl chloride. Subsequent amide formation with 2-chloro-6-fluoroaniline yielded **5** in 57%, (see Scheme 1). Compounds **6** and **7** were synthesized using the same route as **1** except 3-[3,5-bis(trifluoromethyl)phenoxy]aniline and commercially available 3,5-bis(trifluoromethyl)aniline were used as the aniline substrates.

Scheme 1. Synthesis of 5.[a]



[a] Reaction conditions: (a) 3,5-bis(trifluoromethyl)phenol, Cs_2CO_3, DMF 110 °C (79%); (b) 10 mol% Pd/C, H_2, MeOH, then *t*-BuONO, DMF, 50 °C (75% 2-steps); (c) i. NaOH, MeOH, 50 °C; ii. Oxalyl chloride, cat. DMF, CH_2Cl_2; (d) 2-chloro-6-fluoroaniline, Et_3N, CH_2Cl_2 (57% 2-steps).

Methylation of amide (**3**) completely abolished TLR7 activity and retained TLR8 activity of 2.9 (±0.8) μM, which then led us to examine the importance of the carbonyl moiety. Poor inhibition was observed for both TLR7 and TLR8 with the secondary alkyl amine, **4**, indicating the presence of a carbonyl H-bond acceptor is important and a rigid planar benzanilide is superior. The corresponding reverse benzanilide **5** was synthesized to explore different orientations of the NH amide and was determined to be inactive towards TLR7 and active towards TLR8. A notable difference compared to **1** is that compound **5** has the amide NH adjacent to the fluorine atom. Investigators have speculated that a fluorine proximal to an amide N–H can mask the H-bond through an electrostatic interaction; thus, we speculate TLR7 inactivity may be due to H-bond masking caused by the adjacent fluorine atom.[19]

Cumulatively, compounds **3**-**5** show the presence of the -NH or H-bond donating atom is necessary for TLR7 activity. By comparing **4** and **5** we also observed that H-bond acceptors are more important for TLR8 activity. We then synthesized a 1,3-disubstituted derivative, **6**, to explore additional substitution patterns of the B-ring. Compound **6** did not inhibit TLR7, which indicates the 1,4-disubstitution pattern is required for TLR7 activity, and **6** was slightly less active (IC_{50} = 7.10 ± 1.78 μM) towards TLR8 compared to **1**, suggesting the TLR8 binding pocket may tolerate additional substitutions. Lastly, the distance between the C- and A-ring was shown to be important since removing the B-ring resulted in 0% inhibition (**7**), and this motivated us to focus on the optimization of the A- and C-ring for **1** scaffold.

SAR studies and chemical synthesis for 1 analog. Based on our observations for compounds **3**–**7** and ease of synthesis, we selected the 4-phenoxybenzanilide (**11**) core as the candidate scaffold for modulation of the A-ring, (Figure 4). With the goal of rapidly introducing diversity into the A-ring, we generated a library of **1** analogs using standard amide bond forming reactions of **13** with benzoyl or benzoic acid derivatives to synthesize compounds **14a–14n** and **15a–15g**, (Scheme 2). While many benzoyl or benzoic acid derivatives are commercially available, 6-fluorobenzoyl chloride or carboxylic acid derivates with 4- and 6-substituents typically contain halogens or have limited diversity in the alkyl, and electron withdrawing (EWG) groups.

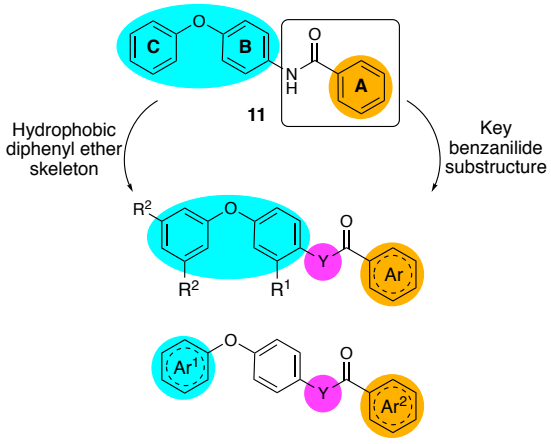
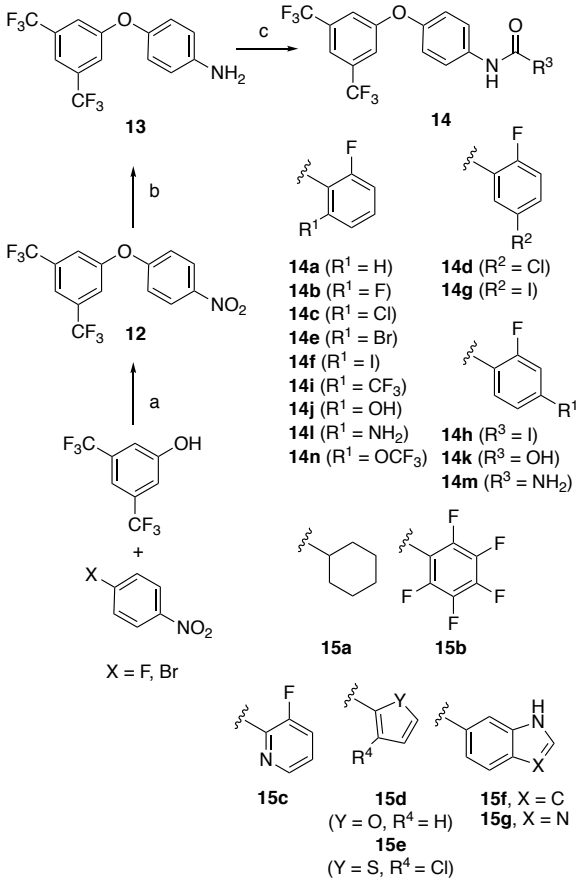


Figure 4. Design of novel TLR7/8 and TLR8 inhibitors bearing a benzanilide substructure.

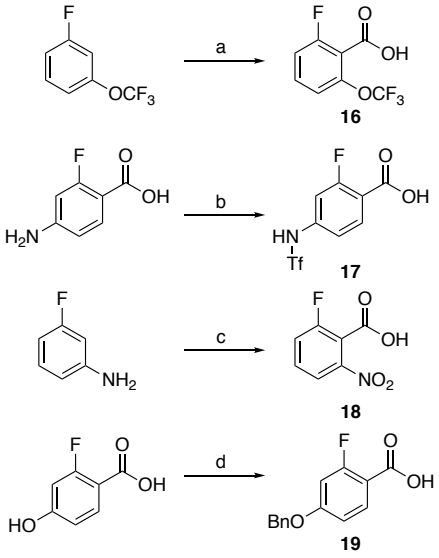
Scheme 1. Synthesis of 14a–14m and 15a–15g.



[a] Reagents and conditions: (a) 3,5-bis(trifluoromethyl)phenol and 1-fluoro-4-nitrobenzene or 1-bromo-4-nitrobenzene, Cs_2CO_3 or K_2CO_3, toluene, 100 °C (61–91%); (b) Method A: $SnCl_2$, EtOH, 70 °C (19–88%) or Method D: 10 mol% Pd/C, H_2, MeOH, rt, overnight; (c) Method A: HATU, carboxylic acid, DMF, *i*-Pr_2NH or Et_3N, aniline, 0 °C–rt , overnight or Method B: aniline, acid chloride, Et_3N, CH_2Cl_2, 0 °C–rt.

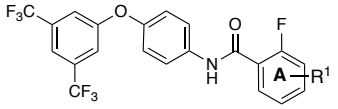
We prepared carboxylic acids that were not commercially available, (Scheme 3) and designed functionalized benzoic acid derivatives amenable to late-stage functionalization for access to a variety of analogs to expand our SAR exploration. The compounds were evaluated in the SEAP assay for both TLR7 and TLR8 inhibition to determine general TLR7/8 selectivity. Initial SAR efforts for the A-ring began by exploring the effects of other halogens at the 6-position, (Table 1). Replacing -Cl with -H, **14a**, decreased the potency for TLR7 inhibition (>50 μM) and had minimal impact on TLR8 selectivity. Encouragingly, we modified the TLR7/8 selectivity to favor TLR8 selectivity by replacing the -Cl with an -I atom. The TLR7 activity for **14f** (**CU-115**) was significantly reduced compared to its TLR8 activity, supporting our hypothesis that TLR selectivity could be optimized for the dual inhibitor. In general, we observed that increasing the size of the halogen atom (6-F, 6-Br, and 6-I) increased TLR8 activity, while TLR7 inhibition decreased. To explore the importance of the 2,6-disubstitution pattern on the A-ring, we prepared the 2,5- (**14d** and **14g**) and the 2,4-disubstituted (**14h**) iodo- derivatives. All the compounds displayed reduced TLR7 and TLR8 activity relative to **1**. Cumulatively, these results suggest the TLR7 binding pocket may be smaller and is less tolerant of changes in substitution patterns of the A-ring.

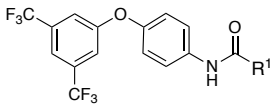
Scheme 2. Synthesis of carboxylic acid substrates 16–19.[a]



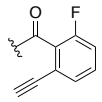
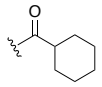
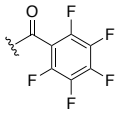
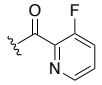
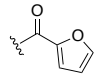
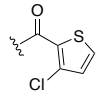
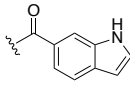
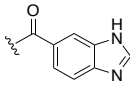
[a] Reaction conditions: (a) LDA, THF, -78 °C then CO_2 **16**, **17** 56%) (B) Tf_2O, CH_2Cl_2 (86%) (C) Oxone, NaOH, $NaHCO_3$, EDTA, H_2O, Acetone (95%) (d) i. BnBr, K_2CO_3, DMF, 70 °C then LiOH, THF, H_2O (52% 2-steps).

Table 1. SAR Modifications to A-ring 1 scaffold.





Compound	R^1	TLR7 IC_{50} (μM)[a]	TLR8 IC_{50} (μM)[a]	Compound	R^1	TLR7 IC_{50} (μM)[a]	TLR8 IC_{50} (μM)[a]
14a[d]	6-H	>50	~3	**14l**	6-NH_2	ND	ND

14b	6-F	NI	NI	**14m**	4-NH_2	>50	>50
14c (1)	6-Cl	2.88 (±0.25)	1.64 (±0.04)	**14n**	6-OCF_3	>50	>50
14d	5-Cl	ND	1.11 (±0.12)	**14o**		NI	NI
14e[d]	6-Br	~1	~6	**15a**		NI	NI
14f (CU-115)	6-I	> 50	1.04 (±0.16)	**15b**		NI	NI
14g	5-I	NI	ND	**15c**		>50	NI
14h	4-I	>50	>50	**15d**		NI	NI
14i	6-CF_3	ND[d]	ND	**15e**		NI	3.2 (±0.21)
14j	6-OH	ND	ND	**15f**		>50	ND
14k	4-OH	NI	>50 uM	**15g**		>50	ND

[a] IC_{50} derived from concentration-response curve in HEK 293-Blue TLR7 and TLR8 cell lines. Data was normalized to a 1 μg/mL R848 control (data are mean ± s.d.; n = 3 independent experiments). [b] NI: 0% inhibition. [c] ND: Not determined. IC_{50} was not determined for compounds displaying 20-30% inhibition at 50 μM. [c] Unstable compound. [d] Compound was insoluble at higher concentration, preventing accurate determination of IC_{50}. An approximate value is provided.

We hypothesized that differences in activity for compounds **1**, **14b**, and **14f** (**CU-115**)could arise from electrostatic effects. The iodine can engage in halogen bonding, an electrostatically driven interaction.[20] To further explore this, we examined the -OCF_3 (**14n**) and the ethynyl group (**14o**). The ethynyl group is a nonclassical bioisostere that has a polarized –CH moiety, and it is a weak hydrogen bond donor.[21] The trifluoromethyl (-OCF_3) group has been used as a bioisostere for larger halogens but cannot participate in halogen bonding like -I. For our inhibitors, replacement of -I with the -OCF_3 and the ethynyl moiety (**14o**) did not improve the potency, which indicates that halogen bonding may not be the dominating factor. The σ-hole effect also enables the -I atom to act as an H-bond acceptor; thus, we installed a -OH and -NH_2 group to explore this possibility at both the 4- and 6-positions. Installation of H-bond donors at the 6-positions leads to loss of TLR7/8 activity for **14k**, **14l**, **14j**, and **14m** further supporting the notion that halogen bonding is not an important factor. Lastly, complete fluorination of the A-ring (**15b**) and installation of a pyridine N- at the 6-position (**15c**) abolished TLR7 and TLR8 activity. All compounds bearing a heterocyclic A-ring **15-15g**, except for **15e**, were inactive or displayed poor activity for TLR7 and TLR8 inhibition or were toxic to HEK 293-Blue TLR cells

lines. Interestingly, thiophene **15e** inhibited TLR8 signaling with an IC_{50} value of 3.2 (±0.21 μM), while 0% inhibition was observed for TLR7 suggesting 5-membered heterocycles may be promising. Although there is precedence for the synthesis of halothiophenes, many approaches require the use of protecting groups or lengthy synthetic routes; thus, the thiophene analogs were not pursued.

Heterocyclic fused-ring derivatives were investigated to reduce the flexibility by fusing the A-ring with the B-ring and ultimately decrease the entropic cost for binding. We pursued benzimidazole instead of the benzoxazole derivative because it contains an NH and the SAR results indicated the amide NH was critical for retaining TLR7 activity. S_NAr of 5-fluoro-2-nitroaniline with 3,5-bis(trifluoromethyl)phenol followed by reduction of the nitro group afforded **23** in 71%. Benzoylation with 2-chloro-6-fluorobenzoyl chloride and then acid catalyzed cyclization yielded **28** in 25% yield (2-steps), see (Scheme 4b). Compound **28** did not display inhibitory activity thus revealing a flexible tricyclic core is necessary. Based on these results, heterocyclic cores were not pursued further, and replacement of the amide with a sulfonamide was ruled out since no inhibition was observed for both TLR7 and TLR8, (Figure 5).

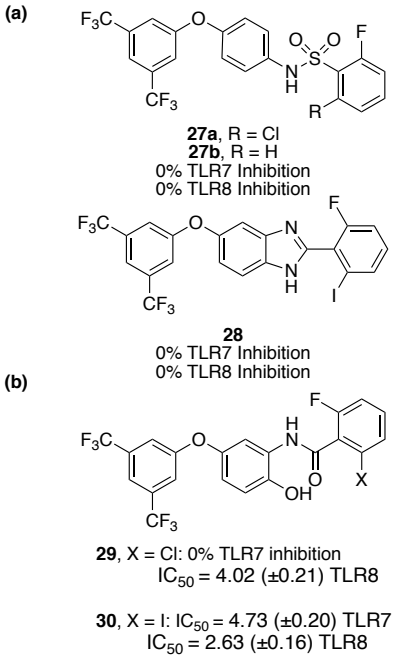


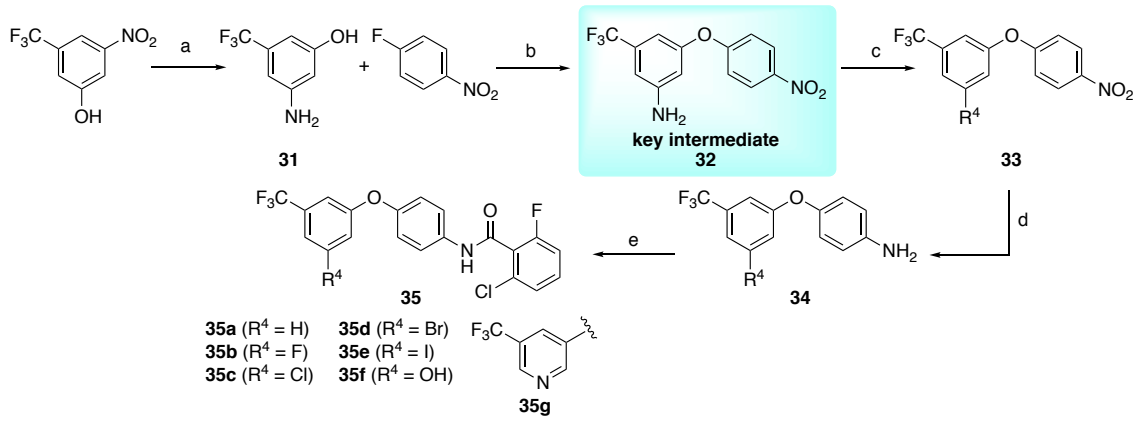
Figure 5. SAR B-ring 1 scaffold.

We then installed a -OH group *ortho*- to the amide for derivatives with different halogen substituents on the A-ring to explore the effect of two H-bond donors between the A- and B-rings. Palladium-catalyzed hydroxylation of **26**, which was synthesized utilizing the general synthetic route described in (Scheme 1) afforded **29** in 91% yield, see (Scheme 4c). Compounds **29** and **30** were comparable in activity to **1**; however, the chlorinated derivative **29** lost TLR7 activity while the iodine derivative **30** regained TLR7 activity with an IC_{50} value of 4.72 (±0.20) μM,

see (Figure 5). We also attempted to replace the B-ring with a 2,4-disubstituted pyridine. However, all attempts to synthesize the pyridine derivative using several amide bond forming reactions yielded mixtures of the imide byproduct, which were inseparable.

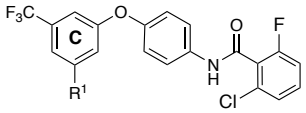
To complete our SAR studies, we introduced diversity into the C-ring since all the targets contained a symmetrical 3,5-bis(trifluoromethyl)phenoxy]phenyl motif. We designed intermediate **32** as a versatile building block for synthesizing **1** analogs with two different substituents at the 3- and 5-positions of the phenoxy C-ring which would allow us to assess the importance of the -CF_3 group and unsymmetrical versus symmetrical 3,5-disubstitution patter (Scheme 5). We envisioned using the Sandmeyer reaction to convert the aniline functional group (**32**) into a variety of halogens or H-bond donating groups such as -OH, see (Table 2) for summarized SAR results.

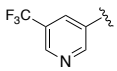
Scheme 3. Synthesis of 35a–35f.[a]



[a]Reaction conditions: (a) 10 mol% H_2 Pd/C, MeOH, rt (b) K_2CO_3, DMF, 90 °C (99% 2-steps) (c) various conditions (d) Fe powder, AcOH, EtOH (e) 2-chloro-6-fluorobenzoyl chloride, Et_3N, CH_2Cl_2, (40–44% 2-steps).

Table 2. SAR modification to C-ring scaffold.



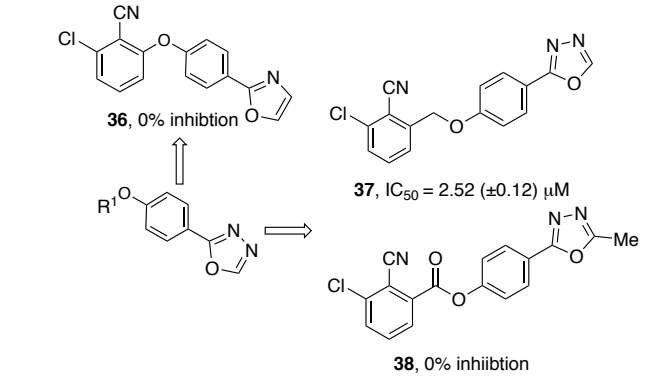
Cmpd	R^1	TLR7 IC50 (μM)[a]	TLR8 IC50 (μM)[a]
35a	H	2.65 (±0.84)	2.41 (±0.27)
35b	F	ND	1.59 (±0.11)
35c	Cl	ND	2.04 (±0.23)
35d	Br	ND	2.32 (±0.57)
35e	I	ND	>5 uM
35f	-OH	NI	NI
35g (CU-72)		5.10 ± 0.84	2.87± 0.21

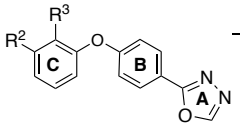
[a] IC_{50} derived from concentration-response curve in Hek 293-Blue TLR8 cell line. Data was normalized to a 1 μg/mL R848 control (data are mean ± s.d.; n = 3 independent experiments). [b] NI: 0% inhibition. [c] ND: Not determined. IC_{50} was not determined for compounds displaying 20-30% inhibition at 50 μM.

Replacing one -CF_3 group with a -H (**35a**) did not change the potency or selectivity indicating that one substituent is sufficient for activity, and replacing -CF_3 group with halogens atom retained TLR8 activity and abolished TLR7 activity, suggesting π-stacking interactions may be playing a role.[22] We observed a decrease in TLR8 activity with decreasing electronegativity for **35b**–**35e** and lost TLR7 activity. This motivated us to install a hydroxyl group because it is an electronegative group that can also act as an H-bond donor or acceptor. Installation of -OH eliminated both TLR7 and TLR8 activity indicating that an H-bond interaction is unfavorable. We then made a derivative containing a 3-phenoxy-5-(trifluoromethyl)pyridine motif because incorporation of a pyridine nitrogen, compound **35g** (**CU-72**), would make the aryl ring more electron deficient and also introduce an H-bond acceptor. Interestingly, compound **35g** displayed inhibitory activity toward both TLR7 and TLR8 suggesting a favorable H-bond interaction in the binding pocket of TLR7. This exciting result affords a new site to modulate TLR7/8 selectivity of the **1** scaffold. Overall, the SAR studies yielded a wealth of information for optimization of **1** and sufficient evidence to advance **CU-115** and **CU-72**, the lead compounds for scaffold **1**, for biological studies.

Overview of key SAR results and potency optimization for 2. 1,3,4-Oxadiazoles are common heterocyclic compounds that exhibit a broad spectrum of biological activities.[23, 24] Our initial SAR efforts focused on determining if the diaryl ether linker between the B- and C-rings was necessary and examining the importance of the 1,3,4-oxadiazole motif by replacing it with a 2-substituted oxazole (**36**). The benzyl derivative **37** inhibited TLR8 with an IC_{50} = 2.52 ±0.12 μM while the oxazole (**36**) and ester **38** derivatives were inactive, (Figure 6). These SAR studies demonstrated that 1,3,4-oxadiazole motif and the diaryl ether linkage are essential for the bioactivity of **2**. A variety of **2** analogs were synthesized in excellent yield using the S_NAr reaction between aryl fluorides and aryl *tert*-butyl dimethyl silyl (TBDMS) or trimethylsilyl (TMS) ethers promoted by Verkade super bases (Scheme S3b).[25] The potency of **2** was improved by replacing -CN with a -NO_2 (**39b**) group (IC_{50} = 0.77 ±0.09 μM), see (Figure 6). Electron donating groups (EDG) that can act as H-bond donor or acceptor did not inhibit TLR8 signaling or were less active (**39c** and **39d**). We slightly improved the potency of **39b** by replacing the Cl- with -I to afford **39f** (**CU-68**) with an IC_{50} value of 0.3

±0.20 μM. **CU-68** was identified as the lead hit for scaffold **2** and advanced for biological evaluation in parallel with the lead hits **CU-115** and **CU-72** benzanilide inhibitors.





Cmpd	R^2	R^3	TLR8 IC_{50} (μM)	TLR7 IC_{50} (μM)
39a	H	H	7.26 (±0.41)	ND[a]
39b	Cl	$-NO_2$	0.77 (±0.09)	ND[a]
39c	Cl	$-NH_2$	5.29 (±0.81)	ND[a]
39d	Cl	-NHAc	NI	ND[a]
39e	Br	-CN	0.88 (±0.20)	ND[a]
39f (CU-68)	I	$-NO_2$	0.30 (±0.02)	> 20

[a] ND, not determined.

Figure 6. Overview of key SAR results and potency optimization for 2.

