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Article

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Design and Activity of Specific Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitors for the Treatment of Clear Cell Renal Cell Carcinoma: Discovery of Clinical Candidate (*S*)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (PT2385)

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ABSTRACT

HIF-2α, a member of the HIF family of transcription factors, is a key oncogenic driver in cancers such as clear cell renal cell carcinoma (ccRCC). A signature feature of these cancers is the over accumulation of HIF-2α protein, often by inactivation of the E3 ligase VHL (von Hippel-Lindau). Herein we disclose our structure based drug design (SBDD) approach that

culminated in the identification of PT2385, the first HIF-2α antagonist to enter clinical trials. Highlights include the use of a putative n → π^*_{Ar} interaction to guide early analog design, the conformational restriction of an essential hydroxyl moiety, and the remarkable impact of fluorination near the hydroxyl group. Evaluation of select compounds from two structural classes in a sequence of PK/PD, efficacy, PK, and metabolite profiling identified **10i** (PT2385, Luciferase EC_{50} = 27 nM) as the clinical candidate. Finally, a retrospective crystallographic analysis describes the structural perturbations necessary for efficient antagonism.

INTRODUCTION