Endosomal and non-endosomal TLR specificity studies. The specificity for the new inhibitors was first tested using stably transfected HEK 293-Blue cells individually overexpressing each human TLR. **CU-68** displayed good selectivity toward TLR8 over all TLRs at 0.5 and 20 μM, see (Figure S3.). **CU-115** and **CU-72** display activity for TLR7 and TLR8 only at low concentrations (0.5 μM) but not at 5 and 20 μM. We speculate that at higher concentrations (5 and 20 μM) the inhibitors could be binding to the nucleic acid ligand (ODN 2006) and this interaction induces a chemical change in the ligand that prevents their binding for TLR9 activation.[26] The inhibitors displayed sufficient selectivity at concentrations < 5 μM and inhibitory activity at low concentrations against TLR7 and TLR8 to advance biological studies in other immune cells. The compounds were nontoxic at low concentration (0.5 and 20 μM) and toxic at 100 μM in Hek 293 TLR7 and TLR8 cells, see (Figure S5a). Of course, nucleic acid binding studies are needed to determine if dsDNA or ssRNA intercalation is a potential inhibitory mechanism.

Secondary cellular assays were used to further confirm that **CU-68** and **CU-115** are inhibiting TLR8. First, we tested inhibition of the hTLR7 pathway using stably transfected HEK 293-Blue cells individually overexpressing each human hTLR7 and determined that **CU-68** and **CU-115** do not inhibit hTLR7 at 0.5, 1, 5, and 20 μM, see (Figure 7a and Table 1). We also used RAW.264.7 murine macrophages cells to evaluate TLR7 inhibition since murine TLR8 has been shown to not respond to R848.[27] For several years, it has been speculated that murine TLR8 is not functional; however, controversial studies have shown TLR8 to be active in murine macrophages, and a general consensus remains to be

established in the field.[28] The RAW.264 cells were stimulated with R848 for activation of nitric oxide (NO) in macrophage cells. We measured the NO levels as an indicator of R848 induced TLR7 activation to evaluate the inhibitory activity. The results showed the inhibitors do not inhibit signaling mediated by TLR7 in RAW.264.7 cells, see (Figure 7b) at < 5 μM for **CU-68** and for **CU-115** only at 1.25 μM and at concentrations > 5 μM **CU-68** and **CU-115** displayed inhibitory activity. Further studies are needed to clarify the observed difference in activity between species. We also conducted cellular toxicity studies by treating Hek-293 TLR7, Hek-293 TLR8, THP-Dual, Raw 264.7, and RAW Dual cell lines with sample compounds. These studies showed that **CU-115**, **CU-72**, and **CU-68** inhibitors were nontoxic at low concentrations (0.5 and 20 μM) for all cell lines used in the cell-based assays, see Figure S5. Toxicity to Hek 293 TLR7 and TLR8 cell lines was observed for **CU-115** and **CU-72** at 100 μM and **CU-68** displayed partial toxicity at 100 μM in THP-Dual cells, see (Figure S7b).

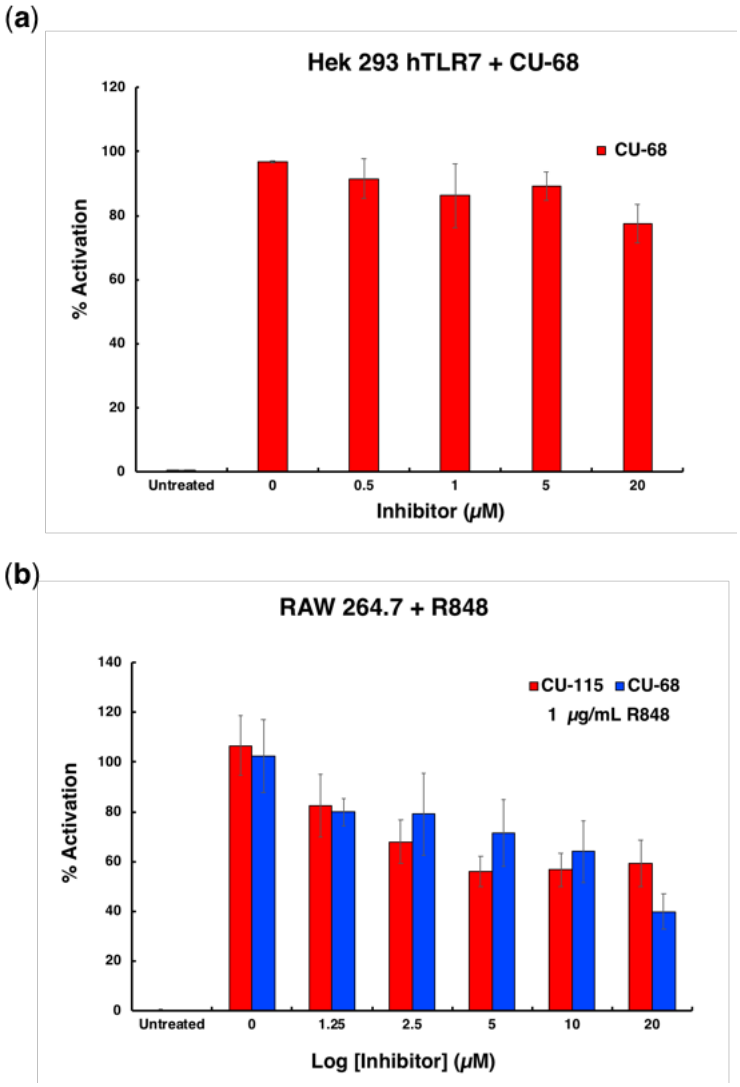


Figure 7. CU-68 and **CU-115** do not inhibit hTLR7 in RAW 264.7 and Hek 293 hTLR7 cells: (a) Effect of **CU-68** and **CU-115** on NF-κB inhibition mediated by endosomal TLR7 in RAW 264.7 murine macrophages. RAW 264.7 macrophage cells were incubated with **CU-68** or **CU-115** for 16 h. Activation of TLR7 mediated by R848 results in the activation of NO synthase and the production of NO in RAW 264.7 cells. The NO level was monitored as an indicator of R848-induced TLR7 activation to evaluate the compound inhibitory activity. At 1.25 μM **CU-68** and **CU-115** do not

inhibit nitric oxide production mediated by TLR7 except at 1.25, 5, 10, and 20μM (39–51% inhibition). Inhibition caused by cellular toxicity was ruled out, see Figure S5c. (b) Effect of **CU-68**, **CU-115**, and **CU-72** on NF-κB inhibition mediated by ssRNA stimulated HEK 293-TLR7 cells. Human embryonic kidney (HEK) 293 cells expressing human toll-like receptor (hTLR) 7 gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were incubated with sample compounds for 16 h. Ligand-induced TLR activation was determined by measuring absorbance at 620 nm for the SEAP protein and comparing wells treated with sample to 50% DMSO treated and untreated cells. (c) For both studies, the data were normalized as [(raw data – untreated cells)/(ligand + solvent control – untreated cells)]. Ligand + solvent is 100% activation, and untreated cells are 0% activation. The data are mean ± s.d.; n = 3 independent experiments.

Therapeutic potential and biophysical characterization of CU-68, CU-115, and CU-72. The inhibition of the biologically relevant ssRNA ligands, which mimic physiological detection of viruses or siRNA molecules, with **CU-68**, **CU-115**, and **CU-72** was examined to explore their therapeutic potential. In the presence of ssRNA ligands, **CU-68** inhibited TLR8 signaling completely at 5 μM while **CU-115** and **CU-72** displayed weaker activity, see (Figure 8a), indicating the benzanilide inhibitors are less potent than **CU-68**. In HEK 293 TLR8 cells stimulated with ssRNA agonist, **CU-68** has an IC_{50} value of 0.62 (±0.04) μM (Figure 8b), which is less potent compared to R848 stimulated HeK 293 TLR8 cells (IC_{50} = 0.30 (±0.02) μM). The activation mechanisms of TLR8 with distinct agonists such as R848 and ssRNA can be mechanistically different. R848 activates TLR8 by binding to the dimer interface of TLR8 near leucine-rich repeat (LRR) 11–24 and LRR16–18.[4a] The conformational change induced by R848 brings the two C termini in closer proximity ultimately activating the cytoplasmic Toll-interleukin-1 (TIR) receptor.[4a] In contrast, ssRNA inducted TLR8 activation is achieved through synergistic binding of two ssRNA degradation products, uridine and short oligonucleotides.[4c] The uridine molecule binds to the same site on the dimerization interface as R848 while the short oligonucleotides binds to the concave surface of the TLR8 horseshoe structure and binding of both molecules is necessary for full activation of TLR8 by ssRNA.[4c] These differences in the activation mechanisms have often times led to discrepancies of IC_{50} values for TLR8 signaling inhibition induced by chemical and ssRNA ligands.[18a] A possible explanation for the differences in activity for **CU-68** as well as **CU-115** and **CU-72** is that a conformational change induced by ssRNA bound to site 2 destabilizes the ligand affinity (i.e. **CU-68**) at site 1, resulting in decreased inhibitory activity. Of course, x-ray crystal structures of **CU-68** bound alone and in complex with ssRNA are needed for further clarification of specific binding mode and the inhibitory mechanism.

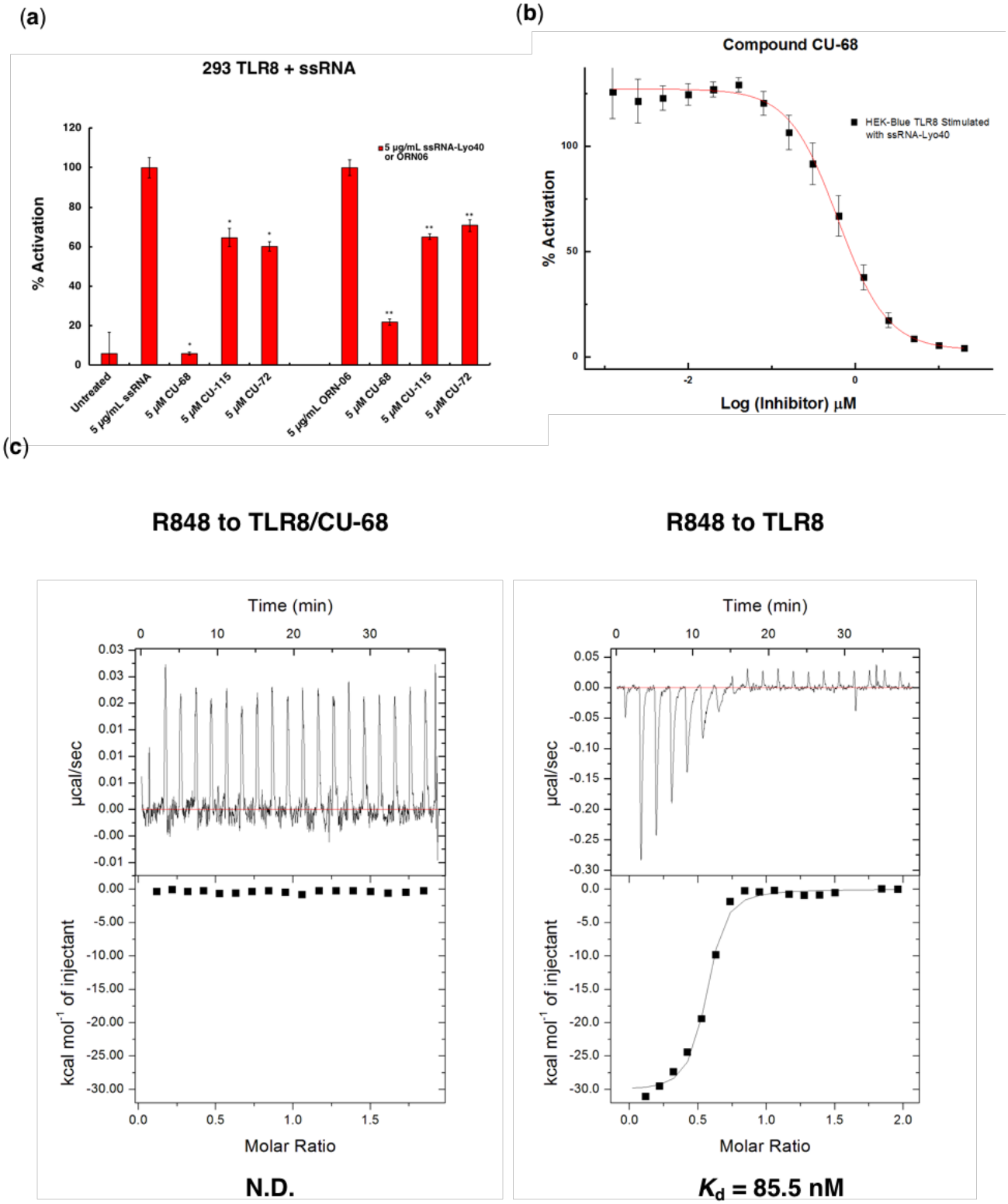


Figure 8. Therapeutic potential of **CU-115**, **CU-72**, and **CU-68** and biophysical characterization of **CU-68**. (a) Effect of **CU-68**, **CU-115**, and **CU-72** on NF-κB inhibition mediated by ssRNA stimulated human embryonic kidney (HEK) 293-TLR8 cells. HEK 293 cells hTLR8 gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were incubated with sample compounds for 16 h. The data were normalized as [(raw data – untreated cells)/(ligand + solvent control – untreated cells)]. Ligand + solvent is 100% activation, and untreated cells are 0% activation. At 5 µM, **CU-68** suppresses the NF-κB inhibition induced by ssRNA-Lyo-40 in HEK 293 TLR8 cells while **CU-115** and **CU-72** displayed weaker activity

(data are mean ± s.d.; n = 3 independent experiments). (b) **CU-68** dose-response-dependent NF-κB inhibition mediated by ssRNA stimulated HEK 293-TLR8 cells (data are mean ± s.d.; n = 3 independent experiments). (c) ITC thermogram of **CU-68** titrated into hTLR8 to determine binding affinity. The titration of R848 into hTLR8 premixed with **CU-68** (left), and the titration of R848 into hTLR8 alone (right), suggesting that **CU-68** prevents R848 from binding to TLR8 (representative of one independent experiment). The raw data are presented on top and the integrated peak areas are shown and fitted below.

Our ongoing efforts have not yielded co-crystal structures of **CU-68**, **CU-115**, and **CU-72** in complex with TLR7 and TLR8 of sufficient resolution for structure elucidation. Thus, the direct binding of **CU-68** to the ectodomain of human TLR8 was confirmed with isothermal titration calorimetry (ITC). Unfortunately, the titration of **CU-68** into TLR8 did not yield sufficient heat signals to determine the dissociation constant (K_d) between **CU-68** and TLR8. Alternatively, we assessed the inhibitory effect of **CU-68** for R848, a previously established nonselective TLR7/8 agonist, [27] binding to TLR8, The heat signals during the titration of R848 into TLR8 was clearly suppressed in the presence of **CU-68**, suggesting that **CU-68** prevented R848 from binding and subsequent structural change of TLR8. Unfortunately, attempts to conduct ITC analyses for **CU-72** did not yield data of sufficient quality to confirm its direct binding to TLR8. Because **CU-72** and **CU-115** both exhibited low solubilities, they could not be used for ITC experiments.

CU-115, CU-72, and CU-68 inhibit endosomal ssRNA sensing pathways. To investigate the NA-sensing pathway selectivity, we tested the effect of **CU-115**, **CU-72A**, and **CU-68** on inhibition of the IFN immune response mediated by human retinoic-acid-inducible protein 1 receptors (RIG-I, also known as Ddx58), and cyclic AMP-GMP synthase (cGAS), which are cytosolic NA sensing receptors. We used human THP1-Dual monocyte gene assays, containing both the Lucia luciferase and the SEAP genes and measured expression of luciferase as an indicator of ligand-induced activation. The THP1-Dual cells were stimulated with 3p-hpRNA, a known RIG-I agonist in the presence or absence of the inhibitors, and to activate the cGAS pathway we used Y-form dsDNA (G3-YSD), a known cGAS agonist. Overall, **CU-68**, **CU-115**, and **CU-72** were unable to suppress activation of the RIG-I and cGAS signaling pathways by biologically relevant immunogenic stimuli at 0.5, 1, and 5 μM concentrations for the THP1-Dual cell line (Figure 9a). **CU 68** inhibited both pathways at 20 μM and for **CU-72** we observed inhibition at 5 and 20 μM in THP1-cells, which could possibly be caused from the inhibitors binding to the RNA or DNA ligands preventing activation. The specificity results are consistent for the RAW-Dual cell line at 0.5 and 1 μM concentrations (Figure S6) and also support our hypothesis the inhibitors may bind to NAs at high concentrations. Of course, further clarification of the inhibitory mechanism is necessary.

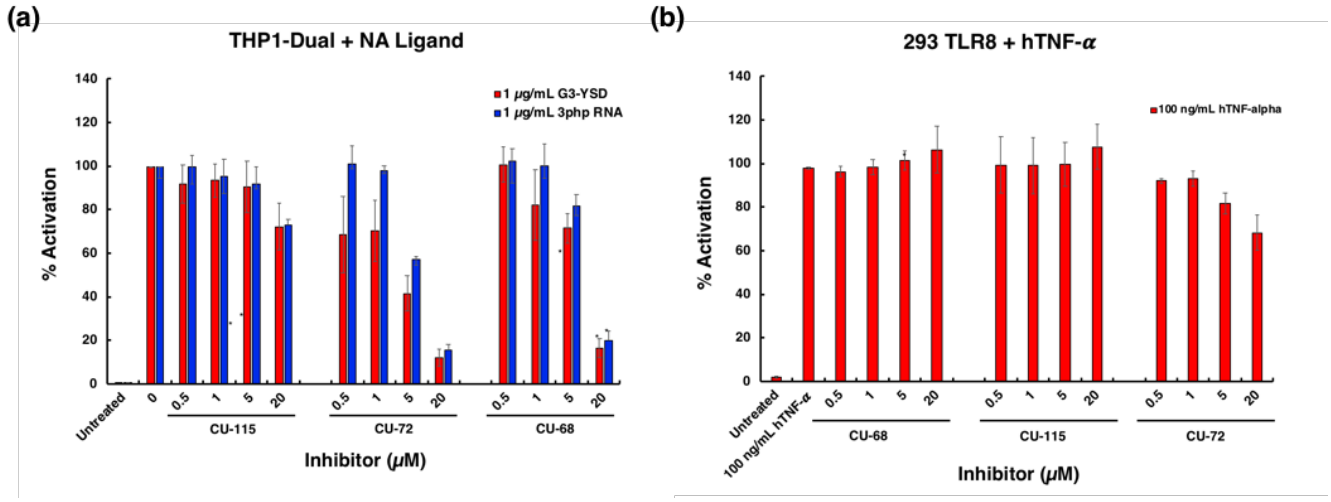


Figure 9. CU-68, **CU-115**, and **CU-72** inhibit ssRNA NA sensing pathways: (a) Effects of **CU-68**, **CU-115**, and **CU-72** treatment on IFN-I inhibition mediated by human cGAS and RIG-I cytosolic sensors. The human THP1-Dual monocyte gene assays, which contains both the Lucia luciferase and the SEAP genes was used. The THP1-Dual cells were stimulated with 3p-hpRNA, a known RIG-I agonist in the presence or absence of the inhibitors and to activate the cGAS pathway we used Y-form dsDNA (G3-YSD), a known cGAS agonist. Quantification of luciferase was used to monitor the expression of luciferase via detection of Lucia luciferase reporter protein secreted by cells. The compounds were considered active if they decreased luciferase levels as indicated by a decrease in luminescence relative light units. At 0.5 and 1 μM **CU-115**, **CU-72**, and **CU-68** do not modulate type-1 IFN transcription mediated by cGAS-STING or the RIG-I pathways. **CU-72** and **CU-68** display off-target effects at > 5 μM (data are mean ± s.d.; n = 3 independent experiments). (b) Effect of **CU-68** and **CU-115** on NF-κB inhibition mediated by hTNF-α in HEK 293 TLR8 cells. Hek 293 cells expressing hTLR8 gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were incubated with sample compounds for 16 h. Ligand-induced TLR activation with hTNF-α was determined by measuring absorbance at 620 nm for the SEAP protein and comparing wells treated with sample to 50% DMSO treated and untreated cells. **CU-68**, **CU-115**, and **CU-72** do not inhibit the immune response mediated by TNF-α which rules out inhibition via NF-kB.

In addition, we investigated the release of pro-inflammatory cytokines using recombinant TNF-α ligand. TNF-α is an inflammatory cytokine produced in several types of immune cells. Signaling induced by TNF-α ultimately leads to activation of NF-kB and mitogen-activated protein kinase (MAPK) signaling pathways. We measured the SEAP levels as an indicator of TNF-α induced immune response to evaluate the inhibitory activity. The results showed that **CU-68**, **CU-115**, and **CU-72** do not inhibit the immune response mediated by TNF-α (Figure 9b), which rules out inhibition via NF-kB. Lastly, enzyme-linked immunosorbent assay (ELISA) was performed to measure upregulation/inhibition of TNF-α in human THP-1 cells (hTHP-1). The results showed that all three inhibitors abolished the TNF-α production activated by R848 in hTHP-1 (Figure 10a). We also investigated the production of interleukin-1 beta (IL-1β) in hTHP-1 cells. The compounds repressed the expression of IL-1β (Figure 10b). These results suggest the inhibitors suppress TLR8 and TLR7 signaling pathways.

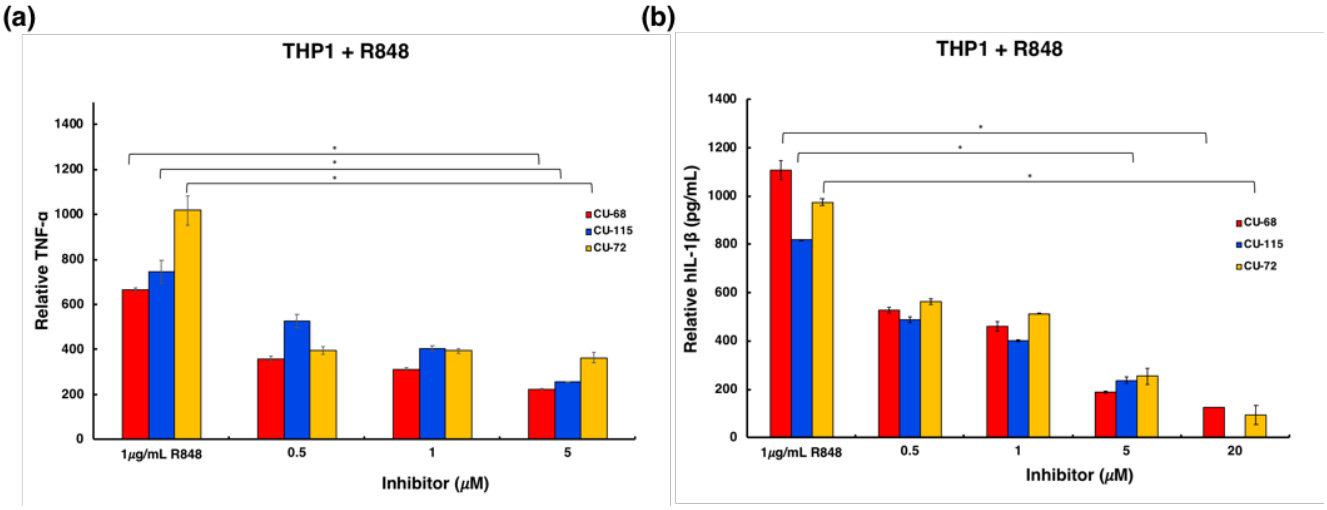


Figure 10. TNF-α and IL-1β in THP-1 cells in the presence and absence of **CU-68**, **CU-115**, or **CU-72**. R848 (a) Dose-dependent response of **CU-68**, **CU-115**, and **CU-72** TLR8-mediated TNF-α production in THP-1 cells with indicated concentration of inhibitor. Hek hTLR8 cells were stimulated with 1 μg/mL R848. Data are mean ± s.d.; n = 3 independent experiments. (d) Dose-dependent response of **CU-68**, **CU-115**, and **CU-72** TLR8-mediated IL-1β production in THP-1 cells with indicated concentration of inhibitor. All inhibitors down-regulated TNF-α and IL-1β production activated by R848 in hTHP-1 cells.

Scheme 4. Synthesis of 5.[a]

CONCLUSIONS

In conclusion, a new benzanilide compound was identified as an interesting hit compound displaying inhibitory activity toward TLR7 and TLR8 signaling pathways. We also identified an additional hit bearing a 1,3,4-oxadiazole motif inhibiting TLR8 exclusively. Our extensive SAR studies led to the development of two distinct scaffold classes of TLR8 inhibitors and a new TLR7/8 dual inhibitor with potential TLR7 activity optimization. The SAR results obtained indicate the importance of the benzanilide substructure and the hydrophobic diphenyl ether skeleton for conserving TLR7 activity. Biological evaluation of **CU-115**, **CU-72**, and **CU-68** inhibitors using human monocyte THP-1, RAW264.7 and Hek 293-Blue TLR cells confirmed they are all active for inhibiting ssRNA-sensing pathways at low concentrations and do not inhibit other non-endosomal TLR and cytosolic NA-sensing pathways (< 5 μM). Our ITC analyses with purified TLR8 protein provided strongly suggestive evidence of its direct binding to the ectodomain of TLR8. Crystallographic studies are needed to identify the specific binding pocket for **CU-68** and additional SAR focused on solubility optimization for characterization studies is warranted for **CU-72** and **CU-115**. In general, the new **1** dual inhibitor represents an important class of inhibitors with potential development for a much needed TLR7 inhibitor. We anticipate the SAR results will be instructive for optimization studies based on the **CU-72** scaffold.

EXPERIMENTAL SECTION

Protein preparation and isothermal titration calorimetry (ITC). The extracellular domain of human Toll-like receptor 8 (hTLR8, residues 27–827) was prepared as described previously[4].

ITC experiments were done in a buffer composed of 25 mM MES pH 5.5, 0.20 M NaCl, and 5% dimethyl sulfoxide (DMSO) at 298 K using a MicroCal iTC200 (GE Healthcare). The titration sequence included a single 0.4 μL injection followed by 18 injections, 2 μL each, with a spacing of 120 s between the injections. The titration conditions were as follows: 100 μM R848 into 10 μM hTLR8 and 50 μM **CU-68**; 100 μM R848 into 10 μM hTLR8. OriginLab software (GE Healthcare) was used to analyze the raw ITC data.

Chemistry. Materials and Methods. Unless otherwise noted, all non-aqueous reactions were run under an atmosphere of dried nitrogen (N_2) in dried glassware. All reagents were reagent grade and used without further purification. Moisture sensitive reagents were added via syringe. All chemicals were obtained from Sigma-Aldrich, Acros, or Strem unless otherwise noted. Flash column chromatography was performed using EM Reagents Silica Gel 60 (230-400). Analytical thin-layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 254-F plates. Visualization was accomplished with UV light, *p*-anisaldehyde stain, and/or iodine. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker-III NMR spectrometer operating at 400 MHz. Chemical shifts are reported relative to the solvent resonance peak δ 7.27 ($CDCl_3$) for ^{1}H and δ 77.23 ($CDCl_3$) for ^{13}C NMR. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants, and number of protons. High-resolution mass spectra were obtained using a VG Autospec using an ionization mode of either ESI or CI. Infrared spectra are reported in cm^{-1} and recorded using an Agilent Technologies Cary 630 FTIR. Unless otherwise noted, all yields refer to isolated yields. A MPA 160 melting point apparatus was used to measure the melting point.

High performance liquid chromatography (HPLC) Purity Method*:* The purity of tested compounds (inhibitor samples > 95% purity) was evaluated using An Agilent Technologies 1200 series HPLC instrument with an Agilent Eclipse XDB-C18 column (reverse phase) Mobile phase (A) 100% HPLC grade acetonitrile (MeCN) with 0.1% HPLC grade trifluoroacetic acid (TFA) and mobile phase (B) 100% HPLC grade water (H_2O) 0.1% HPLC grade TFA. The gradient was 80% A at 0 min then to 80–60 to 5 min then 60% A with 5 min hold (1.0 mL/min). The mobile phase was then changed to 100% B to 10 with a 5 min hold then 60:40 (A:B) with 5 min hold then 80:20 for 7 min. A flow rate of 1.0 mL/min was used for the entire method, with a total assay time of 22 min.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2-chloro-6-fluoro-N-methylbenzamide (3): To a solution of *N*-{4-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-chloro-6-fluorobenzamide (**1**) (0.13 mmol, 60 mg) in DMF (0.27 M) was added sodium hydride 60% in dispersion mineral oil (0.25 mmol, 6 mg) at 0 °C. The mixture was warmed to rt and stirred for 30 min. Methyl iodide (0.19 mmol, 11.7 μL) was then added dropwise at 0 °C and stirred at 0 °C. After 1 h, then more methyl iodide (0.36 mmol, 22 μL) was added and the mixture was stirred at rt overnight. The reaction was then quenched with saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (3x 1 mL). The organic mixture was then washed with 5% LiCl aq (5x 1 mL), dried with Na_2SO_4, and concentrated by rotary evaporation to afford a white solid. Following purification by column chromatography (20% EtOAc in hexane), the title compound was obtained in 84% yield (52 mg, 98% pure): mp 74–75 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) (mixture of rotamers) δ ; 7.58 (br s, 1H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.35 – 7.30 (m, 1 H), 7.20 – 7.10 (m, 1 H), 7.15-7.10 (m, 1 H), 7.14–7.11 (m, 2 H), 7.06 (ddt, *J* = 8.1, 3.7, 0.9 Hz, 2 H), 6.92 (d, J = Hz 1 H), 6.84 (tt, *J* = 8.4, 0.9 Hz, 1 H), 3.55 (s, 3 H, minor rotamer), 3.49 (s, 3 H); ^{13}C NMR (DMSO-d_6, 101 MHz) (mixture of rotamers) δ 163.5, 163.3, 158.3 (d, $^1J_{CF}$ = 251.0 Hz), 158.3 (d, $^1J_{CF}$ = 250.3 Hz), 158.6, 154.4, 141.7, 139.7, 132.4, 130.9 (d, $^3J_{CF}$ = 9.1 HZ), 130.9 (d, $^3J_{CF}$ = 9.0 HZ), 128.1, 128.0 (d, $^2J_{CF3}$ = 36.9Hz, 125.2 (d, $^2J_{CF}$ = 10.7 Hz), 125.3 (d, $^2J_{CF}$ = 10.8 Hz), 122.9 (q, $^1J_{CF3}$ = 274.0 Hz), 121.6, 120.7, 117.9 (q, $^4J_{CF3}$ = 3.1 Hz), 116 (m, $^3J_{CF3}$), 114.0 (d, $^2J_{CF}$ = 21.7 Hz), 113.8 (d, $^2J_{CF}$ = 21.6 Hz), 37.1, 37.0; ^{19}F NMR (365 MHz, $CDCl_3$) δ -63.0, -111.2, 111.5; IR (film) 3070, 2925, 1659, 1614, 1584, 1462, 1365, 1279, 1234, 1171, 1130, 1108, 1007, 955, 895, 854, 823, 702, 683 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_{16}ClF_7N_6O_2$ $[M+H]^+$, *m/z* = 492.0601, found 492.0601.

4-(3,5-Bis(trifluoromethyl)phenoxy)-N-(2-chloro-6-fluorobenzyl)aniline (4)[29]: A vial containing acetic acid (0.1 mL, 1.8 mmol), **12** (0.32 g, 1 mmol), 2-chloro-6-fluorobenzaldehyde (0.24 g, 1.5 mmol), and MeOH (5 mL) was stirred at rt for 30 minutes, then cooled to 0 °C. Sodium cyanoborohydride (0.08g, 1.2 mmol) was added in one portion, and the reaction warmed to rt while stirred for 18 hours. The resulting solution was diluted with 20 mL EtOAc, then washed 2x with 10 mL H_2O, once with 10 mL brine, dried over Na_2SO_4, and concentrated to dryness. Following purification by column chromatography (0-100% CH_2Cl_2 in hexane), the title compound was obtained in 88% yield (0.41 g, 99% pure): mp = 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.49 (s, 1H), 7.30 (s, 2 H), 7.25 – 7.20 (m, 2 H), 7.06 – 6.99 (m, 1 H), 6.94 – 6.89 (m, 2 H), 6.81 – 6.75 (m, 2 H), 4.17 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (d, $^1J_{CF}$ = 249.7 Hz), 160.3, 146.2, 145.4, 135.7 (d, $^3J_{CF}$ = 5.6 Hz), 133.0 (q, $^2J_{CF3}$ = 33.6 Hz), 129.8 (d, $^3J_{CF}$ = 9.8 Hz), 125.8 (d, $^4J_{CF}$ = 3.3 Hz), 124.6 (d, $^2J_{CF}$ = 25.7 Hz), 123.2 (q, $^1J_{CF3}$ = 279.6 Hz), 121.7, 116.8 (d, $^4J_{CF3}$ = 4.1 Hz), 115.3 (sep, $^3J_{CF3}$ = 3.9 Hz),114.8, 114.5 (d, $^2J_{CF}$ = 23.3 Hz), 40.0 (d, 3.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ -63.0, -113.7; IR (film) 3417, 3085, 1610, 1581, 1514, 1454, 1383, 1320, 1286, 1223, 955, 881, 862, 836, 687 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{13}F_7ClNO$ $[M+H]^+$, *m/z* = 464.0652, found 464.0652.

General Procedures for Compounds **3**, **6**, **7**, **13a**-**13o**, and **14**-**14g**:

General Procedure A: Amide Coupling via HATU[30]: To a flame-dried vial was added HATU (0.6 mmol), carboxylic acid (0.56 mmol), and DMF (1 mL). The vial was cooled to 0 °C and diisopropylethylamine (0.6 mmol) was added, then the vial was removed from ice bath. After the vial was stirred for at least 15 minutes, the appropriate aniline (0.5 mmol) dissolved in DMF (1 mL) was added, and the reaction mixture was stirred overnight. After completion, the solvent was removed *in vacuo* and the crude product was partitioned between 5 mL each water and ethyl acetate. The aqueous layer was extracted 3x with 5 mL ethyl acetate, after which the combined organic layers were washed with 5 mL brine, dried over Na_2SO_4, and concentrated to dryness. Purification varied by compound, typically flash chromatography or trituration in cold hexane.

General procedure B: amide coupling via acyl chloride: To a flame-dried flask containing substituted aniline (0.6 mmol) in CH_2Cl_2 (2 mL) was added acid chloride (0.72 mmol) dissolved in CH_2Cl_2 (2 mL). The flask was placed under nitrogen and cooled to 0 °C, after which triethylamine (0.1 mL, 0.72 mmol) was added dropwise. The reaction was allowed to return to rt while stirring overnight. The solvent was removed in vacuo and the resulting residue was partitioned between 10 mL ethyl acetate and water. The aqueous layer was extracted 3x with 5 mL ethyl acetate, and the combined organic layers were sequentially washed with 5 mL 1M NaOH and 5 mL brine, dried over Na_2SO_4, and concentrated to dryness. Purification varied by compound.

N-(3,5-Bis(trifluoromethyl)phenyl)-2-chloro-6-fluorobenzamide (5): Prepared by general method B using 3,5-bis-(trifluoromethyl)aniline 0.52 mmol, 0.52 mmol 2-chloro-6-fluorobenzoyl chloride, 0.78 mmol Et_3N and 2.6 mL CH_2Cl_2. The solid was purified by flash column chromatography (20% EtOAc in hexanes) to afford the title compound as a white solid in 28% yield (56 mg, 99% pure): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, *J* = 1.6 Hz, 2 H), 7.95 (s, 1 H), 7.68 (tt, *J* = 1.5, 0.8 Hz, 1 H), 7.39 (td, *J* = 8.3, 6.0 Hz, 1 H), 7.29 – 7.26 (m, 1 H), 7.10 (td, *J* = 8.6, 1.0 Hz, 1 H). ; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.8, 158.3, 138.6, 132.6 (q, $^2J_{CF3}$ = 33.8 Hz), 132.2, 132.1, 126.0 (d, $^4J_{CF}$ = 3.5 Hz), 123.0 (q, $^1J_{CF3}$ = 274.0 Hz), 124.2 (d, $^2J_{CF}$ = 20.5 Hz), 119.8 (q, $^4J_{CF3}$ = 3.0 Hz), 118.5 (q, $^3J_{CF3}$ = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0, -112.0; IR (film) 3253, 3093, 1722, 1670, 1558, 1502, 1473, 1454, 1380, 1305, 1279, 1231, 1171, 1134, 1063, 951, 903, 884, 795, 773, 683, 527 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_7ClF_7NO$ $[M+H]^+$, *m/z* = 386.0177, found 386.0180.

4-[3,5-Bis(trifluoromethyl)phenoxy]-N-(2-chloro-6-fluorophenyl)benzamide (6): A vial containing methyl 4-(3,5-bis(trifluoromethyl)phenoxy)benzoate (0.15 g, 0.41 mmol), 2 M NaOH (2 mL, 4 mmol), and MeOH (4 mL) was sealed and heated at 50 °C for 2.5 hours, then partitioned between 10 mL each 3 M HCl and EtOAc. The aqueous layer was extracted 3x with 10 mL EtOAc, and the combined organic layers washed with 10 mL brine, dried over Na_2SO_4, and concentrated to dryness. The resulting white solid was added to a vial containing CH_2Cl_2 (5 mL) and DMF (1 drop), then placed under N_2 and cooled to 0 °C. Oxalyl chloride (0.086 mL, 1 mmol) was added and the mixture gradually warmed to rt while stirring for 30 minutes. Volatiles were removed *in*

vacuo, then 2-fluoro-6-chloroaniline (0.09 g, 0.62) dissolved in CH_2Cl_2 (5 mL) was added, followed by Et_3N (0.28 mL, 2 mmol). This mixture was stirred for 3 h, then concentrated. The residue was partitioned between 10 mL each EtOAc and H_2O, and the aqueous layer extracted 3x with 10 mL EtOAc. Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was triturated with hexane and then purified by column chromatography (0-100% CH_2Cl_2 in hexane) to afford the title compound in 57% yield (0.111g, 99% pure) as a tan solid : mp = 178–180 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.40 (s, 1 H), 8.21 – 8.16 (m, 2 H), 7.87 (s, 1 H), 7.78 – 7.75 (s, 2 H), 7.46 – 7.38 (m, 2 H), 7.37 – 7.30 (m, 2 H), 7.30 – 7.23 (m, 1 H); ^{13}C NMR (101 MHz, Acetone-d_6) (rotamers) δ 165.12, 165.1, 159.9 (d, $^1J_{CF}$ = 248.8 Hz), 159.4, 158.6, 134.1 (d, $^4J_{CF}$ = 2.6 Hz),133.7 (q, $^2J_{CF3}$ = 33.7 Hz), 131.0, 130.8 (d, $^4J_{CF}$ = 3.0 Hz), 129.5 (dd, $^3J_{CF}$ = 2.2, 5.8, Hz), 125.9 (d, $^4J_{CF}$ = 3.5 Hz), 123.8 (q, $^1J_{CF3}$ = 273.2 Hz), 120.2 (q, $^4J_{CF3}$ = 4.0 Hz), 117.8 (sep, $^3J_{CF3}$ = 4.0 Hz), 119.8, 115.4 (d, $^2J_{CF}$ = 21.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0, -114.1; IR (film) 3245, 1666, 1502, 1465, 1450, 1376, 1283, 1246, 1167, 1126, 951, 873, 780, 706, 687, 668, 653 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{11}ClF_7NO_2$ $[M+H]^+$, *m/z* = 478.0445, found 478.0443.

***N*-{3-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-chloro-6-fluorobenzamide (7)**: Prepared by general method B using with 0.15 mmol 3-[3,5-bis(trifluoromethyl)phenoxy]aniline, 0.18 mmol 2-chloro-6-fluorobenzoyl chloride, 0.3 mmol Et_3N, and 5 mL CH_2Cl_2. Purified by column chromatography (0-60% CH_2Cl_2 in hexane) to afford the title compound as a white solid in 70% yield (51 mg, 99% pure): mp = 100–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.60 – 7.58 (m, 1 H), 7.58 – 7.55 (m, 1 H), 7.43 (s, 2 H), 7.41 – 7.33 (m, 3 H), 7.26 – 7.23 (m, 1 H), 7.08 (td, *J* = 8.5, 1.0 Hz, 1 H), 6.88 – 6.83 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.6, 157.2 (d, $^1J_{CF}$ = 273.6 Hz), 158.4, 139.3, 133.4 (q, $^2J_{CF3}$ = 33.8 Hz), 132.6 (d, $^4J_{CF}$ = 4.9 Hz), 131.9 (d, $^3J_{CF}$ = 9.2 Hz), 130.9, 126.0 (d, $^4J_{CF}$ = 3.6 Hz), 125.0 (d, $^2J_{CF}$ = 21.3 Hz), 123.9 (q, $^1J_{CF3}$= 274.0 Hz), 118.3 (d, $^4J_{CF3}$ = 4.0 Hz), 116.7 (sep, $^3J_{CF3}$ = 3.9 Hz), 116.6, 116.2, 114.8 (d, $^2J_{CF}$ = 21.7 Hz), 112.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -112.2; IR (film) 3253, 3201, 3137, 3085, 1674, 1659, 1607, 1577, 1555, 1488, 1454, 1372, 1331, 1305, 1279, 1223, 1175, 1126, 985, 940, 907, 881, 851, 795, 773, 735, 698, 571, 519 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{11}ClF_7NO_2$ $[M+H]^+$, *m/z* = 478.0445, found 478.0443.

Methyl 4-(3,5-bis(trifluoromethyl)phenoxy)-3-nitrobenzoate (9): Prepared by general method C with 4.8 mmol 1-Bromo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene 5.8 mmol 3,5-bis(trifluoromethyl)phenol, 14.4 mmol Cs_2CO_3, and 20 mL DMF. Purified by column chromatography (0-50% CH_2Cl_2 in hexane) to afford the title compound as a pale yellow oil in 79% yield (1.55 g): ^{1}H NMR (400 MHz, CDCl3) δ 8.70 (d, *J* = 2.1 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.74 (s, 1H), 7.49 (s, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 156.3, 151.8, 141.4, 135.5, 133.9 (q, $^2J_{CF3}$ = 34.3 Hz), 127.8, 127.4, 122.6 (q, $^1J_{CF3}$ = 274.1 Hz), 120.9, 121.9, 119.1 (q, $^4J_{CF3}$ = 3.8 Hz), 118.5 (q, $^3J_{CF3}$ = 4.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; IR (film) 3324, 3093, 1733, 1648, 1607, 1543, 1510, 1462, 1443, 1279, 1242, 1171, 1126, 951, 761, 706, 687 cm^{-1}; HRMS (ESI-) calcd for $C_{16}H_9F_6NO_5$ $[M+Li]^+$, *m/z* = 416.0545, found 416.0548.

General procedure C: Fe reduction of nitroarenes:

A flask containing the nitroarene (1 mmol), iron powder (4 mmol), 4 mL glacial AcOH, and 4mL EtOH was heated at reflux for 70 minutes. The mixture was filtered through a pad of Celite, concentrated *in vacuo*, then partitioned between 10 mL each EtOAc and H_2O. Residual acid was quenched with the addition of saturated $NaHCO_3$, and the aqueous layer extracted 3x with 10 mL EtOAc. The combined organic layers were washed with 10 mL brine, dried over Na_2SO_4, and concentrated to dryness.

General Procedures D: Pd reduction of nitroarenes for Compounds **10**, **31**, **14k**, **14l**, **35b**, and **35f**:[31].

A flask was charged with nitroarene (9.6 mmol) and 10% Pd/C (2.9 mmol), then placed under vacuum and backfilled with three times with N_2. MeOH (80 mL) degassed by sparging with N_2 was added, after which H_2 was introduced via a balloon. The reaction was monitored by TLC; at completion, the mixture was filtered through a pad of Celite and concentrated to dryness. Purification method varied by compound

Methyl 4-(3,5-bis(trifluoromethyl)phenoxy)benzoate (10) From the nitroarene, the aniline was obtained by general procedure D with 2.1 mmol **7,** 0.6 mmol 10% Pd/C, and 25 mL MeOH. The resulting white solid was dissolved in DMF (5 mL) and added to a solution of *tert*-butyl nitrite (0.36 mL, 3 mmol) in DMF (5 mL) at 50 °C. The mixture was stirred for 1 hour, then partitioned between 20 mL EtOAc and 20 mL H_2O. The aqueous layer was extracted 3x with 10 mL EtOAc, and the combined organic layers washed 3x with 10 mL 5% LiCl, 1x with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness. Following purification by column chromatography (0-50% CH_2Cl_2 in hexane), the title compound was obtained as a yellow solid in 75% yield (0.56 g): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.07 (m, 2H), 7.65 (s, 1H), 7.45 (s, 2H), 7.10 – 7.04 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 166.3, 159.5, 157.5, 133.6 (q, $^2J_{CF3}$ = 33.9 Hz), 132.3, 127.0, 121.6 (q, $^1J_{CF3}$ = 272.3 Hz), 119.3 ($^4J_{CF3}$ = 3.7 Hz), 118.8, 117.5 ($^3J_{CF3}$ = 3.7 Hz), 52.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (*Note: **3** was fully characterized*).

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluorobenzamide (14a): Prepared by general method B using 0.36 mmol 2-fluorobenzoyl chloride, 0.3 mmol **13**, 0.9 mmol pyridine, and 2 mL CH_2Cl_2. The crude product was purified by column chromatography (0-45% CH_2Cl_2 in hexane), then recrystallized from boiling methanol to afford the title compound as a white solid in 81% yield (0.11 g, 99% pure): mp = 192–193 °C; ^{1}H NMR (400 MHz, CDCl3) δ 8.52 (d, *J* = 16.0 Hz, 1H), 8.20 (td, *J* = 8.0, 1.9 Hz, 1 H), 7.77 – 7.72 (m, 2 H), 7.59 – 7.52 (m, 2 H), 7.38 (s, 2 H), 7.35 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.24 – 7.17 (m, 1 H), 7.12 – 7.08 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.6 (d, $^1J_{CF}$ = 247.1 Hz), 161.3 (d, $^4J_{CF}$ = 3.6 H), 151.4, 135.0, 134.0 (d, $^3J_{CF}$ = 9.6 Hz), 133.2 (q, $^2J_{CF3}$ = 33.8 Hz), 132.3 (d, $^4J_{CF}$ = 1.9 Hz), 125.2 (d, $^3J_{CF}$ = 3.3 Hz), 122.9 (q, $^1J_{CF3}$ = 273.9 Hz), 122.6, 121.0 (d, $^2J_{CF}$ = 11.3 Hz), 120.7, 117.6 (q, $^4J_{CF3}$ = 4.1 Hz), 116.2 (d, $^2J_{CF}$ = 25.3 Hz), 116.3, 116.14 (sep, $^3J_{CF3}$ = 3.7 Hz), 116.06; ^{19}F NMR (365 MHz, CDCl3) δ -62.97, -113.14; IR (film) 3376, 3119, 3096, 1663, 1610, 1540, 1510, 1488, 1462, 1372, 1190, 1167, 1130, 951, 866, 843, 758, 683, 624 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{13}F_7NO_2$ $[M+H]^+$, *m/z* = 444.0830, found 444.0832.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2,6-difluorobenzamide (14b): Prepared by general method B using 0.78 mmol 2,6-difluoro-benzoyl chloride, 0.78 mmol 4-[3,5-bis(trifluoromethyl)phenoxy]aniline, 1.6 mmol Et_3N, and 3 mL CH_2Cl_2. Purified by column chromatography (50% CH_2Cl_2 in hexane to 100% CH_2Cl_2) to afford product as a white solid in 54% yield (0.192 g, 99% pure): mp = 160–162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1 H), 7.74 – 7.67 (m, 2 H), 7.57 (tq, *J* = 1.5, 0.7 Hz, 1 H), 7.51 – 7.39 (m, 1 H), 7.42 – 7.36 (m, 2 H), 7.13 – 7.05 (m, 2 H), 7.05 – 6.96 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.3 (d, $^3J_{CF}$ = 6.0 Hz), 158.9, 158.8 (d, $^3J_{CF}$ = 7.0 Hz), 158.4, 151.6, 134.5, 133.1 ($^2J_{CF3}$ = 32.8 Hz), 132.2 (dd, $^3J_{CF}$ = 11.6 Hz), 121.5 (q, $^1J_{CF3}$ = 273.5 Hz), 122.2, 120.7, 117.6 $^4J_{CF3}$ = 3.6 Hz), 116.2 (sep, $^3J_{CF3}$ = 3.6 Hz), 112.4 (d, ^{2}J$_{CF}$ = 25.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ -63.0, -111.7; IR (film) 3316, 3253, 3190, 3119, 3063, 1670, 1625, 1607, 1536, 1514, 1465, 1376, 1279, 1234, 1190, 1171, 1130, 1108, 1074, 1011, 955, 877, 843, 825, 795, 735, 717, 702, 683, 646, 594, 579 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{12}F_8NO_2$ $[M+H]^+$, *m/z* = 462.0735, found 462.0736.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-chloro-6-fluorobenzamide (14c, 1):Prepared by general B with 0.6 mmol **12**, 0.72 mmol 2-chloro- 6-fluorobenzoyl chloride, 0.72 mmol Et_3N, and 4 mL CH_2Cl_2. Purified by column chromatography (0-80% CH_2Cl_2 in hexane) to yield title product as a white solid in 96% yield (0.69 g, 99% pure): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 2 H), 7.58 (d, *J* = 1.6 Hz, 1 H), 7.49 (s, 1 H), 7.45 – 7.34 (m, 3 H), 7.29 (dt, *J* = 8.1, 0.9 Hz, 1 H, 7.17 – 7.06 (m, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97, -112.27; IR (film) 3260, 1666, 1610, 1532, 1510, 1454, 1376, 1279, 1175, 1126, 955, 881, 784, 683, 568 cm^{-1};

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-5-chloro-2-fluorobenzamide (14d): Prepared by general method A using 0.55 mmol **13**, 0.5 mmol 5-chloro-2-fluorobenzoic acid, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. Purification by column chromatography (0-100% CH_2Cl_2 in hexane) afforded the title compound as a white powder in 75% yield (0.18 g, 99% pure): mp = 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 15.6 Hz, 1H), 8.17 (dd, *J* = 6.7, 2.8 Hz, 1 H), 7.78 – 7.69 (m, 2 H), 7.57 (s, 1 H), 7.50 (ddd, *J* = 8.8, 4.4, 2.8 Hz, 1 H), 7.38 (s, 2 H), 7.17 (dd, *J* = 11.4, 8.8 Hz, 1 H), 7.14 – 7.06

(m, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 161.9 (dd, $^3J_{CF}$ = 8.2, 1.7 Hz), 159.3 (d, $^2J_{CF3}$ = 249.3 Hz), 160.5, 152.0, 137.1 (d, $^3J_{CF}$ = 9.1 Hz), 133.7 (q, $^2J_{CF3}$ = 33.5 Hz), 133.6 (d, $^3J_{CF}$ = 9.0 Hz), 130.9 (d, $^4J_{CF}$ = 3.1 Hz), 130.2 (d, $^4J_{CF}$ = 3.3 Hz), 126.8 (dd, $^3J_{CF}$ = 8.2, 4.5 Hz), 124.2 (q, $^1J_{CF3}$ = 272.1 Hz), 122.9 (d, $^3J_{CF}$ = 9.2 Hz), 121.7, 119.1 (d, $^2J_{CF}$ = 25.0 Hz), 118.7 (d, $^4J_{CF}$ = 3.0 Hz), 116.7 (sep, $^3J_{CF3}$ = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97, -116.14; IR (film) 3342, 1655, 1610, 1543, 1510, 1480, 1462, 1372, 1283, 1190, 1167, 1130, 1108, 951, 873, 854, 821, 676 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{11}F_7ClNO_2$ $[M+Li]^+$, *m/z* = 484.0527, found 484.0533.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-bromo-6-fluorobenzamide (14e): As general procedure A, with 0.5 mmol **13**, 0.56 mmol 2-bromo-6-fluorobenzoic acid, 0.6 mmol HATU, 0.6 mmol DIPEA, and 2 mL CH_2Cl_2. Purification by flash chromatography (0-60% CH_2Cl_2 in hexane) followed by trituration in cold hexane yielded a white-tan solid in 76% yield (0.20 g, 99% pure): mp = 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2 H), 7.58 (t, *J* = 1.4, 0.7 Hz, 1 H), 7.52 (s, 1 H), 7.45 (dt, *J* = 8.0, 0.9 Hz, 1 H), 7.39 (dt, *J* = 1.7, 0.6 Hz, 2 H), 7.32 (td, *J* = 8.3, 5.9 Hz, 1 H), 7.15 (td, *J* = 8.5, 1.0 Hz, 1 H), 7.12–7.08 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 159.6 (d $^1J_{CF}$ = 252.8 Hz), 159.0, 151.9, 134.5, 133.4 (d, $^2J_{CF3}$ = 33.7 Hz), 132.2 (d, $^3J_{CF}$ = 8.7 Hz), 129.1 (d, $^4J_{CF}$ = 3.5 Hz), 127.2 (d, $^2J_{CF}$ = 21.1 Hz), 123.1 ($^1J_{CF3}$ = 272.8 Hz), 122.5, 120.92, 120.85 (d, $^2J_{CF}$ = 4.23 Hz), 117.8 (d, $^4J_{CF}$ = 4.5), 116.4 (sep, $^3J_{CF3}$ = 3.9 Hz), 115.4 (d, $^3J_{CF}$ = 21.6 Hz);^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97, -111.60; IR (film) 3264, 1666, 1610, 1532, 1510, 1462, 1279, 1171, 1126, 955, 877, 870, 843, 780, 706, 683 cm^{-1}; HRMS (ES-) $[M-H]^-$ for $C_{21}H_{10}BrF_7NO_2$, *m/z* 519.9783, found 519.9781.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-iodobenzamide (14f, CU-115): Prepared by general method B using 0.36 mmol 2-fluoro-6-iodobenzoyl chloride, 0.3 mmol **13**, 0.9 mmol pyridine, and 2 mL CH_2Cl_2. Purified by column chromatography (0-75% CH_2Cl_2 in hexane) to afford product as a white solid in 94% yield (0.16 g, 99% pure): mp = 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 3 H), 7.58 (s, 1 H), 7.40 (s, 2 H), 7.21 – 7.14 (m, 2 H), 7.14 – 7.09 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.94, -110.81. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 158.8 (d, $^1J_{CF}$ = 253.4 Hz), 159.0, 151.9, 135.5 (d, $^4J_{CF}$ = 3.48 Hz), 134.5, 133.4 (q, $^2J_{CF3}$ = 34.3 Hz), 132.6 (d, $^3J_{CF}$ = 8.4 Hz), 130.9 (d, $^2J_{CF}$ = 20.2 Hz), 123.0 (q, $^1J_{CF3}$ = 272.9 Hz), 122.5, 117.8 (d, $^4J_{CF}$ = 3.2 Hz), 120.9, 116.4 (sep, $^3J_{CF3}$ = 3.9), 116.1 (d, $^2J_{CF}$ = 21.7 Hz), 93.6 (d, $^3J_{CF}$ = 2.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -110.8; IR (film) 3290, 1655, 1514, 1279, 1175, 884 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{10}ClN_3O_2$ $[M+H]^+$, *m/z* = 312.0540, found 312.0541.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2-fluoro-5-iodobenzamide (14g): Prepared by general procedure B using 0.5 mmol **12**, 0.55 mmol 2-fluoro-5-iodobenzoyl chloride, 1 mmol Et_3N, and 5 mL CH_2Cl_2. Purified by column chromatography (0-100% CH_2Cl_2 in hexane) to afford the title compound as a white solid in 89% yield (0.25 g, 99% pure): mp = 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 7.3, 2.4 Hz, 1 H), 8.41 (d, *J* = 15.4 Hz, 1 H), 7.83 (ddd, *J* = 8.6, 4.8, 2.4 Hz, 1 H), 7.75 – 7.68 (m, 2 H), 7.57 (s, 1 H), 7.38 (s, 2 H), 7.13 – 7.06 (m, 2 H), 6.98 (dd, *J* = 11.8, 8.6 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (d, $^1J_{CF}$ = 248.3 Hz), 159.8 (d, $^4J_{CF}$ = 3.6 Hz), 158.9, 151.6, 142.6 (d, $^3J_{CF}$ = 9.4 Hz), 140.9, 134.6, 133.2 (q, $^2J_{CF3}$ = 33.8 Hz), 127.0, 122.9 (q, $^1J_{CF3}$ = 273.9 Hz), 123.0 (d, $^2J_{CF}$ = 12.4 Hz), 122.6, 120.7, 118.3 (d, $^2J_{CF}$ = 26.3 Hz), 117.6 (d, $^4J_{CF3}$ = 4.0 Hz), 116.2 (q, $^3J_{CF3}$ = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0, -114.9; IR (film) 3324, 3096, 3070, 1543, 1506, 1465, 1376, 1283, 1164, 1126, 955, 877, 854, 832, 817, 687, 609, 512 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{11}F_7INO_2$ $[M+H]^+$, *m/z* = 569.9801, found 569.9790.

N-{4-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-4-iodobenzamide (14h): Prepared by general method A using 0.5 mmol 2-fluoro-4-iodobenzoic acid, 0.55 mmol **13**, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. The crude product was purified by column chromatography (0-100% CH_2Cl_2 in hexane) followed by recrystallization from hot hexane to afford title compound as white crystals in 19% yield (53 mg, 98% pure): mp = 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 15.6 Hz, 1 H), 7.90 (t, *J* = 8.4 Hz, 1 H), 7.76 – 7.68 (m, 3 H), 7.61 (dd, *J* = 11.4, 1.6 Hz, 1 H), 7.57 (s, 1 H), 7.38 (s, 2 H), 7.15 – 7.06 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) 160.63 (d, $^4J_{CF}$ = 3.0 Hz), 150.59 (d, $^4J_{CF}$ = 3.7 Hz), 158.9, 158.2, 151.6. 134.8 (d, $^3J_{CF}$ = 3.3 Hz), 134.7, 133.4, 133.1 (q, $^2J_{CF3}$ = 31.3 Hz), 125.4 ($^2J_{CF}$ = 26.5 Hz), 121.5 ($^1J_{CF3}$ = 273.4 Hz), 122.6, 120.7, 117.6 ($^3J_{CF3}$

= 3.4 Hz), 116.2 (sep, $^3J_{CF3}$ = 3.8 Hz), 98.7 ($^3J_{CF}$ = 9.0 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97, -111.49; IR 3387, 3067, 1670, 1603, 1547, 1506, 1465, 1368, 1279, 1190, 1167, 1141, 1119, 951, 899, 854, 832, 706, 687, 635, 590, 512 (film) cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{11}F_7INO_2$ $[M+H]^+$, *m/z* = 569.9801, found 569.9792.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2-fluoro-6-(trifluoromethyl)benzamide (14i): Prepared by general procedure B using 0.5 mmol **13**, 0.55 mmol 2-fluoro-6-(trifluoromethyl)benzoyl chloride, 1 mmol Et_3N, and 5 mL CH_2Cl_2. Purified by column chromatography (0-100% CH_2Cl_2 in hexane) to afford the title compound as a tan solid in 75% yield (0.19 g, 99% pure): mp = 204–206 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.01 (s, 1 H), 7.92 – 7.84 (m, 2 H), 7.81 – 7.74 (m, 2 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.65 – 7.59 (m, 3 H), 7.29 – 7.23 (m, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) 159.3, 158.4, 158.2 (d, $^1J_{CF}$ = 248.0 Hz), 150.3, 135.05, 134.95, 131.9 (q, $^2J_{CF3}$ = 33.6 Hz), 130.9 (d, $^3J_{CF}$ = 8.8 Hz), 120.9, 122.2 (q, $^1J_{CF3}$ = 273.2 Hz), 121.3 (sep, $^3J_{CF3}$ = 4.7 Hz), 120.6, 120.5, 119.7, 119.1 (d, $^2J_{CF}$ = 22.4 Hz), 117.0 (d, $^4J_{CF3}$ = 3.6 Hz), 115.0 (sep, $^3J_{CF3}$ = 4.0 Hz); ^{19}F NMR (376 MHz, Acetone-d_6) δ -59.9, -63.5, -115.9; IR (film) 3271, 3074, 1670, 1536, 1514, 1465, 1380, 1324, 1283, 1164, 1126, 955, 918, 884, 847, 683, 512 cm^{-1}; HRMS (ESI+) calcd for $C_{22}H_{11}F_{10}NO_2$ $[M+H]^+$, *m/z* = 512.0709, found 512.0709.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-hydroxybenzamide (14j)[32]: To a flame-dried flask was added **13** (0.48g, 1.5 mmol), 2-fluoro-6-hydroxybenzoic acid (0.23 g, 1.5 mmol), phosphorous trichloride (0.10 mL, 1.13 mmol), and chlorobenzene (7.5 mL), after which the mixture was heated at reflux for 4 hours. After cooling, the crude product was purified by column chromatography (0-75% CH_2Cl_2 in hexane) to afford the title compound as a white solid in 49% yield (0.34 g, 99% pure): mp = 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.90 (s, 1 H), 8.78 (d, *J* = 23.1 Hz, 1 H), 7.70 – 7.64 (m, 2H), 7.59 (s, 1 H), 7.42 – 7.34 (m, 3 H), 7.14 – 7.09 (m, 2 H), 6.87 (dt, *J* = 8.5, 1.0 Hz, 1 H), 6.68 (ddd, *J* = 13.2, 8.2, 1.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ; 166.4 (d, *J* = 3.8 Hz), 164.0 (d, *J* = 4.2 Hz), 161.1 (d, $^1J_{CF}$ = 246.2 Hz), 158.7, 152.2, 134.3 (d, $^2J_{CF}$ = 13.9 Hz), 133.6, 133.3 (q, $^2J_{CF3}$ = 33.7 Hz), 122.9 (q, $^1J_{CF3}$ = 273.9 Hz), 123.6, 120.6, 117.8 (d, $^4J_{CF3}$ = 3.7 Hz), 116.4 (sep, $^3J_{CF3}$ = 3.9 Hz), 115.2 (d, $^4J_{CF}$ = 2.8 Hz), 105.8 (d, $^2J_{CF}$ = 26.4 Hz), 103.6 (d, $^3J_{CF}$ = 11.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.98, -111.43; IR (film) 3446, 1659, 1607, 1555, 1506, 1376, 1279, 1234, 1015, 955, 881, 866, 843, 806, 620, 601, 519 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{12}F_7NO_3$ $[M+H]^+$, *m/z* = 460.0784, found 460.0789.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-4-hydroxybenzamide (14k): The benzyl-protected intermediate was prepared by general method A with **19** (0.53 g, 1.7 mmol), **13** (0.37 g, 1.5 mmol), HATU (0.63 g, 1.7 mmol), DIPEA (0.5 mL, 2 mmol), and DMF (4 mL), then recrystallized from hot ethanol to afford pure intermediate in 63% yield (0.52 g, 99% pure). A portion of the intermediate (0.30 g, 0.55 mmol) was added to a flask with 10% Pd/C (0.016g, 0.15 mmol) and backfilled with nitrogen, after which MeOH (15 mL) and a hydrogen balloon were added. The crude mixture stirred overnight, then filtered first through Celite, then through a small silica plug to afford the title compound as a tan solid in 99% yield (0.25 g,): mp = 197–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 16.8 Hz, 1H), 8.11 (t, 1H), 7.76 – 7.67 (m, 2H), 7.56 (s, 1 H), 7.38 (s, 2 H), 7.14 – 7.06 (m, 2 H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.69 (dd, *J* = 13.7, 2.4 Hz, 1 H), 5.45 (s, 1 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 162.2 (d, $^1J_{CF}$ = 248.7 Hz), 162.94, 162.92, 162.8, 162.7, 160.6, 137.6, 133.7 (q, $^2J_{CF3}$ = 33.6 Hz), 133.3 (d, $^4J_{CF}$ = 4.4 Hz), 124.2 (q, $^1J_{CF3}$ = 272.0 Hz), 122.9, 118.6 (d, $^4J_{CF}$ = 3.0 Hz), 116.7 (sep, $^3J_{CF3}$ = 4.0 Hz), 115.5 (d, $^2J_{CF}$ = 13.4 Hz), 113.0 (d, $^4J_{CF}$ = 2.6 H), 103.8 (d, $^2J_{CF}$ = 26.4 Hz); IR (film) 3443, 3178, 1648, 1610, 1543, 1506, 1465, 1409, 1376, 1279, 951, 884, 842, 706, 701, 683, 635, 609, 533, 512 cm^{-1}; HRMS (ESI-) calcd for $C_{21}H_{12}F_7NO_3$ $[M]^-$, *m/z* = 458.0267, found 458.0613.

2-Amino-N-(4-(3,5-bis(trifluoromethyl)phenoxy)phenyl)-6-fluorobenzamide (14l): A vial containing *N*-{4-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-nitrobenzamide (62 mg, 0.13 mmol) and 10% Pd/C (10 mg, 0.1 mmol) was backfilled with nitrogen, after which MeOH (3 mL) and a hydrogen balloon were added. After stirring overnight, the reaction mixture was filtered through Celite, then concentrated *in vacuo*. Following purification by column chromatography (0-100% CH_2Cl_2 in hexane), the title compound was afforded in 95% yield as a tan soft solid

(57 mg, 96% pure): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 17.5 Hz, 1 H), 7.73 – 7.63 (m, 2 H), 7.56 (s, 1 H), 7.38 (s, 2 H), 7.16 (td, *J* = 8.2, 6.5 Hz, 1 H), 7.12 – 7.04 (m, 2 H), 6.51 (dt, *J* = 8.4, 0.9 Hz, 1H), 6.43 (ddd, *J* = 13.2, 8.1, 1.1 Hz, 1H), 6.00 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.52, 164.50, 162.1 (d, $^1J_{CF}$ = 243.7 Hz), 159.1, 152.1, 152.0, 151.4, 135.0, 133.3 (q, $^2J_{CF3}$ = 33.8 Hz), 132.9 (d, $^3J_{CF}$ = 9.6 Hz), 123.1, 123.06, (q, $^1J_{CF3}$ = 273.6 Hz), 120.8, 117.7 (d, $^4J_{CF}$ = 3.9 Hz), 116.2 (sep, $^3J_{CF3}$ = 3.9 Hz), 113.5 (d, $^4J_{CF}$ = 2.4 Hz), 103.3 (d, $^2J_{CF}$ = 26.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -111.7; HRMS (ESI+) calcd for $C_{21}H_{13}F_7N_2O_2$ $[M+H]^+$, *m/z* = 459.0944 , found 459.0947.

4-Amino-N-{4-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-fluorobenzamide (14m): Prepared by general method A with 0.5 mmol **17**, 0.55 mmol **13**, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF to obtain trifluoroacetamide protected compound. After removing solvents *in vacuo*, the crude trifluoroacetamide was added to K_2CO_3 (0.14 g, 1 mmol) and MeOH (10 mL) and then heated at reflux for 4 hours. After cooling, the solvent was removed *in vacuo* and the resulting residue was partitioned between 5 mL each H_2O and EtOAc. The aqueous layer was 3x with 5 mL EtOAc, then combined organic layers were washed 5 mL H_2O, 5 mL brine, and dried over Na_2SO_4. Crude product was purified by column chromatography (0-30% EtOAc in hexane) to afford title compound as a tan solid in 39% yield over 2 steps (32 mg, 98% pure). Note: compound is oxidized rapidly on standing. mp = 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 17.5 Hz, 1 H), 7.99 (t, *J* = 9.2, 8.6 Hz, 1 H), 7.77 – 7.67 (m, 2 H), 7.55 (s, 1 H), 7.37 (s, 2 H), 7.11 – 7.02 (m, 2 H), 6.55 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.39 (dd, *J* = 14.7, 2.2 Hz, 1 H), 4.20 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 244.1Hz), 161.8 (d, $^4J_{CF}$ = 4.0 Hz), 159.3, 152.1 (d, $^3J_{CF}$ = 13.0 Hz), 151.0, 135.6, 133.9 (d, $^4J_{CF}$ = 4.0 Hz), 133.3 (q, $^2J_{CF3}$ = 33.7 Hz), 123.1 (q, $^2J_{CF3}$ = 272.9 Hz), 122.5, 120.9, 117.6 (d, $^4J_{CF3}$ = 3.5 Hz), 116.1 (sep, $^3J_{CF3}$ = 3.8 Hz), 111.4 (d, $^4J_{CF}$ = 1.7 Hz), 110.2 (d, $^3J_{CF}$ = 11.33 Hz), 101.9 (d, $^3J_{CF}$ = 29.2 Hz); ^{19}F NMR (376 MHz, CDCl3) δ -62.97, -111.81; IR (film) 3480, 3458, 3353, 3242, 3089, 3063, 1674, 1640, 1618, 1540, 1514, 1462, 1376, 1279, 1182, 1130, 1108, 951, 884, 858, 843, 706, 687, 590, 568, 534 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{13}F_7N_2O_2$ $[M+H]^+$, *m/z* = 459.0944, found 459.0944.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-(trifluoromethoxy)benzamide (14n): Prepared by general procedure A using 0.4 mmol **16**, 0.44 mol, **13**, 0.44 mmol HATU, 0.8 mmol DIPEA, and 3 mL DMF. Purified by column chromatography (0-60% CH_2Cl_2 in hexane), then recrystallized from hot MeOH to afford the title compound as white crystals in 21% yield (45 mg, 97% pure): mp = 179–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2 H), 7.58 (s, 1 H), 7.55 – 7.48 (m, 2 H), 7.40 (s, 2 H), 7.23 – 7.15 (m, 2 H), 7.13 – 7.07 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.41, -62.96, -111.47. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (d, $^1J_{CF}$ = 253.3 Hz), 158.7 (d, $^2J_{CF}$ = 16.0 Hz), 151.8, 146.6 (d, $^3J_{CF}$ = 6.2 Hz), 134.2, 133.3 (q, $^2J_{CF3}$ = 33.9 Hz), 132.0 (d, $^3J_{CF}$ = 9.7 Hz), 122.9 (q, $^1J_{CF3}$ = 273.9 Hz), 122.4, 121.6, 120.7, 119.5 (d, $^2J_{CF}$ = 20.8 Hz), 118.9 (d, $^3J_{CF}$ = 16.8 Hz), 117.7 (q, $^4J_{CF}$ = 4.1 Hz), 116.9 (d, $^4J_{CF3}$ = 1.8 Hz), 116.3 (sep, $^4J_{CF3}$ = 3.8 Hz), 114.9 (d, $^2J_{CF}$ = 21.7 Hz);IR (film) 3264, 3063, 1666, 1622, 1536, 1510, 1469, 1380, 1380, 1264, 1233, 1219, 1167, 1126, 955, 887, 884, 866, 847, 706 cm^{-1}; HRMS (ESI+) calcd for $C_{22}H_{11}F_{10}NO_3$ $[M+H]^+$, *m/z* = 528.0657, found 528.0663.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2-ethynyl-6-fluorobenzamide (14o): To a dry THF solution of N-{4-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-[2-(trimethylsilyl)ethynyl]benzamide (80 mg, 0.15 mmol) was added a solution of tetrabutylammonium fluoride (TBAF) (0.20 mL 1 M TBAF in THF, 0.20 mmol) dropwise at 25 °C under N_2. The mixture was stirred at rt and monitored by TLC. After 18 h, the mixture was concentrated by rotary evaporation and dissolved with CH_2Cl_2 and washed with H_2O. The organic mixture was dried with Na_2SO_4, filtered, and concentrated by rotary evaporation to afford a white solid. The solid was purified by flash column chromatography (15% EtOAc:Hexanes) to afford a colorless oil (3 mg, 97% pure) in 4% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ ; 7.60 – 7.53 (m, 2 H), 7.59–7.57 (m, 1 H), 7.50 (m, 2), 7.44 (d, *J* = 9.0 Hz, 2 H), 7.25–7.22 (m, 1 H), 7.19 (d, *J* = 8.9 Hz, 2 H), 4.89 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.8 (d, $^1J_{CF}$ = 263.0, 157.9, 155.0; 142.3 (d, $^4J_{CF}$ = 2.0 Hz), 138.7 (d, $^3J_{CF}$ = 3.2 Hz), 134.4 (d, $^3J_{CF}$ = 7.7 Hz), 133.5 (q, $^2J_{CF3}$ = 34.1 Hz) 130.7, 130.1, 120.1, 121.5, 120.7, 118.8 (d, $^4J_{CF3}$ = 3.8 Hz), 117.7 (d, $^2J_{CF}$ = 19.1 Hz), 117.01, (sep $^3J_{CF3}$ = 2.9 Hz)116.1 (d, $^3J_{CF}$ = 4.1 Hz), 91.5 (unresolved quartet); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0, -116.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 ; IR (film) 3335,

3275, 3115, 3078, 1696, 1648, 1614, 1599, 1514, 1491, 1465, 1451, 1286, 1242, 1175, 1130, 1026, 858, 814, 784, 706, 687 cm^{-1}; HRMS (ESI+) calcd for $C_{23}H_{12}F_7NO_2$ $[M+H]^+$, *m/z* = 468.0835, found 468.0831.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)cyclohexanecarboxamide (15a): To a solution of 4-[3,5-bis(trifluoromethyl)phenoxy]aniline (0.31 mmol) and Et_3N (0.37 mmol) in CH_2Cl_2 (0.3 M) was added cyclohexanecarbonyl chloride (0.37 mmol) at 0 °C .The reaction was warmed up to and stirred overnight at rt. A solid precipitated from the solution. The reaction mixture was diluted with 5.0 mL of CH_2Cl_2 and washed with 10 mL H_2O. The mixture was extracted CH_2Cl_2 3x with 5.0 mL. The organic mixture was then dried with Na_2SO_4, filtered and concentrated by rotary evaporation to afford a white solid. The solid was purified by flash column chromatography (15% EtOAc:Hexanes) to afford a white solid (53 mg, 99% pure) in 33% yield: mp = 178–179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, *J* = 8.9 Hz, 2 H), 7.56 – 7.50 (m, 1 H), 7.39 – 7.30 (m, 2 H), 7.19 (s, 1 H), 7.02 (d, *J* = 9.3 Hz, 2 H), 2.25 (tt, *J* = 11.8, 3.5 Hz, 1 H), 1.96 (d, *J* = 3.5 Hz, 2 H), 1.86 (dd, *J* = 10.5, 4.9 Hz, 2 H), 1.79 – 1.67 (m, 1 H), 1.64 – 1.49 (m, 4 H), 1.45 – 1.17 (m, 4 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.4, 159.1, 150.7, 135.4, 133.1 (q, $^2J_{CF3}$ = 33.8 Hz), 122.9 (q, $^4J_{CF3}$ = 274.2 Hz), 121.7 120.8, 117.4 (d, $^4J_{CF3}$ = 3.2 Hz), 116.0 (sep, $^3J_{CF3}$ = 4.0 Hz), 46.5, 29.7, 25.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; IR (film) 3294, 2936, 1666, 1607, 1529, 1510, 1462, 1376, 1286, 1238, 1171, 1134, 1108, 955, 881, 862, 843, 706, 683, 512 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{18}F_6N_2O_2$ $[M+H]^+$, *m/z* = 433.1346, found 433.1350.

N-(4-(3,5-Bis(trifluoromethyl)phenoxy)phenyl)-2,3,4,5,6-pentafluorobenzamide (15b): Prepared by general procedure B using 0.39 mmol **13**, 1.2 mmol 2-fluoro-6-(trifluoromethyl)benzoyl chloride, 1.2 mmol Et_3N, and 4 mL CH_2Cl_2. Purified by column chromatography (5% EtOAc in hexane) to afford the title compound as a white solid in quantitative yield (0.200 g, 99% pure): mp = 86–88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (tt, *J* = 1.5, 0.8 Hz, 1H), 7.37 – 7.36 (m, 2H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.07 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.9, 157.1, 156.9, 144.3 (m, J_{CF}), 141.7 (m, J_{CF}), 138.9 (m, J_{CF}), 136.3 (m J_{CF});133.7 (q, $^2J_{CF3}$ = 34.0 Hz), 131.7, 130.2, 122.7 (1, $^1J_{CF3}$ = 278.9 Hz), 120.3, 119.0 (q, $^3J_{CF3}$ = 3.8 Hz), 117.7 (sep, $^3J_{CF3}$ = 3.9 Hz) ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.19, -140.02 (m), -148.28 (t, $^3J_{FF\text{-}o}$ = 21.4 Hz), -159.17– -159.29 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.19, -140.02 (m), -148.28 (t, $^3J_{FF\text{-}o}$ = 21.4 Hz), -159.17– -159.29 (m); IR (film) 1722, 1659, 1599, 1506, 1372, 1327, 1283, 1234, 1175, 1160, 1141, 1115, 1000, 951, 895, 881, 773, 706, 687, 523 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_9F_{11}NO_2$ $[M+H]^+$, *m/z* = 516.0453 , found 516.0441.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-3-fluoropyridine-2-carboxamide (15c) Prepared by general procedure A with 0.55 mmol **13**, 0.5 mmol 3-fluoropyridine-2-carboxylic acid, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. Purified by column chromatography (0-100% CH_2Cl_2 in hexane) followed by trituration in cold hexane to afford the title compound as a white-tan solid in 82% yield (0.18 g, 99% pure): mp = 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.47 (s, 1 H), 7.87 – 7.82 (m, 2 H), 7.66 – 7.59 (m, 1 H), 7.59 – 7.54 (m, 2 H), 7.38 (s, 2 H), 7.13 – 7.08 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 160.0, 159.2, 151.2, 143.9 (d, $^3J_{CF}$ = 5.6 Hz),137.3, 135.1, 133.3 (q, $^2J_{CF3}$ = 33.8 Hz), 128.7 (d, $^3J_{CF}$ = 5.4 Hz), 127.0 (d, $^2J_{CF}$ = 19.7 Hz), 121.7, 120.9, 117.7 (d, $^4J_{CF}$ = 2.9 Hz), 116.2 (sep, $^3J_{CF3}$ = 3.8 Hz) (unresolved C-CF_3 quartet);^{19}F NMR (376 MHz, $CDCl_3$) δ -62.99, -118.07; IR (film) 3335, 3078, 1700, 1618, 1532, 1506, 1458, 1376, 1279, 1223, 1175, 1149, 1130, 1108, 1093, 1015, 951, 903, 884, 858, 843, 825, 802, 780, 739, 702, 624, 594, 571 cm^{-1}; HRMS (ES-) $[M-H]^-$ for $C_{20}H_{10}F_7N_2O_2$, *m/z* 443.0630, found 443.0633.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}furan-2-carboxamide (15d): Prepared by general method B using 4-[3,5-bis(trifluoromethyl)phenoxy]aniline 0.31 mmol , 0.37 mmol 2-furyl chloride, 0.62 mmol Et_3N and 1.2 mL CH_2Cl_2. The solid was purified by flash column chromatography (15% EtOAc:Hexanes) to afford the title compound as a white solid in 38% yield (25 mg, 99% pure): mp = 136–137 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.77 – 7.69 (m, 2 H), 7.60 – 7.50 (m, 2 H), 7.38 (dd, *J* = 1.5, 0.8 Hz, 2 H), 7.30 – 7.24 (m, 1 H), 7.12 – 7.04 (m, 2 H), 6.58 (dd, *J* = 3.5, 1.8 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.1, 151.2, 147.6, 144.3, 134.7, 133.0 (q, $^2J_{CF3}$ = 34.1 Hz), 121.6 (q, $^1J_{CF3}$ = 273.9 Hz), 121.9, 120.7, 117.5 $^4J_{CF3}$ =4.1

z=Hz), 11;6.1 ($^4J_{CF3}$ = 4.3 Hz), 115.5, 112.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; (film) 3342, 1685, 1659, 1610, 1536, 1510, 1465, 1376, 1279, 1231, 1178, 1134, 1015, 955, 884, 858, 758, 706, 687 cm^{-1}; HRMS (ES+) $[M-H]^-$ for $C_{19}H_{11}F_6NO_3$, *m/z* 438.0541, found 438.0532.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-3-chlorothiophene-2-carboxamide (15e): Prepared by general procedure A with 0.5 mmol **13**, 0.5 mmol 3-chlorothiphene-2-carboxylic acid, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. Following trituration in ice-cold hexane the title compound was isolated as a pink solid in 87% yield (0.20 g, 96% pure): mp = 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.74 – 7.69 (m, 2H), 7.56 (d, *J* = 5.3 Hz, 2H), 7.38 (s, 2H), 7.12 – 7.07 (m, 2H), 7.06 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.4, 151.6, 134.6, 133.3, 133.0 (q, $^2J_{CF3}$ = 42.5 Hz), 130.5, 129.7, 123.2, 123.0 (q, $^1J_{CF3}$ = 272.9 Hz), 122.5, 120.9, 117.7 (d, $^3J_{CF3}$ = 3.0 Hz), 116.3 (sep, $^3J_{CF3}$ = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.99; IR (film) 3342, 1640, 1607, 1536, 1510, 1465, 1428, 1372, 1283, 1190, 1167, 1130, 955, 918, 884, 858, 843, 825, 724, 706, 683, 594, 516, 516 cm^{-1}; HRMS (ES-) $[M-H]^-$ calcd for $C_{19}H_9ClF_6NO_2S$, *m/z* 463.9947, found 463.9953.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-1H-indole-5-carboxamide (15f): Prepared by general procedure A using 0.55 mmol **13**, 0.5 mmol indole-5-carboxylic acid, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. Trituration in ice-cold hexane followed by column chromatography (0-100% EtOAc in hexane) afforded the title compound as a white solid in 67% yield (0.17 g, 97% pure): mp = 171–173 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.27 (dd, *J* = 1.8, 0.7 Hz, 1 H), 7.85 – 7.80 (m, 2 H), 7.75 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.66 (s, 1H), 7.52 – 7.46 (m, 3 H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.60 (dd, *J* = 3.2, 0.9 Hz, 1 H); ^{13}C NMR (101 MHz, MeOD) δ 170.4, 161.1, 152.3, 139.7, 137.9, 134.3 (q, $^2J_{CF3}$ = 33.6 Hz), 129.0, 127.4, 126.6, 124.48, 124.45 ($^1J_{CF3}$ = 273.1 Hz), 121.9, 121.8, 121.7, 118.6 (d, $^4J_{CF3}$ = 3.9 Hz), 116.8 (sep, $^3J_{CF3}$ = 4.0 Hz), 121.1, 103.7; ^{19}F NMR (376 MHz, Methanol-d$_4$) δ -64.57; IR (film) 2478, 2452, 2419, 2393, 1618, 1592, 1570, 1510, 1469, 1432, 1402, 1372, 1324, 1286, 1253, 1193, 1164, 1126, 1018, 1003, 951, 895, 858, 825, 784, 754, 732, 706, 687, 586, 545, 523 cm^{-1}; HRMS (ESI-) calcd for $C_{23}H_{14}F_6N_2O_2$ $[M+H]^+$, *m/z* = 463.0881, found 463.0885.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-1H-benzimidazole-5-carboxamide (15g): As general procedure A with 0.55 mmol **13**, 0.5 mmol 5-benzimidizole carboxylic acid, 0.55 mmol HATU, 1 mmol DIPEA, and 4 mL DMF. Purified by column chromatography (0-100% EtOAc in CH_2Cl_2) followed by recrystallization from MeOH to give an iridescent white solid in 28% yield (0.066g, 92% pure): mp = 113–115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1 H), 10.37 (s, 1H), 8.39 (s, 1 H), 8.26 (s, 1H), 7.93 (d, *J* = 8.9 Hz, 2 H), 7.85 (d, *J* = 13.2 Hz, 2 H), 7.69 (s, 1 H), 7.59 (s, 2 H), 7.26 – 7.20 (m, 2 H); ^{13}C NMR (101 MHz, Acetone-d$_6$) δ 165.0, 158.8, 142.9, 142.2, 131.8 (q, $^2J_{CF3}$ = 33.5 Hz), 127.8, 122.3 (q, $^1J_{CF3}$ = 267.6 Hz), 121.6, 121.0, 121.0, 119.8, 119.6, 118.1, 116.6 (q, $^4J_{CF3}$ = 4.0 Hz), 114.7 (m, $^3J_{CF3}$ = 3.7 Hz), 110.8, 110.4; ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -61.47; IR 1648, 1607, 1532, 1506, 1231, 1175, 1126, 955, 884, 862, 836, 706, 683 (film) cm^{-1} HRMS (ESI+) calcd for $C_{22}H_{13}F_6N_3O_2$ $[M+H]^+$, *m/z* = 466.0990, found 466.1022.

2-Fluoro-6-(trifluoromethoxy)benzoic acid (16)[33]: To a flame-dried flask containing THF (5 mL) was added lithium diisopropylamide (2M in THF; 0.6 mL, 1.2 mmol) under N_2. After cooling to -78 °C, 3-(trifluoromethyl)fluorobenzene (0.18 g, 1. mmol) was added, and the reaction stirred 2 hours at -78 °C. CO_2 from a flask containing dry ice was bubbled through the solution as it was allowed to warm to rt over 1 hour, then quenched by addition of H_2O. The mixture was concentrated *in vacuo*, then dissolved in 10 mL 1M NaOH and washed twice with 10 mL EtOAc. Following acidification with 3M HCl, the aqueous layer was extracted 3x with 10 mL EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a white solid (0.126 g, 56%) which was used without further purification: mp = 92–95 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.14 (s, 1 H), 7.66 (td, *J* = 8.5, 6.5 Hz, 1 H), 7.43 (ddd, *J* = 9.3, 8.5, 0.9 Hz, 1 H), 7.39 – 7.34 (m, 1 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 162.7, 161.8, 159.3, 147.1(dd, $^4J_{CF}$ = 2.2, 3.3 Hz), 133.5 (d, $^3J_{CF}$ = 9.9 Hz), 121.3 (q, $^1J_{CF3}$ = 257.7 Hz), 118.4 (d, $^2J_{CF}$ = 20.5 Hz), 118.0, (dd, $^4J_{CF}$ = 1.1, 1.4 Hz), 117.4, 116.0 (d, $^3J_{CF}$ = 21.6 Hz);' ^{19}F NMR (376

MHz, DMSO-d_6) δ -56.63, -112.65; IR (film) 2903, 2676, 1711, 1622, 1599, 1473, 1417, 1246, 1216, 1175, 1134, 1037, 881, 881, 810, 776, 650, 553 cm^{-1}; HRMS (ESI+) calcd for $C_8H_4F_4O_3$ $[M+Na]^+$, m/z = 246.9994, found 247.001.

2-Fluoro-4-(2,2,2-trifluoroacetamido)benzoic acid (17)[34]: A flame-dried flask containing trifluoroacetic anhydride (0.56 mL, 4 mmol) was cooled to 0 °C. 2-fluoro-4-aminobenzoic acid (0.155 g, 1 mmol) was added in portions, after which the flask was allowed to warm to rt while stirring for 2 hours. The mixture was partitioned between 20 mL ice water and 10 mL CH_2Cl_2. The aqueous layer was extracted twice with 10 mL CH_2Cl_2, then the combined organic layers were concentrated to afford semi-pure product (0.216 g, 86%) which was used without further purification: mp = 255–258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (td, J = 8.3, 5.3 Hz, 1 H), 7.61 (dt, J = 8.2, 1.0 Hz, 1 H), 7.39 (ddd, J = 9.5, 8.4, 1.0 Hz, 1 H); ^{13}C NMR (Acetone-d_6, 101 MHz) δ 162.5, 159.9, 154.2 (d, $^2J_{CF}$ = 38.3 Hz), 141.0 (d, $^3J_{CF}$ = 11.3 HZ), 132.2 (d, $^4J_{CF}$ = 2.4 Hz), 114.7 (q, $^1J_{CF3}$ = 288.9 Hz), 114.9 (d, $^4J_{CF}$ = 3.7 Hz), 114.6 (d, $^3J_{CF}$ = 10.6 Hz), 107.6 (d, $^2J_{CF}$ = 28.2 Hz); ^{13}C NMR (101 MHz, Acetone) δ 162.3 ($^1J_{CF}$ = 282.5 Hz), 162.4, 154.2 (q, $^2J_{CF3}$ = 38.2 Hz), 141.0 (d, $^3J_{CF}$ = 11.3 Hz), 132.2 (d, $^4J_{CF}$ = 2.2 Hz), 114.7 (q, $^1J_{CF3}$ = 288.7 Hz), 114.9 (d, $^3J_{CF}$ = 3.6 Hz) 114.6 (d, $^3J_{CF}$ = 10.6 Hz), 107.6 (d, $^2J_{CF}$ = 28.1 Hz), ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.61, -104.02. IR (film) 3316, 2925, ,1726, 1681, 1599, 1421, 1167, 761 cm^{-1}; HRMS (ESI+) calcd for $C_9H_5F_4NO_3$ $[M+H]^+$, m/z = 252.0284, found 252.0284.

2-Fluoro-6-nitrobenzoic acid (18)[35]: NaOH (0.07 g, 1.8 mmol) was added to 12 mL H_2O and cooled in an ice bath under vigorous stirring, after which 2-amino-6-fluorobenzoic acid (0.23 g, 1.5 mmol) and $NaHCO_3$ (1.26 g, 15 mmol) were added in one portion. After stirring 15 minutes, two pre-chilled solutions were added simultaneously with rate of solution A roughly twice that of solution B. Solution A: Oxone (2.8 g, 9 mmol), ethylenediaminetetraacetic acid (EDTA) (15 mg), 12 mL H_2O. Solution B: 6 mL H_2O, 6 mL acetone. After 25 minutes, the bright green mixture was removed from ice bath and stirred at rt for 6 hours, then quenched by addition of $NaHSO_3$ and concentrated under reduced pressure. The residue was partitioned between 15 mL EtOAc and 15 mL 3M HCl, after which the aqueous layer was extracted 3x with 10 mL EtOAc. Combined organic layers were washed 1x with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a yellow solid in 95% yield (0.26 g) which was used without further purification: mp = 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dt, J = 8.2, 1.0 Hz, 1 H), 7.65 (td, J = 8.3, 5.4 Hz, 1 H), 7.52 (td, J = 8.4, 1.1 Hz, 1 H); ^{13}C NMR (Acetone-d_6, 101 MHz) δ 163.3, 161.1, 158.6, 133.1 (d, $^3J_{CF}$ = 8.9 Hz), 122.5 (d, $^2J_{CF}$ = 22.2 Hz), 121.3 (d, $^4J_{CF}$ = 3.3 Hz), 120.0 (d, $^2J_{CF}$ = 23.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.24; IR (film) 2880, 2828, 2661, 1715, 1622, 1532, 1476, 1462, 1357, 1294, 1260, 1134, 817, 799, 769, 739, 691, 616, 575, 538 cm^{-1}; HRMS (ESI+) calcd for $C_7H_4FNO_4$ $[M+Na]^+$, m/z = 208.0022 , found 208.0023.

4-(Benzyloxy)-2-fluorobenzoic acid (19)[36]: To a flame-dried flask was added 2-fluoro-4-hydroxybenzoic acid (0.624 g, 4 mmol), K_2CO_3 (1.66 g, 12 mmol), DMF (12 mL), and benzyl bromide (1.67 mL, 14 mmol). The mixture was heated at 70 °C for 12 hours, then cooled and partitioned between 10 mL ice water and 10 mL EtOAc. The aqueous layer was extracted twice with 5 mL EtOAc, then combined organic layers were concentrated. To the resulting reside was added LiOH monohydrate (1.25 g, 30 mmol), THF (10 mL), and H_2O (10 mL) and the mixture heated at reflux 8 hours. After cooling, THF was removed under reduced pressure, then 10 mL EtOAc was added. The aqueous layer was extracted 3x with 10 mL EtOAc. Combined organic layers were washed 3x with 5 mL 5% LiCl, 1x 10 mL brine, then dried over Na2SO4 and concentrated to dryness. The crude product was recrystallized from EtOH to obtain pure product as white crystals (0.514 g, 52%): mp = 165–167 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, J = 8.7 Hz, 1 H), 7.44 – 7.40 (m, 4 H), 7.40 – 7.34 (m, 1 H), 6.83 (ddd, J = 8.8, 2.5, 0.6 Hz, 1 H), 6.74 (dd, J = 12.7, 2.4 Hz, 1 H), 5.12 (s, 2 H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 164.d (d, $^1J_{CF}$ = 258.6 Hz), 165.0 (d, $^3J_{CF}$ = 3.6 Hz), 164.8 (d, $^3J_{CF}$ = 11.4 Hz), 163.0, 137.2, 134.5 (d, $^4J_{CF}$ = 2.9 Hz), 229.03 (d, $^4J_{CF}$ = 2.9 Hz), 129.4, 129.0, 128.7, 112.0 (d, $^4J_{CF}$ = 3.0), 103.9 (d, $^3J_{CF}$ = 26.4 Hz) ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.79; IR (film) 2925–2564, 1678, 1417, 1246, 1152, 739 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{11}FO_3$ $[M+H]^+$, m/z = 247.0770, found 247.0774.

2-Chloro-6-fluorobenzene-1-thiol (21)[37]: 2-Chloro-6-fluoroaniline (0.332 mL, 3 mmol) was suspended in H_2O (9 mL) and cooled to 0 °C. H_2SO_4 (0.4 mL, 7.2 mmol) in H_2O (4.5 mL) was added, followed by dropwise addition of $NaNO_2$ (0.435 g, 6 mmol) in H_2O (4.5 mL). The mixture was stirred at 0 °C for one hour, then added dropwise to a solution of potassium ethyl xanthogenate (3.97 g, 24.3 mmol) in H_2O (9 mL) at 85 °C, rinsing with 1.5 mL MeCN. The mixture was stirred for 1.5 hours, then cooled and extracted 4x with 10 mL CH_2Cl_2. Combined organic layers were washed with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness. The residue was taken up in EtOH (12 mL) and solid KOH was added (0.643 g, 11.5 mmol) and heated at reflux for 14 hours. The solvent was removed under reduced pressure to yield a red-brown residue (0.3 g, 61%) which was carried over crude (*final target inhibitor, **26** was characterized*).

2-Chloro-6-fluorobenzene-1-sulfonyl chloride (22)[38]: Crude 2-chloro-6-fluorobenzene-1-thiol (0.14g, 0.86 mmol), Oxone (1.32 g, 2.15 mmol), KCl (0.07g, 0.9 mmol), and H_2O (3 mL) were added to a flask and stirred at rt for 30 minutes. The mixture was partitioned between 10 mL H_2O, 10 mL EtOAc and the aqueous layer was extracted 3x with 10 mL EtOAc and the combined organic layers were washed with 10 mL brine, dried over Na_2SO_4, and concentrated to dryness. Semi-pure product was isolated by column chromatography (0-100% CH_2Cl_2 in hexane) as a red oil in 19% yield (0.038 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (td, *J* = 8.3, 5.2 Hz, 1 H), 7.47 – 7.42 (m, 1 H), 7.26 – 7.22 (m, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.69. *This substrate was not fully characterized because the compound was difficult to purify. Thus, the final target inhibitor, **21a**, was fully characterized.*

4-[3,5-Bis(trifluoromethyl)phenoxy]benzene-1,2-diamine (23): Iron powder (12.3 mmol) and 5-[3,5-bis(trifluoromethyl)phenoxy]-2-nitroaniline (4.1 mmol) were weighed into microwave vial. The reaction vessel was sealed with a Teflon cap and purged with N_2. Then degassed EtOH (1 M) and degassed glacial acetic acid (1 M) were added, and the solution was stirred at 100 °C. After 5, the mixture was cooled to rt and neutralized at 0 °C with saturated $NaHCO_3$ aq. The mixture was extracted with EtOAc (3x 5 mL) and washed with 5% LiCl aq solution (5 mL). The organic mixture was dried with Na_2SO_4, filtered, and concentrated by rotary evaporation to afford a brown solid. The solid was purified by column chromatography (1–5% MeOH in CH_2Cl_2) to afford the title product as a brown solid in 71% yield (0.69 g): mp = 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (tp, *J* = 1.5, 0.8 Hz, 1 H), 7.33 (dt, *J* = 1.5, 0.6 Hz, 2 H), 6.72 (d, *J* = 8.3 Hz, 1 H), 6.40 (m, 2 H), 3.42 (s, 4 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 160.0, 148.2, 136.9, 132.9 (q, $^2J_{CF3}$ = 33.6 Hz), 131.7, 123.0 (q, $^1J_{CF3}$ = 270.7 Hz), 117.9, 116.9 (d, $^4J_{CF3}$ = 4.1 Hz), 115.2 (sep, $^3J_{CF3}$ = 3.9 Hz), 111.3, 108.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; IR (film) 3417, 3312, 3212, 1614, 1514, 1465, 1372, 1283, 1249, 1175, 1156, 1130, 1111, 985, 884, 851, 825, 746, 720, 706, 683 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{10}F_6N_2O$ $[M+H]^+$, *m/z* = 337.0775, found 337.0765.

5-[3,5-Bis(trifluoromethyl)phenoxy]-2-nitroaniline (24): Prepared by general procedure B with 2.5 mmol 5-fluoro-2-nitroaniline, 3 mmol 3,5-bis(trifluoromethyl)phenol, 7.5 mmol K_2CO_3, and 12 mL DMF. Purified by column chromatography (0-100% CH_2Cl_2 in hexane) to obtain the title compound as a vivid yellow solid in 90% yield (0.82 g): mp = 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 9.3, 0.4 Hz, 1H), 7.72 (s, 1H), 7.51 (s, 2H), 6.35 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (dd, *J* = 2.5, 0.4 Hz, 1H), 6.20 (s, 2H); ^{13}C NMR (101 MHz, Acetone) δ 162.8, 157.4, 148.9, 134.0 (q, $^2J_{CF3}$ = 33.9 Hz), 129.6, 129.1, 123.9 (q, $^1J_{CF3}$ = 273.3 Hz), 128.8, (d, $^4J_{CF3}$ = 7.2 Hz), 119.0 (sep, $^3J_{CF3}$ = 3.9 Hz), 108.0, 106.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97; IR (film) 3495, 3368, 1640, 1614, 1573, 1502, 1368, 1279, 1246, 1223, 1175, 1126, 1108, 981, 933, 884, 858, 758, 702, 687 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_8F_6N_2O_3$ $[M+H]^+$, *m/z* = 367.0517, found 367.0519.

4-[3,5-Bis(trifluoromethyl)phenoxy]-2-bromoaniline (25): 4-[3,5-Bis(trifluoromethyl)phenoxy]-2-bromo-1-nitrobenzene (0.43 g, 1 mmol), Fe powder (0.22 g, 4 mmol), AcOH (4 mL), EtOH (4 mL) were added to a flask and heated at reflux for 70 minutes. After cooling, the mixture was quenched with saturated $NaHCO_3$, then extracted 3x with 10 mL EtOAc. The combined organic layers were washed with 10 mL saturated $NaHCO_3$ then 10 mL brine, dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a brown oil in 94% yield (0.37 g) which was used without further purification: ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.31 (s, 2H), 7.20 (d, *J* = 2.6 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.19 – 4.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 146.3, 142.2, 133.2 (d, $^2J_{CF3}$ = 33.6 Hz), 125.0, 123.1 (q, $^1J_{CF3}$ = 273.7 Hz), 121.0, 117.0 (d, $^4J_{CF3}$ = 3.7 Hz), 116.6, 115.9 (sep, $^3J_{CF3}$ = 3.8 *J* Hz), 109.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.96; IR (film) 3480, 3379, 1715, 1622, 1590, 1499, 1465, 1372, 1279, 1175, 1126, 955, 884, 817, 683 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_8BrF_6NO$ $[M+H]^+$, *m/z* = 399.9772, found 399.9771.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]-2-bromophenyl}-2-chloro-6-fluorobenzamide (26): Prepared by general method B using 0.58 mmol 4-[3,5-bis(trifluoromethyl)phenoxy]-2-bromoaniline, 0.7 mmol 2-fluoro-6-chlorobenzoyl chloride, 1.7 mmol Et_3N and 5 mL CH_2Cl_2. Purified by trituration in cold hexane afforded title compound as a brown solid in 65% yield (0.21 g, 95% pure): mp = 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 9.0 Hz, 1 H), 7.91 (s, 1 H), 7.62 (s, 1 H), 7.46 – 7.37 (m, 3 H), 7.36 – 7.29 (m, 2 H), 7.18 – 7.10 (m, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 160.4 (d, $^1J_{CF}$ = 253.0 Hz), 161.60, 161.56, 159.4 (d, $^4J_{CF}$ = 1.2 H), 133.82 (q, $^2J_{CF3}$ = 33.6 Hz), 133.7 (d, $^3J_{CF}$ = 9.1 Hz), 132.8, 132.7 (d, $^3J_{CF}$ = 9.4 Hz), 127.9 (d, $^3J_{CF}$ = 8.4 Hz), 126.4 (d, $^4J_{CF}$ = 3.4 Hz), 125.0, 124.0, 120.3, (q, $^1J_{CF3}$ = 272.3 Hz), 121.7, 119.8 (d, $^3J_{CF3}$ = 3.0 Hz), 118.1 (d, $^2J_{CF}$ = 10.9 Hz), 117.8 (sep, $^3J_{CF3}$ = 3.9 Hz), 115.4 (d, $^2J_{Cf}$ = 21.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.93, -111.98; IR (film) 3253, 1678, 1614, 1588, 1532, 1488, 1465, 1376, 1283, 1253, 1175, 1126, 955, 903, 884, 730, 702, 657 cm^{-1}; HRMS (ESI-) calcd for $C_{21}H_{10}BrClF_7NO_2$ $[M]^-$, *m/z* = 553.9393, found 553.9366.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-chloro-6-fluorobenzene-1-sulfonamide (27a)[39]: To a flame-dried vial was added **21** (0.038 g, 0.17 mmol), **13** (0.055 g, 0.17 mmol), and CH_2Cl_2 (1 mL). After cooling to 0 °C, pyridine (0.5 mL, 6.2 mmol) was added dropwise. The reaction was stirred at rt for 5 hours, after which the solvent was removed *in vacuo*. The residue was partitioned between 10 mL each water and ethyl acetate, and the aqueous layer extracted 3x with 5 mL ethyl acetate. The combined organic layers were washed with 5 mL brine, dried over Na_2SO_4, and concentrated to dryness. The crude product was purified by column chromatography (0-100% CH_2Cl_2 in hexanes, then 0-100% EtOAc) and finally recrystallized from hot hexane to give the product as tan crystals in 44% yield (0.037 g, 97% pure): mp = 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1 H), 7.44 (td, *J* = 8.2, 5.4 Hz, 1H), 7.34 (dt, *J* = 8.1, 1.2 Hz, 1 H), 7.27 (s, 2 H), 7.26 – 7.22 (m, 2 H), 7.14 – 7.08 (m, 2 H), 6.98 – 6.94 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 159.8, 158.6, 153.2, 134.5 (d, $^3J_{CF}$ = 10.8 Hz), 134.0,133.6, 133.2, 128.1 (d, $^4J_{CF}$ = 3.6 Hz), 124.1, 123.0 (q, $^1J_{CF3}$ = 273.7 Hz), 121.1, 118.0 (d, $^4J_{CF3}$ = 2.6 Hz), 116.67 (sep, $^3J_{CF3}$ = 3.9 Hz), 116.65 (d, $^2J_{CF}$ = 24.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.04, -103.90. IR (film) 3271, 1592, 1577, 1506, 1458, 1372, 1350, 1283, 1246, 1171, 1145, 1126, 1108, 951, 918, 791, 612, 512 cm^{-1}; HRMS (ES-) $[M-H]^-$ for $C_{20}H_{10}ClF_7NO_3S$, *m/z* 511.9958, found 511.9966.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]phenyl}-2-fluorobenzene-1-sulfonamide (27b)[39]: To a flame-dried vial was added 2-fluorobenzene-1-sulfonyl chloride (0.146 g, 0.75 mmol), **13** (0.161 g, 0.5 mmol), CH_2Cl_2 (6 mL). After cooling to 0 °C, pyridine (0.5 mL, 6 mmol) was added dropwise. The reaction was stirred at rt for 4.5 hours, after which the solvent was removed *in vacuo*. The residue was partitioned between 10 mL each H_2O and EtOAc, and the aqueous layer extracted 3x with 5 mL EtOAc. The combined organic layers were washed with 5 mL brine, dried over Na_2SO_4, and concentrated to dryness. Following purification by column chromatography (0-80% CH_2Cl_2 in hexanes) the tile compound was obtained as a white solid in 78% yield (0.186 g, 98% pure): mp = 164–166 °C; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1 H), 7.63 (dddd, *J* = 8.3, 7.6, 5.0, 1.8 Hz, 2 H), 7.36 – 7.31 (m, 2 H), 7.30 – 7.22 (m, 4 H), 7.03 – 6.98 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (1, $^1J_{CF}$ = 255.3 Hz), 158.6, 153.1, 135.8 (d, $^3J_{CF}$ = 8.7 Hz), 127.9 (q, $^2J_{CF3}$ = 34.0 Hz), 132.9, 131.2, 126.7, 124.6 (d, $^2J_{CF}$ = 38.4 Hz), 124.4, 123.0 (q, $^1J_{CF3}$ = 273.8 Hz), 121.0, 117.9 (d, $^4J_{CF3}$ = 3.6 Hz), 117.0 (d, $^2J_{CF}$ = 21.0 Hz), 116.6 (sep, $^3J_{CF3}$, 3.8 Hz); ^{19}F NMR (376 MHz, Methanol-d_4) δ -64.61, -111.37; IR (film) 3275, 1618, 1603, 1506, 1476, 1462, 1380, 1380, 1342, 1283, 1249, 1178, 1156, 1126, 1078, 1022, 955, 933, 903, 877, 862, 847, 769, 687, 609, 560 cm^{-1}; HRMS (ESI-) calcd for $C_{20}H_{12}F_7NO_3S$ $[M+H]^+$, *m/z* = 478.0348 , found 478.0352.

5-[3,5-Bis(trifluoromethyl)phenoxy]-2-(2-fluoro-6-iodophenyl)-1H-1,3-benzodiazole (28) [40] : : N-{2-Amino-5-[3,5-bis(trifluoromethyl)phenoxy]phenyl}-2-fluoro-6-iodobenzamide (94 mg, 0.16 mmol) was dissolved in 1.6 mL of glacial acetic acid and stirred at reflux. After 5 h, the mixture

was cooled to rt and poured into ice H_2O (1.6 mL). The resulting precipitate was filtered and washed with H_2O (2.0 mL) and diethyl ether (2.0 mL) to afford a white solid in 25% yield (23 mg, 95% pure): mp 238–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1 H), 9.17 (s, 1 H), 7.88 (s, 1 H), 7.80 (d, J = 7.8 Hz, 1 H), 7.70 (d, J = 8.2 Hz, 3 H), 7.57 (d, J = 2.6 Hz, 1 H), 7.47 – 7.38 (m, 1 H), 7.37 – 7.26 (m, 1 H), 7.11 – 7.04 (m, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -111.7; IR (film) 3335, 3275, 3078, 1700, 1648, 1610, 1543, 1521, 1491, 1469, 1450, 1435, 1372, 1286, 1249, 1178, 1126, 1063, 1063, 1022, 985, 936, 918, 899, 862, 825, 787, 709, 687, 616, 586, 516 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{10}F_7IN_2O$ $[M+H]^+$, m/z = 566.9804, found 566.9799.

N-{4-[3,5-Bis(trifluoromethyl)phenoxy]-2-hydroxyphenyl}-2-chloro-6-fluorobenzamide (29): Prepared by general method B using 2-amino-5-[3,5-bis(trifluoromethyl)phenoxy]phenol 0.10 mmol , 0.11 mmol 2-chloro-6-fluorobenzoyl chloride, 0.21 mmol pyridine and 0.5 mL CH_2Cl_2. The solid was purified by flash column chromatography (20% EtOAc:Hexanes) to afford the title compound as an orange solid in 91% yield (47 mg, 99% pure): mp = 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 9.0 Hz, 1 H), 7.93 (s, 1 H), 7.62 (dp, J = 1.5, 0.8 Hz, 1 H), 7.50 – 7.44 (m, 2 H), 7.47 – 7.35 (m, 2 H), 7.32 – 7.23 (m, 2 H), 7.17 (d, J = 2.7 Hz, 1 H), 7.15 – 7.02 (m, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) (mixture of rotamer) δ 160.8, 158.9 (d, $^1J_{CF}$ = 254.3 Hz), 160.3, 160.0, 158.3, 151.2, 140.4, 133.2 (q, $^2J_{CF3}$ = 34.2 Hz), 132.9 (d, $^3J_{CF}$ = 10.2 Hz), 125.8 (dd, $^2J_{CF}$ = 26.1 Hz), 123.5, 121.5 (q, $^1J_{CF3}$ = 275.2 Hz), 117.9 (q, $^4J_{CF3}$ = 4.1 Hz), 116.7 (q, $^3J_{CF3}$ = 3.7 Hz), 114.9, 114.7, 114.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0, -111.2, -112.0; IR (film) 3409, 3249, 1774, 1704, 1607, 1581, 1525, 1502, 1454, 1421, 1376, 1320, 1283, 1246, 1171, 1130, 1089, 1041, 1007, 981, 925, 903, 888, 854, 828, 791, 732, 586, 571, 557 cm^{-1}; HRMS (ESI-) calcd for $C_{21}H_{11}ClF_7NO_3$ $[M]^-$, m/z = 494.0394, found 494.0394.

N-{5-[3,5-Bis(trifluoromethyl)phenoxy]-2-hydroxyphenyl}-2-fluoro-6-iodobenzamide (30)[41]: 2-Fluoro-6-iodobenzoic acid was dissolved with $SOCl_2$ and refluxed at 80 °C for 45 minutes. The mixture was cooled to rt and concentrated by rotary evaporation and used for benzoxazole synthesis. The resulting benzoyl chloride was treated with 2-amino-5-[3,5-bis(trifluoromethyl)phenoxy]phenol (100 mg, 0.297 mmol, 1 equiv.) in dioxane (2.0 mL) followed by addition of CH_3SO_3H (58 μL, 0.891 mmol, 3 equiv.). The resultant mixture was stirred magnetically at 100 °C (oil bath). After complete consumption of 2-amino-5-[3,5-bis(trifluoromethyl)phenoxy]phenol (2 h, TLC), the dioxane was removed by rotary evaporation under reduced pressure and the residue was diluted with EtOAc (10 mL) followed by saturated aq. $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (3Å~5 mL). The combined EtOAc extracts were washed with H_2O (3Å~5 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to afford a brown oil. The solid was purified by flash column chromatography (20% EtOAc in hexanes) to afford the title compound as oil solid in 58% yield (100 mg, 99% pure): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.77 – 7.70 (m, 1 H), 7.69 (s, 1 H), 7.60 (s, 1 H), 7.46 – 7.41 (m, 2 H), 7.26 – 7.15 (m, 2 H), 6.79 (d, J = 2.6 Hz, 1 H), 6.65 (dd, J = 8.7, 2.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 164.1, 157.8, 154.1, 150.2, 149.0, 135.0 (d, $^4J_{CF}$ = 3.5 Hz), 132.8 (q, $^2J_{CF3}$ = 34.0 Hz), 132.5 (d, $^3J_{CF}$ = 8.9 Hz), 123.4, 121.6, 117.7 (q, $^4J_{CF3}$ = 4.1 Hz), 116.1 (q, $^3J_{CF3}$ = 4.1 Hz), 115.6 (d, $^2J_{CF}$ = 21.5 Hz), 111.5, 110.6 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5, -110.7; HRMS (ESI+) calcd for $C_{21}H_{11}F_7INO_3$ $[M+H]^+$, m/z = 585.9750, found 585.9757.

3-Amino-5-(trifluoromethyl)phenol (31): Prepared by general method D with 3 mmol 3-nitro-5-(trifluoromethyl)phenol, 1 mmol 10% Pd/C, and 10 mL MeOH as a brown oil in quantitative yield which was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 6.29 (s, 1H), 6.20 (s, 1H), 6.15 (s, 1H), 5.45 (s, 2H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 162.30, 159.2, 159.0, 154.5, 151.1, 132.1 (q, $^2J_{CF3}$ = 31.4 Hz), 126.4, 125.1 (q, $^1J_{CF3}$ 272.4), 115.3, 107.9 (q, $^4J_{CF}$ = 4.1 Hz), 107.1 (q, $^4J_{CF3}$ = 4.0 Hz), 104.5, 102.9 (q, $^4J_{CF3}$ = 4.1 Hz), ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.64; IR (film) 3383, 1704, 1659, 1629, 1607, 1365, 1272, 1164, 1115, 1003, 895, 847, 717, 698, 646 cm^{-1}; HRMS (ESI+) calcd for $C_7H_6F_3NO$ $[M+H]^+$, m/z = 178.0480, found 178.0477.

3-(4-Nitrophenoxy)-5-(trifluoromethyl)aniline (32): Prepared by general method C with 1 mmol 3-amino-5-(trifluoromethyl)phenol, 3 mmol K_2CO_3, 1 mmol 4-fluoronitrobenzene, and 5 mL DMF. Purified by column chromatography (0-100% CH_2Cl_2 in hexane) to afford the title compound as a yellow oil which solidified on standing in 99% yield: mp = 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 2 H), 7.09 – 7.02 (m, 2 H), 6.76 (s, 1 H),

6.68 (s, 1 H), 6.52 (s, 1 H), 4.00 (s, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 163.4, 157.3, 152.2, 143.8, 126.7, 124.8 (q, $^{2}J_{CF3}$ = 272.8 Hz), 109.2 (d, $^{4}J_{CF3}$ = 1.5 Hz), 108.0 (q, $^{3}J_{CF3}$ = 4.0 Hz), 104.8 (q, $^{3}J_{CF3}$ = 4.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.14; IR (film) 3502, 3484, 3402, 3383, 3111, 3082, 1629, 1610, 1588, 1514, 1491, 1368, 1346, 1231, 1164, 1011, 907, 858, 836, 761, 717, 694, 646 cm^{-1}; HRMS (ESI-) calcd for $C_7H_6F_3NO$ $[M]^-$, m/z = 176.0323, found 176.0316.

2-Chloro-6-fluoro-N-{4-[3-(trifluoromethyl)phenoxy]phenyl}benzamide (35a): A flask containing 1-(4-nitrophenoxy)-3-(trifluoromethyl)benzene (0.071 g, 0.25 mmol), Fe powder (0.060 g, 1 mmol), AcOH (1.5 mL), EtOH (1.5 mL) was heated at reflux for 90 minutes and then concentrated *in vacuo*. The residue was filtered through Celite, then partitioned between 10 mL EtOAc and 10 mL 1 M NaOH. The aqueous layer was extracted 3x with 10 mL EtOAc, and combined organic layers were washed 2x with 10 mL 1M NaOH, then 10 mL brine, dried over Na_2SO_4 and concentrated. To a solution of the resulting residue in CH_2Cl_2 (5 mL) at 0 °C was added 2-chloro-6-fluorobenzoyl chloride (0.15g, 0.8 mmol) and Et_3N (0.21 mL, 1.5 mmol), and then stirred allowed to warm while stirring overnight. After removing solvents *in vacuo*, the residue was partitioned between 10 mL each EtOAc and H_2O, and the aqueous layer extracted 3x with 10 mL EtOAc. The combined organic layers were washed with 10 mL brine, dried over Na_2SO_4, and concentrated to dryness. Following purification by column chromatography (0-60% CH_2Cl_2 in hexane), the title compound was obtained as a white sold in 40% yield (0.040 g, 92% pure): mp = 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2 H), 7.53 (s, 1 H), 7.49 – 7.44 (m, 1 H), 7.43 – 7.35 (m, 2 H), 7.30 (dt, J = 8.2, 0.9 Hz, 1 H), 7.27 (s, 1 H), 7.21 – 7.16 (m, 1H), 7.16 – 7.11 (m, 1H), 7.11 – 7.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $^{1}J_{CF}$ = 252.2 Hz), 160.5, 158., 153.1, 133.6, 132.7 (d, $^{3}J_{CF}$ = 15.3 Hz), 132.6 (d, $^{3}J_{CF}$ = 10.2 Hz), 131.8 (d, $^{2}J_{CF}$ = 40.7 Hz), 130.5, 126.0 (d, $^{4}J_{CF}$ = 3.5 Hz), 125.2 (d, $^{2}J_{CF}$ = 21.1 Hz), 125.1 (d, $^{4}J_{CF3}$ = 4.4 Hz), 122.3, 121.4, 120.4, 119.8 (q, $^{4}J_{CF3}$ = 3.8 Hz),115.1 (d, $^{3}J_{CF}$ = 7.7 Hz), 114.8 (d, $^{2}J_{CF}$ = 21.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.66, -112.32; IR (film) 3201, 3141, 3063, 2925, 1663, 1618, 1566, 1506, 1450, 1331, 1285, 1260, 1223, 1193, 1167, 1115, 1097, 1067, 910, 881, 847, 795, 780, 754, 728, 661, 523 cm^{-1}; HRMS (ESI-) calcd for $C_{20}H_{12}ClF_4NO_2$ $[M+H]^+$, m/z = 408.0414, found 408.0416.

2-Chloro-6-fluoro-N-(4-(3-fluoro-5-(trifluoromethyl)phenoxy)phenyl)benzamide (35b): The aniline intermediate was prepared by general method D with 0.11 mmol 1-fluoro-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene, 0.09 mmol 10% Pd/C, and 3 mL MeOH. After filtration through Celite and concentration *in vacuo,* the crude aniline was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Et_3N (0.05 mL, 0.3 mmol) and 2-chloro-6-fluorobenzoyl chloride (0.03 g, 0.2 mmol) were added, and the mixture stirred while warming to rt over 3 hours. The crude mixture was concentrated and then purified by column chromatography (0-100% CH_2Cl_2 in hexane) to afford the title compound as a tan solid in 84% yield (39 mg, 96% pure): mp = 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2 H), 7.50 (s, 1 H), 7.39 (td, J = 8.2, 5.9 Hz, 1H), 7.29 (dt, J = 8.1, 1.0 Hz, 1 H), 7.15 – 7.07 (m, 3 H), 7.06 – 7.01 (m, 2 H), 6.84 (dt, J = 9.7, 2.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{CF}$ = 250.2 Hz), 159.9 (d, $^{1}J_{CF}$ = 252.8 Hz), 160.6, 160.02, 160.00, 156.2, 152.2, 134.4, 132.7 (d, $^{3}J_{CF}$ = 5.0 Hz), 131.9 (d, $^{3}J_{CF}$ = 9.2 Hz), 126.1 (d, $^{4}J_{CF}$ = 3.5 Hz),122.4, 121.1, 115.0 (d, $^{2}J_{CF}$ = 21.8 Hz), 110.7 (sep, $^{3}J_{CF3}$ = 3.5 Hz), 108.5 (d, $^{2}J_{CF}$ = 24.3 Hz), 107.4 (d, $^{3}J_{CF}$ = 4.0 Hz), 107.1 (d, $^{3}J_{CF}$ = 3.8 Hz), (two unresolved quartets); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -108.0, -112.3; IR (film) 3257, 1663, 1603, 1529, 1510, 1450, 1354, 1320, 1208, 1175, 1126, 1089, 1000, 903, 877, 847, 769, 737, 519 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{11}ClF_5NO_2$ $[M+H]^+$, m/z = 428.0477, found 428.0475.

2-Chloro-N-{4-[3-chloro-5-(trifluoromethyl)phenoxy]phenyl}-6-fluorobenzamide (35c): Prepared by general method B using 0.5 mmol substituted aniline and 0.6 mmol acyl chloride. Following column chromatography (0-100% CH_2Cl_2 in hexane) the title compound was isolated as a white solid in 92% yield (0.20 g, 99% pure): mp = 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2 H), 7.65 (s, 1 H), 7.37 (td, J = 8.2, 5.9 Hz, 1 H), 7.33 – 7.30 (m, 1 H), 7.27 (dt, J = 8.1, 0.9 Hz, 1 H), 7.14 – 7.09 (m, 3 H), 7.09 – 7.04 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $^{1}J_{CF}$ = 253.0 Hz), 160.6, 159.2, 152.1, 136.1, 134.3, 133.4 (q, $^{2}J_{CF}$ = 33.5 Hz), 132.7 (d, $^{3}J_{CF}$ = 5.1 Hz), 131.8 (d, $^{3}J_{CF}$ = 9.2 Hz), 126.0 (d, $^{4}J_{CF}$ = 3.6 Hz), 125.1 (d, $^{2}J_{CF}$ = 21.3 Hz), 123.1 (q, $^{1}J_{CF3}$ = 274.0 Hz), 122.3, 121.0, 120;9, 119.9 (q, $^{4}J_{CF3}$ = 3.8, 7.2 Hz), 114.8 (d, $^{2}J_{CF}$ = 21.8 Hz), 113.2 (dd, $^{3}J_{CF}$ = 3.8, 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -

112.3; IR (film) 3245, 1666, 1610, 1588, 1555, 1532, 1506, 1450, 1413, 1339, 1275, 1197, 1167, 1130, 1093, 955, 907, 862, 847, 780, 709, 694, 516 cm^{-1}; HRMS (ESI-) calcd for $C_{20}H_{11}Cl_2F_4NO_2$ $[M]^-$, m/z = 442.0025, found 442.0021.

N-{4-[3-Bromo-5-(trifluoromethyl)phenoxy]phenyl}-2-chloro-6-fluorobenzamide (35d): Prepared by general method B using 0.5 mmol substituted aniline and 0.6 mmol acyl chloride. Following column chromatography (0-75% CH_2Cl_2 in hexane) the title compound was isolated as a white solid in 90% yield (0.22 g, 99% pure): mp = 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2 H), 7.59 – 7.54 (s, 1 H), 7.46 (s, 1 H), 7.38 (td, J = 8.2, 5.9 Hz, 1 H), 7.29 – 7.26 (m, 2 H), 7.17 (s, 1 H), 7.12 (dd, J = 8.5, 1.0 Hz, 1 H), 7.10 – 7.05 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (d, $^1J_{CF}$ = 253.0 Hz), 160.5, 159.1, 152.1, 134.3, 133.6 (q, $^2J_{CF3}$ = 33.5 Hz), 132.7 (d, $^3J_{CF}$ = 5.2 Hz), 131.8 (d, $^3J_{CF}$ = 9.2 Hz), 126.0 (d, $^4J_{CF}$ = 3.4 Hz), 125.2 (d, $^2J_{CF}$ = 21.4 Hz), 124.0, 122.9 (q, $^1J_{CF3}$ = 274.1 Hz), 123.5, 122.8 (q, $^4J_{CF3}$ = 3.9 Hz), 122.3, 120.9, 114.9 (d, $^2J_{CF}$ = 21.8 Hz), 113.7 (dd, $^3J_{CF3}$ = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9, -112.3; IR (film) 3253, 1666, 1581, 1555, 1529, 1510, 1506, 1447, 1409, 1372, 1249, 1193, 1167, 1126, 1126, 1093, 944, 907, 858, 843, 694, 516 cm^{-1}; HRMS (ESI-) calcd for $C_{20}H_{11}BrClF_4NO_2$ $[M]^-$, m/z = 485.9520, found 485.9520.

2-Chloro-6-fluoro-N-{4-[3-iodo-5-(trifluoromethyl)phenoxy]phenyl}benzamide (35e): A flask containing 1-Iodo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (0.20 g, 0.5 mmol), iron powder (0.12 g, 2 mmol), glacial acetic acid (2.5 mL) and EtOH (2.5 mL) was heated at reflux for 90 minutes and then concentrated *in vacuo*. The residue was filtered through Celite, then partitioned between 10 mL EtOAc and 10 mL 1 M NaOH. The aqueous layer was extracted 3x with 10 mL EtOAc, and combined organic layers were washed 2x with 10 mL 1M NaOH, then 10 mL brine, dried over Na_2SO_4 and concentrated. To a solution of the resulting tan residue in CH_2Cl_2 (5 mL) at 0 °C was added 2-chloro-6-fluorobenzoyl chloride (0.15g, 0.8 mmol) and Et_3N (0.21 mL, 1.5 mmol), and then stirred allowed to warm while stirring overnight. After removing solvents *in vacuo*, the crude material was sequentially triturated with hexane and then CH_2Cl_2 to afford the title compound as a white solid in 44% yield (0.12g, 99% pure): mp = 193–195 °C; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.94 – 7.88 (m, 2 H), 7.78 (s, 1 H), 7.63 (s, 1 H), 7.54 (td, J = 8.3, 6.1 Hz, 1 H), 7.39 (dt, J = 8.1, 0.9 Hz, 1 H), 7.33 (s, 1 H), 7.27 (td, J = 8.7, 1.0 Hz, 1 H), 7.24 – 7.18 (m, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 160.3 (d, $^1J_{CF}$ = 249.8 Hz), 161.1, 161.96, 160.12, 152.3, 136.8 (d, $^3J_{CF}$ = 9.2 Hz), 134.2 (d, $^2J_{CF}$ = 33.1 Hz), 133.5 (q, $^2J_{CF}$ = 33.0 Hz), 132.7 (d, $^4J_{CF}$ = 5.8 Hz), 132.6 (d, $^3J_{CF}$ = 9.3 Hz), 130.9, 129.0 (q, $^4J_{CF}$ = 3.8 Hz), 126.5 (d, $^3J_{CF}$ = 3.4 Hz), 125.1, 122.4, 122.3, 121.6, 115.5 (d, $^2J_{CF}$ = 21.9 Hz), 114.9 (q, $^4J_{CF3}$ = 3.8 Hz), 95.2; ^{19}F NMR (376 MHz, Acetone-d_6) δ -63.40, -115.04; IR (film) 3260, 1670, 1607, 1581, 1532, 1510, 1454, 1439, 1409, 1320, 1253, 1234, 1175, 1126, 1089, 1089, 940, 903, 858, 843, 780, 691, 516 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{11}F_4INO_2$ $[M+H]^+$, m/z = 535.9537, found 535.9545.

2-Chloro-6-fluoro-N-{4-[3-hydroxy-5-(trifluoromethyl)phenoxy]phenyl}benzamide (35f): From the nitroarene, the aniline was first prepared by general procedure D with 0.2 mmol 3-(4-nitrophenoxy)-5-(trifluoromethyl)phenol, 0.1 mmol 10% Pd/C, and 5 mL MeOH. The resulting oil was added to a flame dried vial containing pyridine (0.05 mL, 0.3 mmol) and CH_2Cl_2 (3 mL), then cooled to 0 °C. 2-chloro-6-fluorobenzoyl chloride (0.058 g, 0.3 mmol) in CH_2Cl_2 (2 mL) was added and the vial was allowed to warm to rt while stirring overnight. The mixture was concentrated, then dissolved in 3 mL dioxane and 3 mL 1M NaOH and stirred 1 hour. After concentration, the residue was partitioned between 10 mL each EtOAc and H_2O, the aqueous layer was adjusted to pH 1 with 1 M HCl and extracted 3x with 10 mL EtOAc. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (0-30% EtOAc in hexane) and the title compound was isolated in 21% yield (17 mg, 99% pure) as a clear oil: ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.39 – 8.31 (m, 2 H), 7.71 (td, J = 8.4, 6.1 Hz, 1 H), 7.61 (s, 1H), 7.57 (s, 1 H), 7.54 – 7.49 (m, 2 H), 7.41 (ddd, J = 9.4, 8.5, 1.0 Hz, 1H), 7.39 – 7.34 (m, 2 H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 162.6, 160.9 (d, $^1J_{CF}$ = 254.7 Hz), 161.6, 152.9, 152.9, 144.9, 134.8 (d, $^3J_{CF}$ = 9.6 Hz), 134.0 (d, $^2J_{CF}$ = 33.8 Hz), 133.2 (d, $^4J_{CF}$ = 4.5 Hz), 127.2 (d, $^3J_{CF}$ = 3.8 Hz), 127.1, 124.2 (q, $^1J_{CF3}$ = 273.2 Hz), 121.5 (d, $^2J_{CF}$ = 19.5 Hz), 119.7, 118.6, 116.20 (sep, $^3J_{CF3}$ = 2.4 Hz), 116.15 (d, $^2J_{CF}$ = 25.7 Hz) (one unresolved carbon); ^{19}F NMR (376 MHz, Acetone) δ -63.2, -112.8; IR (film) 3093,

2925, 1771, 1607, 1588, 1517, 1502, 1491, 1447, 1339, 1246, 1216, 1175, 1126, 1111, 1085, 985, 907, 854, 795, 750, 702 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{12}ClF_4NO_3$ $[M+Li]^+$, *m/z* = 432.0602, found 432.8556.

2-Chloro-6-fluoro-N-(4-{[5-(trifluoromethyl)pyridin-3-yl]oxy}phenyl)benzamide (35g): Prepared by general method B using 4-{[5-(trifluoromethyl)pyridin-3-yl]oxy}aniline 0.16 mmol , 0.19 mmol 2-chloro-6-fluorobenzoyl chloride, 0.32 mmol Et_3N and 1.6 mL CH_2Cl_2. The solid was purified by flash column chromatography (15% EtOAc in hexanes) to afford the title compound as a white solid in 38% yield (25 mg, 99% pure): mp = 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1 H), 7.74 (d, *J* = 9.7 Hz, 2 H), 7.63 (br s, 1 H), 7.48 (ddd, *J* = 2.6, 1.9, 0.7 Hz, 1 H), 7.40 (td, *J* = 8.3, 5.9 Hz, 1 H), 7.30 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.16 – 7.06 (m, 1 H), 7.13 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 159.6 (d, $^1J_{CF}$ = 248.Hz), 151.8, 143.9, 140.5 (q, $^4J_{CF3}$ = 4.2 Hz), 134.4, 132.5 (d, $^3J_{CF}$ = 5.0 Hz), 131.7 (d, $^3J_{CF}$ = 9.2 Hz), 125.9 (d, $^4J_{CF}$ = 3.4 Hz), 125.0 (d, $^2J_{CF}$ = 21.3) 124.4, 122.3, 121.0 (q, $^3J_{CF3}$ = 3.5 Hz), 120.5, 114.7 (d, $^2J_{CF}$ = 21.9 Hz) (*unresolved quartet for -CF_3*); ^{19}F NMR (365 MHz, $CDCl_3$) δ -62.2, -112.2; δ; IR (film) 3320, 1670, 1607, 1577, 1525, 1506, 1469, 1447, 1416, 1313, 1260, 1246, 1197, 1171, 1141, 1119, 1078, 1018, 933, 903, 881, 843, 817, 787, 765, 750, 661, 612, 568, 534 cm^{-1}; HRMS (ESI+) calcd for $C_{19}H_{11}ClF_4N_2O_2$ $[M+H]^+$, *m/z* = 411.0523, found 411.1728.

2-Chloro-6-[4-(1,3-oxazol-2-yl)phenoxy]benzonitrile (36): The general procedure E was followed using 4-(1,3-oxazol-2-yl)phenol (82 mg, 0.51 mmol), 2-chloro-6-fluorobenzonitrile (79 mg, 0.51 mmol), and NaH in 60% mineral oil (21 mg, 0.51mmol) in DMF (2.5 mL). Purification by column chromatography (eluent 1% MeOH in CH_2Cl_2) provided **36** in 53% yield (80 mg, 99% pure) as an oil: ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 0.8 Hz, 1 H), 8.11 – 8.03 (m, 2 H), 7.76 – 7.67 (m, 1 H), 7.54 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.41 (d, *J* = 0.8 Hz, 1 H), 7.39 – 7.31 (m, 2 H), 7.09 (dd, *J* = 8.5, 0.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 160.6, 160.0, 156.8, 140.7, 137.2, 136.5, 129.1, 128.7, 125.3, 124.5, 120.6, 117.4, 113.6, 104.8; IR (film) 3130, 3089, 2236, 1264, 929, 862 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_9ClN_2O_2$ $[M+H]^+$, *m/z* = 297.0431, found 297.0432.

2-((4-(1,3,4-Oxadiazol-2-yl)phenoxy)methyl)-6-chlorobenzonitrile (37): 4-(1,3,4-Oxadiazol-2-yl-phenol (49 mg, 0.30 mmol), 2-(bromomethyl)-6-chlorobenzonitrile (90 mg, 0.390 mmol), and cesium carbonate (195 mg, 0.60 mmol) were weighed into a microwave vial. The reaction vial was sealed and stirred at 80 °C overnight. The reaction progress was monitored using TLC. The reaction was cooled to rt, diluted with H_2O, and neutralized with 1 M HCl. The aqueous mixture was extracted with CH_2Cl_2 3x with 10 mL. The organic mixture was dried with Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification of the residue with column chromatography (eluent 1% MeOH in CH_2Cl_2) provided **37** (22 mg, 98% pure) in 34% yield as white solid: mp = 130–132 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.44 (s, 1 H), 8.06 (d, *J* = 8.9 Hz, 2 H), 7.62 – 7.57 (m, 2 H), 7.56 – 7.48 (m, 1 H), 7.16 (d , *J* = 9.0 H), 2 H), 5.33 (d, *J* = 0.7 Hz, 2 H).; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 160.7, 152.3, 142.2, 137.7, 133.8, 129.5, 129.1, 127.6, 126.3, 117.2, 115.4, 114.0, 112.0, 67.5; IR (film) 3152, 2962, 2925, 2236, 1618, 1596, 1502, 1462, 1447, 1394, 1316, 1301, 1253, 1234, 1190, 1111, 1074, 1026, 959, 840, 784, 743, 706, 683, 638, 624, 564, 527 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{11}ClN_3O_2$ $[M+H]^+$, *m/z* = 312.0540, found 312.0541.

3-Chloro-2-cyanophenyl 4-(5-methyl-1,3,4-oxadiazol-2-yl)benzoate (38)[41]: 4,5-Methyl-1,3,4-oxazdiazol-2-ylbenzoic acid (253 mg, 1.24 mmol) was refluxed in thionyl chloride (1.24 mL, 1 M) until formation of HCl stopped. The excess $SOCl_2$ was removed by rotary evaporation to afford a solid, which was azeotroped with anhydrous benzene. The residue was dissolved in CH_2Cl_2 (3.3 mL), and the resulting solution was added drop wise to 2-chloro-6-hydroxybenzonitrile (90.5 mg, 0.589 mmol), DMAP (21.6 mg, 0.177 mmol), and Et_3N (3.3 mL, 0.18 M). The mixture was stirred overnight at rt. The mixture was diluted with CH_2Cl_2, and the solution was washed two times with 1 M aqueous HCl (14 mL) and two times with water (14 mL). The organic mixture was dried with Na_2SO_4, filtered, and concentrated. Purification of the residue with column chromatography provided **38** (80 mg, 94% pure) in 40% yield as white solid: mp = 162–165 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 6.38 (d, *J* = 8.8 Hz, 2 H), 6.26 (d, *J* = 8.8 Hz, 2 H), 5.79 (dd, *J* = 8.3, 1.0 Hz, 1 H), 5.74 (dd, *J* = 8.3, 0.9

Hz, 1 H), 0.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 163.9, 163.4, 162.3, 153.0, 137.4, 133.5, 130.7, 129.9, 128.6, 126.8, 126.5, 120.8, 111.9, 108.0, 10.6; IR (film) 3100, 2925, 2244, 1752, 1596, 1573, 1555, 1454, 1417, 1264, 1234, 1178, 1052, 1015, 903, 866, 787, 773, 717, 687, 557, 531 cm^{-1}; HRMS (ESI+) calcd for $C_{17}H_{11}ClN_3O_3$ $[M+H]^+$, *m/z* = 340.0484, found 340.0488.

General procedure E: S_NAr with phenol and aryl fluoride[43]: To a microwave reaction vial was added aryl fluoride (2.5 mmol), phenol (3.0 mmol), K_2CO_3 (7.5 mmol), and DMF (12.5 mL). The vial was sealed with a crimp cap and heated at 90 °C for 24-76 hours, after which it was cooled, and the mixture was diluted with 10 mL water and 30 mL EtOAc. The organic layer was separated, and the aqueous layer was extracted 3x with 10 mL EtOAc. The combined organic layers were washed 3x with 10 mL 5% LiCl, 1x with 10 mL 1 M NaOH, and 1x with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness.

2-(4-phenoxyphenyl)-1,3,4-oxadiazole (39a): A mixture of 4-phenoxybenzohydrazide (2.20 mmol) and tritethylorthoformate (10.9 mmol) was heated at 110 °C. After 12 h, the mixture was cooled to rt, and then concentrated by rotary evaporation. The excess triethyl orthoformate was removed by azeotropic distillation with toluene. Purification by column chromatography (eluent 1% MeOH in CH_2Cl_2 with 0.1 % trifluoroacetic acid) provided **39a** in (315 mg, 99% pure) in 58% yield as a white solid: ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (s, 1 H), 8.08 – 7.99 (m, 2 H), 7.46 – 7.36 (m, 2 H), 7.25 – 7.16 (m, 1 H), 7.13 – 7.03 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 161.0, 155.5, 152.4, 130.1, 129.0, 124.6, 120.1, 118.2, 117.8, 77.3, 77.0, 76.7; HRMS (ESI+) calcd for C14H10N2O2 $[M+H]^+$, m/z = 239.0820, found 239.0815.

2-(4-(3-Chloro-2-nitrophenoxy)phenyl)-1,3,4-oxadiazole (39b):The general diaryl ether synthesis procedure was followed using 4-(1,3,4)-oxadiazol-2-ylphenol (50 mg, 0.31 mmol), 2-chloro-6-fluoronitrobenzene (54 mg, 0.31 mmol), and 60% NaH in mineral oil (8.9 mg, 0.37 mmol) in DMF (1.5 mL). Purification by column chromatography (eluent 1% MeOH in CH_2Cl_2) provided **39b** in (27 mg, 99% pure) in 28% yield as a yellow solid: mp = 139–140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (s, 1 H), 8.16 – 8.07 (m, 2 H), 7.40 (t, *J* = 8.3 Hz, 1 H), 7.32 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.23 – 7.15 (m, 2 H), 6.99 (dd, *J* = 8.3, 1.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ; 164.0, 158.6, 152.6, 148.8, 131.4, 129.3, 126.7, 125.6, 120.1, 119.4, 119.1, 118.4; IR (film) 3078, 1588, 1542, 1495, 1458, 1424, 1268, 1238, 1219, 1197, 1178, 1149, 1104, 1074, 955, 940, 847, 814, 758, 739, 676, 633, 516 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_8ClN_3O_4$ $[M+H]^+$, *m/z* = 318.0277, found 318.0280.

2-Chloro-6-[4-(1,3,4-oxadiazol-2-yl)phenoxy]aniline (39c). To a stirred solution of 2-[4-(3-chloro-2-nitrophenoxy)phenyl]-1,3,4-oxadiazole 8b (89 mg, 0.3 mmol) and ammonium chloride (24 mg, 0.5 mmol) in DL-α-tocopherol methoxypolyethylene glycol succinate solution (TPGS-750-M) (0.65 mL, 2 wt. % in water) was added zinc dust (100 mg, 1.5 mmol). The resulting emulsion was stirred at room temperature for 6 h and then filtered through a 1 cm thick layer of silica gel using ethyl acetate as the eluent to afford compound **39c** as a white solid in 92% yield (80.6mg, 98% pure): mp = 102–103 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.48 (s, 1 H), 8.14 (d, *J* = 9.0 2 H), 7.46 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.40 (t, *J* = 8.2 Hz, 1 H), 7.20 (d *J* = 9.0, 2 H), 6.94 (dd, *J* = 8.3, 1.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 163.3, 160.2, 154.2, 141.1, 137.81, 128.8, 126.1, 120.0, 118.6, 117.4, 117.2, 116.3; IR (film) 3446, 3338, 3096, 3070, 1614, 1581, 1532, 1514, 1495, 1480, 1462, 1421, 1421, 1376, 1257, 1238, 1190, 1171, 1070, 940, 903, 847, 780, 743, 706, 642, 583, 519 cm-1; HRMS (ESI+) calcd for $C_{14}H_{10}ClN_3O_2$ $[M+H]$+, *m/z* = 288.0540, found 288.0544.

N-{2-chloro-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]phenyl}acetamide (39d): Prepared by general method B using 0.18 mmol acetic anhydride, 0.09 mmol 2-chloro-6-[4-(1,3,4-oxadiazol-2-yl)phenoxy]aniline, 0.27 mmol Et_3N, and 0.5 mL CH_2Cl_2. The crude product was purified by column chromatography (1-5% MeOH in CH_2Cl_2) to afford the title compound as a white solid in 44% yield (0.13 g, 96% pure): mp = 194–196 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1 H), 8.09 – 8.01 (m, 2 H), 7.31 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.23 (d, *J* = 8.1 Hz, 3 H), 7.11 (d, J = 8.7 Hz, 3 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 6.79 (s, 1 H), 2.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.2, 159.9, 152.6, 152.4, 146.5, 133.4, 129.1, 128.6, 126.9, 125.8, 119.1, 118.7, 118.4; IR (film) 3297, 3096, 1684, 1517, 1271, 1109, 707 cm^{-1}; $[M+H]^+$, calcd for $C_{16}H_{12}ClN_3O_3$ *m/z* = 330.0645, found 330.0649.

2-Bromo-6-[4-(1,3,4-oxadiazol-2-yl)phenoxy]benzonitrile (39e)[44]: To a room temperature stirred solution of 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (35μL, 99 μmol) in DMF (0.1 M) under a nitrogen atmosphere was added an 2-bromo-6-fluorobenzonitrile (0.66 mmol). The solution was allowed to stir for 2 min and then a 2-{4-[(tert-butyldimethylsilyl)oxy]phenyl}-1,3,4-oxadiazole (200 mg 0.72 mmol) was added. The reaction was then transferred to a preheated oil bath at 80°C and allowed to stir for 8-12 h. After allowing the mixture to cool to rt, the solution was poured into a saturated solution of brine (7 mL). After extracting with ether (15 mL), the organic layer was dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by column chromatography (50% EtOAc in hexanes) to yield the title compound as white solid in 80% yield (236 mg, 99% pure): ^{1}H NMR (Acetone-d_6, 400 MHz) δ 9.02 (s, 1 H), 8.19 (d, *J* = 9.0 Hz, 2 H), 7.71 – 7.61 (m, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 7.25 – 7.13 (m, 1 H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 163.9, 159.8, 158.0, 152.6, 134.5, 129.4, 128.0, 126.8, 120.4, 120.0, 116.7, 113.9. 108.6; IR (film) 2232, 1272, 1104 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_8BrN_3O_2$ $[M+H]^+$, *m/z* = 341.9878, found 341.9878.

2-[4-(3-Iodo-2-nitrophenoxy)phenyl]-1,3,4-oxadiazole (39f, CU-68): The general procedure E was followed using 4-(1,3,4)-oxadiazol-2-ylphenol (150 mg, 0.93 mmol), 1-fluoro-3-iodo-2-nitrophenol (247 mg, 0.93 mmol), and K_2CO_3 (381 mg, 2.8 mmol) in DMF (1.9 mL). Purification by column chromatography (eluent 1% MeOH:CH_2Cl_2) provided **39f** in (171 mg, 99% pure) in 45% yield as a white solid: mp = 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.14 – 8.05 (m, 2 H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.23 – 7.12 (m, 3 H), 7.05 (dd, *J* = 8.4, 1.1 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 164.2, 159.0, 152.8, 148.1, 135.4, 132.4, 129.4, 120.3, 120.1, 119.4, 118.6, 86.4; IR (film) 3145, 3070, 1588, 1521, 1495, 1454, 1413, 1365, 1260, 1238, 1216, 1193, 1167, 1111, 1070, 1018, 962, 948, 903, 869, 851, 784, 746, 713, 691, 657 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_8IN_3O_4$ $[M+H]^+$, *m/z* = 409.9638, found 409.9629.

1-(4-Nitrophenoxy)-3-(trifluoromethyl)benzene (40a)[45]: EtOH (10 mL), AcOH (3 mL) were added to a flask containing 3-(4-nitrophenoxy)-5-(trifluoromethyl)aniline (**32**) (0.149g, 0.5 mmol). NaNO2 (0.34 g, 5 mmol) in H_2O (3 mL) was added, followed by $NaHSO_3$ (0.52 g, 5 mmol) in 4 mL H_2O. The mixture was stirred at rt 8 hours, then concentrated under reduced pressure and the resulting residue was partitioned between 10 mL EtOAc and 10 mL H_2O. The aqueous layer was extracted twice with 10 mL EtOAc, and combined organic layers were washed 2x with 10 mL 1M NaOH, 1x with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness. Purified by column chromatography (0-40% CH_2Cl_2 in hexane) to afford the title compound as a yellow oil in 49% yield (69 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.22 (m, 2H), 7.60 – 7.49 (m, 2H), 7.36 (s, 1H), 7.28 (d, 1H), 7.08 – 7.03 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75; HRMS (ESI+) calcd for $C_{13}H_8F_3NO_3$ $[M+Li]^+$, *m/z* = 290.0616, found 290.0619.

1-Fluoro-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (40b)[46]: To a flame-dried flask was added boron trifluoride ethyl etherate (0.15 mL, 1.2 mmol) under nitrogen, then cooled to -15 °C. **32** (0.22g, 0.75 mmol) in CH_2Cl_2 (2 mL) was added, followed by dropwise addition of *tert*-butyl nitrite (0.11 mL, 0.9 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred for 10 minutes at -15 °C, then 15 minutes at rt, then diluted with hexane and filtered to isolate the aryl diazonium tetrafluoroborate salt as a white solid. After drying under a stream of air, the salt was mixed with sand to form a small cake which was placed into a small foil packet. The packet was placed into a beaker with an evaporating dish and ice setup on top, after which the beaker was placed on a hot plate set to maximum for 15 minutes, during which a solid appeared on the dish. The solid was collected and purified by column chromatography (0-35% CH_2Cl_2 in hexane) to afford the title compound as a pale yellow solid in 36% yield (81 mg): mp = 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.24 (m, 2H), 7.21 (d, *J* = 8.1, 1.6, 0.8 Hz, 1H), 7.18 – 7.07 (m, 3H), 6.99 (dd, *J* = 9.0, 0.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 162.2, 161.3, 157.0 (d, $^3J_{CF}$ = 10.7 Hz), 144.0, 134.1 (dq, $^2J_{CF3}$ = 9.6, 24.7 Hz), 126.4, 122.9 (dq, $^1J_{CF3}$ = 3.4, 273.8 Hz), 118.6, 112.8 (sep, $^4J_{CF3}$ = 3.7 Hz), 111.0 (dd, $^2J_{CF}$ = 1.0, 23.5 Hz), 109.6 (q, $^3J_{CF3}$ = 3.7, 7.5 Hz);

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.99, -106.50; IR (film) 3093, 1610, 1588, 1529, 1506, 1491, 1462, 1350, 1260, 1223, 1193, 1171, 1126, 1097, 996, 899, 877, 854, 758, 698, 523 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_7F_4NO_3$ $[M+H]^+$, *m/z* = 302.0440, found 302.0433.

1-Chloro-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (40c): Prepared by general method E with 2.4 mmol 3-chloro-5-(trifluoromethyl)phenol, 2 mmol 1-fluoro-4-nitrobenzene, 6 mmol K_2CO_3, and 8 mL DMF. Following purification by column chromatography (0-45% CH_2Cl_2 in hexane), the title compound was obtained as an oil in 98% yield (0.62 g): ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.36 – 8.29 (m, 2H), 7.67 (s, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 7.38 – 7.30 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 156.4, 144.0, 136.7, 134.0 (q, $^2J_{CF3}$ = 34.1 Hz), 126.4, 122.8 (q, $^1J_{CF3}$ = 274.1 Hz), 123.6 (d, $^4J_{CF3}$ = 1.0 Hz), 122.3 (q, $^3J_{CF3}$ = 3.8 Hz), 118.5, 115.4 (q, $^3J_{CF3}$ = 3.8 Hz);^{19}F NMR (376 MHz, Acetone) δ -63.4; IR (film) 3089, 1584, 1521, 1491, 1447, 1350, 1320, 1242, 1171, 1130, 1093, 948, 877, 854, 836, 802, 754, 694, 635 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_7ClF_3NO_3$ $[M+Li]^+$, *m/z* = 324.0227, found 324.0227.

1-Bromo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (40d): Prepared by general method **C** with 2.4 mmol 3-bromo-5-(trifluoromethyl)phenol, 2 mmol 1-fluoro-4-nitrobenzene, 6 mmol K_2CO_3, and 8 mL DMF. Following purification by column chromatography (0-45% CH_2Cl_2 in hexane), the title compound was obtained as a white solid in 97% yield (0.7 g, 97% pure): mp = 60–62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.24 (m, 2H), 7.63 (s, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 7.14 – 7.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 156.3, 144.0, 134.7, 134.3, 134.0, 133.7, 126.7, 126.5, 126.4, 125.19, 125.15, 125.12, 125.08, 124.0, 121.3, 118.4, 116.0, 115.94, 115.90, 115.86; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; IR (film) 3413, 3067, 3022, 2966, 1715, 1618, 1543, 1439, 1354, 1290, 1264, 1234, 1156, 1130, 981, 903, 873, 832, 780, 758, 698, 635 cm^{-1}; HRMS (ESI+) calcd for $C_8H_6FNO_4$ $[M+Li]^+$, *m/z* = 206.0441, found 206.0443.

1-Iodo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (40e)[47]: KI (0.332 g, 2 mmol), $NaNO_2$ (0.172 g, 2.5 mmol) in H_2O (3.5 mL) was added to a solution of TsOH monohydrate (0.86 g, 4.5 mmol) and **14** (0.298 g, 1 mmol) in MeCN (6 mL), then stirred at rt 3.5 hours. The reaction was quenched by addition of saturated $NaHCO_3$, then extracted 4x with 10 mL EtOAc. Combined organic layers were washed twice with 10 mL 1M NaOH, twice with 10 mL 1M $Na_2S_2O_3$, once with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness. Purified by column chromatography (0-60% CH_2Cl_2 in hexane) afforded the title compound as a yellow solid in 82% yield (0.33 g): mp = 82–84 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 – 8.24 (m, 2H), 7.82 (s, 1H), 7.60 (s, 1H), 7.31 (s, 1H), 7.11 – 7.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 155.9, 143.9, 134.2 (q, $^2J_{CF3}$ = 33.6 Hz), 132.2, 130.9 (q, $^3J_{CF3}$ = 3.9 Hz), 126.4, 122.4 (q, $^1J_{CF3}$ = 274.3 Hz), 118.3, 116.7 (q, $^3J_{CF3}$ = 3.7 Hz), 94.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.87; IR (film) 3111, 3082, 1577, 1514, 1491, 1439, 1316, 1238, 1167, 1130, 1111, 1093, 936, 858, 758, 691, 631 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_7INO_3$ $[M+H]^+$, *m/z* = 409.9501, found 409.9507.

3-(4-Nitrophenoxy)-5-(trifluoromethyl)phenol (40f)[48]: To a flame-dried vial was added 1-Iodo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene (**36e**) (0.20 g, 0.5 mmol), copper (I) iodide (0.027 g, 0.14 mmol), 1,10-phenanthroline (0.13 g, 0.7 mmol), and KOH (0.08g, 1.5 mmol). After backfilling with nitrogen 3x, 1 mL each of H_2O and DMSO degassed by sparging were added, and the mixture heated at 130 °C for 21 hours. At completion, the mixture was partitioned between 10 mL EtOAc and 10 mL H_2O, and the aqueous layer extracted 3x with 10 mL EtOAc. The combined organic layers were washed with 10 mL brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by column chromatography (0-30% EtOAc in hexane) to afford the title compound as a brown oil in 45% yield (65 mg): ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.52 (s, 1H), 8.36 – 8.26 (m, 2H), 7.31 – 7.21 (m, 2H), 7.06 (d, *J* = 2.2, 1.5, 0.7 Hz, 1H), 6.98 (s, 1H), 6.91 (s, 1H); ^{13}C NMR (101 MHz, Acetone) δ 163.0, 160.5, 157.6, 144.2, 133.5 (q, $^2J_{CF3}$ = 32.8 Hz), 126.8, 124.5 (q, $^1J_{CF3}$ = 272.9 Hz), 118.9, 111.6 (d, $^4J_{CF3}$ = 1.0 Hz), 109.8, 108.6 (q, $^3J_{CF3}$ = 4.0 Hz), 108.6 (q, $^3J_{CF3}$ = 4.0 Hz); ^{19}F NMR (376 MHz, Acetone) δ -63.4; HRMS (ESI-) calcd for $C_{13}H_8F_3NO_4$ $[M]^-$, *m/z* = 298.0327, found 298.0331.

3-(4-Nitrophenoxy)-5-(trifluoromethyl)pyridine (40g): 4-Fluoroanitrobenzene (3.1 mmol), 5-(trifluoromethyl)-pyridine (3.1 mmol), and K_2CO_3 (9.2 mmol) were dissolved in DMF (0.5 M). The reaction vessel was sealed and stirred at 120 °C. The reaction progress was monitored by TLC. After 24 h, the

mixture was cooled to rt and diluted with 5 mL EtOAc. The organic mixture was washed with 5% LiCl aq (5 x 5 mL) and then dried with Na_2S_4 to afford a yellow solid. The solid was purified by column chromatography (15% EtOAc:Hexanes) to afford the title product as a yellow solid in 63% yield (0.55 g): mp = 77 –78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.8 Hz, 1 H), 8.29 (d, *J* = 2.6 Hz, 1 H), 7.96 – 7.86 (m, 2 H), 7.26 (ddd, *J* = 2.6, 1.9, 0.7 Hz, 1 H), 6.80 – 6.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.2, 151.8, 145.7 (q, $^4J_{CF3}$ = 1.4 Hz), 144.2, 142.8 (q, $^3J_{CF3}$ = 4.1 Hz), 128.1 (q, $^2J_{CF3}$ = 33.8 Hz), 126.5, 122.9 (q, $^1J_{CF3}$ = 274.2 Hz), 124.0 (q, $^3J_{CF3}$ = 3.7 Hz), 118.3, ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2; IR (film) 3119, 3074, 1584, 1517, 1491, 1465, 1439, 1339, 1313, 1257, 1238, 1208, 1126, 1111, 1082, 1030, 977, 925, 858, 758, 717, 668, 627, 531, 512 cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_7F_3N_2O_3$ $[M+H]^+$, *m/z* = 285.0486, found 285.0489.

4-[3-Chloro-5-(trifluoromethyl)phenoxy]aniline (41a): Prepared by general method **E** with 1.8 mmol of 1-chloro-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene, 7.3 mmol Fe, 7 mL AcOH, and 7 mL EtOH. Following purification by column chromatography (0-100% CH_2Cl_2 in hexane), the title compound was isolated as an oil in 86% yield (0.47 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 1H), 7.06 – 7.01 (m, 2H), 6.91 – 6.84 (m, 2H), 6.75 – 6.68 (m, 2H), 3.68 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 146.8, 144.0, 135.8, 133.6 (q, $^2J_{CF3}$ = 33.4 Hz), 123.2 (q, $^1J_{CF3}$ = 273.9 Hz), 121.8, 120.1 (d, $^4J_{CF3}$ = 1.0 H), 118.9 (q, $^3J_{CF3}$ = 3.9 Hz), 116.5, 112.2 (q, $^3J_{CF3}$ = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; IR (film) 3245, 3085, 2977, 1588, 1506, 1450, 1378, 1327, 1283, 1264, 1264, 1238, 1175, 1126, 1093, 1052, 951, 869, 780, 758, 724, 702, 650, 631, 527, 512 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_9ClF_3NO$ $[M+H]^+$, *m/z* = 288.0403, found 288.0405.

4-[3-Bromo-5-(trifluoromethyl)phenoxy]aniline (41b): Prepared by general method **E** with 1.9 mmol of 1-bromo-3-(4-nitrophenoxy)-5-(trifluoromethyl)benzene, 7.7 mmol Fe, 7 mL AcOH, and 7 mL EtOH. Following purification by column chromatography (0-100% CH_2Cl_2 in hexane), the title compound was isolated as an oil in 92% yield (0.58 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.21 – 7.15 (m, 1H), 7.11 – 7.06 (m, 1H), 6.91 – 6.84 (m, 2H), 6.75 – 6.68 (m, 2H), 3.68 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 146.6, 143.9, 133.2 (q, $^2J_{CF3}$ = 33.4 Hz), 122.9 (q, $^1J_{CF3}$ = 274.0 Hz), 123.2, 122.8, 121.64, 121.62 ($^4J_{CF3}$ = 4.0 Hz), 116.4, 112.6 (q, $^3J_{CF3}$ = 3.8 Hz); IR (film) 3461, 3376, 3085, 1715, 1625, 1581, 1510, 1443, 1324, 1227, 1193, 1171, 1130, 1093, 944, 858, 836, 810, 698 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; HRMS (ESI+) calcd for $C_{13}H_9BrF_3NO$ $[M+H]^+$, *m/z* = 331.9898, found 331.9903.

3-[3,5-Bis(trifluoromethyl)phenoxy]aniline (41c)[49]: Trifluoroacetate protected 3-iodoaniline was prepared by mixing 3-iodoaniline (0.44 g, 2 mmol), ethyl trifluoroacetate (0.37 mL, 3 mmol), and MeCN (10 mL) with stirring at 50 °C overnight, then concentrated *in vacuo*. The residue was partitioned between 10 mL EtOAc and 10 mL H_2O, the organic layer extracted 3x with 10 mL EtOAc, and the combined organic layers were washed with 10 mL brine, dried over Na_2SO_4, and concentrated to yield 2,2,2-trifluoro-N-(3-iodophenyl)acetamide as a brown solid (0.59g, 94% crude). Then, a flame-dried vial containing 2,2,2-trifluoro-N-(3-iodophenyl)acetamide (0.32g, 1 mmol), CuI (0.06g, 0.3 mmol), N,N-dimethyl glycine hydrochloride (0.04g, 0.3 mmol) and cesium carbonate (0.81 g, 2.5 mmol) was backfilled with nitrogen 3x, then 3,5-bis(trifluoromethyl)phenol (0.23 mL, 1.5 mmol) and dioxane degassed by sparging (5 mL) were added. The mixture was stirred at 90 °C for 33 hours, then filtered through a pad of silica with 25 mL EtOAc, after which the EtOAc was successively washed with 5 mL each sat. bicarb, 10% aq. NH_3, brine, dried over Na_2SO_4 and concentrated to dryness. Following column chromatography (0-100% CH_2Cl_2/hexane), a mixture of protected and unprotected product was obtained. To this mixture, 2M NaOH (3 mL) and dioxane (4 mL) were added and the mixture heated at reflux for 2 hours. After solvent removal *in vacuo,* the residue was partitioned between 10 mL each EtOAc and H_2O, and the aqueous layer extracted 3x with 10 mL EtOAc. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness to afford the title compound as a white solid in 51% yield (0.16g): mp = 53–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 1H), 7.39 (s, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.55 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 6.42 (ddd, *J* = 8.0, 2.3, 0.9 Hz, 1H), 6.37 (t, *J* = 2.2 Hz, 1H), 3.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 156.2, 148.7, 133.2 (q, $^2J_{CF3}$ = 33.8 Hz), 125.8 (q, $^1J_{CF3}$ = 273.9 Hz), 119.0, 118.1 (d $^4J_{CF3}$ = 3.3 Hz), 116.1 (sep, 3JCF3 = 3.9 Hz), 112.0, 109.6, 106.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; IR

(film) 3458, 3376, 1629, 1610, 1588, 1495, 1465, 1372, 1279, 1126, 977, 888, 851, 791, 702, 683, 579, 549, 527 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_9F_6NO$ $[M+H]^+$, m/z = 322.0667, found 322.0668.

4-{[5-(Trifluoromethyl)pyridin-3-yl]oxy}aniline (41d): Iron powder (3.2 mmol) and **41g** (1.1 mmol) were weighed into a microwave vial. The reaction vessel was sealed with a Teflon cap and purged with N_2. Then degassed EtOH (1 M) and degassed glacial acetic acid (1 M) were added, and the solution was stirred at 100 °C. After 5 h, the mixture was cooled to rt and neutralized at 0 °C with saturated $NaHCO_3$ aq. The mixture was extracted with EtOAc (3x 1 mL) and washed with 5% LiCl aq solution (1 mL). The organic mixture was dried with Na_2SO_4, filtered, and concentrated by rotary evaporation to afford a tan solid. The solid was purified by column chromatography (20% EtOAc:Hexanes) to afford the title product as a white solid in 22% yield (59 mg): mp = 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.49 (m, 2 H), 7.35 (ddd, J = 2.7, 1.9, 0.7 Hz, 1 H), 6.94 – 6.86 (m, 2 H), 6.79 – 6.71 (m, 2 H); 13C NMR ($CDCl_3$, 101 MHz) δ; 155.3, 146.7, 143.3 (q, $^4J_{CF3}$ = 1.5 Hz), 139.6 (q, $^3J_{CF3}$ = 4.2 Hz), 127.2 (q, $^2J_{CF3}$ = 33.1 Hz), 121.8, 121. 76 (q, $^1J_{CF3}$ = 273.2 Hz), 121.3, 119.9 (q, $^3J_{CF3}$ = 3.6 Hz), 116.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3; IR (film) 3409, 3327, 3219, 3074, 2921, 1774, 1704, 1651, 1510, 1465, 1376, 1335, 1320, 1283, 1253, 1175, 1082, 1041, 1030, 1026, 981, 925, 892, 854, 836, 791, 758, 713, 683, 642, 627, 605, 579 cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_9F_3N_2O$ $[M+H]^+$, m/z = 255.0745 found 255.0745.

5-[3,5-Bis(trifluoromethyl)phenoxy]-2-nitroaniline (42): To a solution of 4-bromo-2-nitroanline and K_2CO_3 in DMF (0.5 M) was added 3,5-bistrifluoromethylphenol. The resulting solution was stirred at 120 °C. for 18 h. The reaction mixture was then cooled to rt and diluted with 30 mL of EtOAc. The organic mixture was washed with H_2O (3 x 10 mL) and 5% LiCl aq (3 x 20 mL). The mixture was then dried with Na_2SO_4, filtered and concentrated by rotary evaporation to afford an orange solid in 84% (4.2 g): mp = 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 9.1, 0.6 Hz, 1 H), 7.72 (tp, J = 1.5, 0.7 Hz, 1 H), 7.51 (dd, J = 1.6, 0.8 Hz, 2 H), 6.40 – 6.30 (m, 2 H), 6.20 (br s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 156.0, 146.7, 133.7 (q, $^2J_{CF3}$ = 34.1 Hz), 129.4, 129.0, 122.7 (q, $^1J_{CF3}$ = 274.0 Hz) ,120.2 (q, $^4J_{CF3}$ = 3.8 HZ), 118.3 (sep, $^3J_{CF3}$ = 3.8 Hz), 107.8, 105.6; IR (film) 3495, 3368, 1644, 1614, 1573, 1502, 1484, 1465, 1432, 1368, 1331, 1279, 1246, 1175, 1126, 1108, 981, 936, 888, 858, 758, 702, 687 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_8F_6N_2O_3$ $[M+H]^+$, m/z = 367.0517, found 367.0520.

4-[3,5-Bis(trifluoromethyl)phenoxy]-2-bromo-1-nitrobenzene (43)[50]: A solution of 5-[3,5-bis(trifluoromethyl)phenoxy]-2-nitroaniline (0.73 g, 2 mmol) and KNO_2 (0.681 g, 8 mmol) dissolved in DMSO (5 mL) was added dropwise a mixture of 48% HBr (1 mL) and DMSO (5 mL). The mixture was stirred at 35 °C for 35 minutes, then poured into K_2CO_3 (2.5 g) in 50 mL ice water. The mixture was extracted 3x with 10 mL Et_2O, then combined organic layers were washed with 10 mL brine, dried over Na_2SO_4 and concentrated to dryness. Purified by column chromatography (0-40% CH_2Cl_2 in hexane) to afford title product as a yellow solid in 71% yield (0.61 g): mp = 66–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 1 H), 7.76 (s, 1 H), 7.52 (s, 2 H), 7.38 (d, J = 2.6 Hz, 1 H), 7.05 (dd, J = 9.0, 2.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 157.5, 146.9, 134.3 (q, $^2J_{CF3}$ = 33.9 Hz), 129.9 (m, $^3J_{CF3}$ = 14.8 Hz), 128.9, 125.4 (t, $^4J_{CF3}$ = 2.8 Hz), 124.0 (q, $^1J_{CF3}$ = 273.4 Hz) 122.0, 120.0 (d, $^4J_{CF3}$ = 3.8 Hz), 119.6 (sep, $^3J_{CF3}$ = 7.2 Hz), 119.3, 116.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.96; IR (film) 3104, 2925, 1584, 1532, 1462, 1372, 1346, 1279, 1234, 1175, 1130, 1108, 1037, 959, 884, 828, 706, 683 cm^{-1}; HRMS (ESI-) calcd for $C_{14}H_6BrF_6NO_3$ $[M]^-$, m/z = 427.9357, found 427.9349.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Complete set of detailed procedures for virtual screening, biochemical cell-based assays, and chemical synthesis. Spectral data for chemical compounds is also included (PDF).

^{1}H NMR, ^{13}NMR, LC, HRMS, of compounds **1**–**7**, **14a**–**14m**, **15a**–**15e**, **16**–**19**, **27a**, **27b**, **28**–**30**, **39a**–**39f**. Protocols for virtual high throughput screen, secreted embryonic alkaline phosphatase (SEAP) assay, nitric oxide assay, interferon regulatory factor (IRF)-lucia assay, human TNF-α and IL-β enzyme-linked immunosorbent assay, TLR selectivity studies, and cytotoxicity studies (PDF)

Molecular formula strings (CVS)

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Author Contributions

The manuscript was written through the contributions of all authors. ‡R. P.-S. (design of project, synthesis, biochemical assays, interpretation of biochemical data and SAR data for **1** and **2** series) and R. A. (synthesis, assisted in biochemical assays, interpretation of biochemical data and SAR data for **1** series) contributed equally. S. Z. (conducted high throughput screen), C. J. (assisted in TLR and cytosolic NA sensor specificity studies for **CU-115**, **CU-72**, and **CU-68**) and P. N. (assisted in the synthesis of **2** targets and intermediates). All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

NA, nucleic acids; TLRs, Toll-like receptors; ssRNA, single-stranded RNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IFNs, type I interferons; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; TNF-α, Tumor Necrosis factor-alpha; R848, Resiquimod; IRAK 4, Interleukin-1 receptor-associated kinase 4; HTS, high throughput screen; SAR, structure-activity relationship; NO, nitric oxide; HEK293-BLUE cells human embryonic kidney cells; RIG-I, human or Ddx58 retinoic-acid-inducible protein 1 receptors; cGAS, cyclic AMP-GMP synthase; 3p-hpRNA, 5' triphosphate hairpin RNA; G3-YSD, Y-from DNA cGAS agonist; MAPK, mitogen-activated protein kinase; SEAP, secreted embryonic alkaline phosphatase; ELISA, enzyme-linked immunosorbent assay; IL-1β, interleukin 1 beta; S_NAr nucleophilic aromatic substitution; rt, room temperature; DMSO, dimethyl sulfoxide; DMF, dimethylformamide; TPGS-750-M, DL-α-tocopherol methoxypolyethylene glycol succinate solution; HATU, 1-[bis(dimethylamino)methylene]-*1H*,1,2,3-triazolo(4,5-b)pyridinium 3-oxid hexafluorophosphate; DIPEA, *N*,*N*-diisopropylethylamine; EDTA, ethylenediaminetetraacetic acid, LDA, lithium diisopropyl amide.

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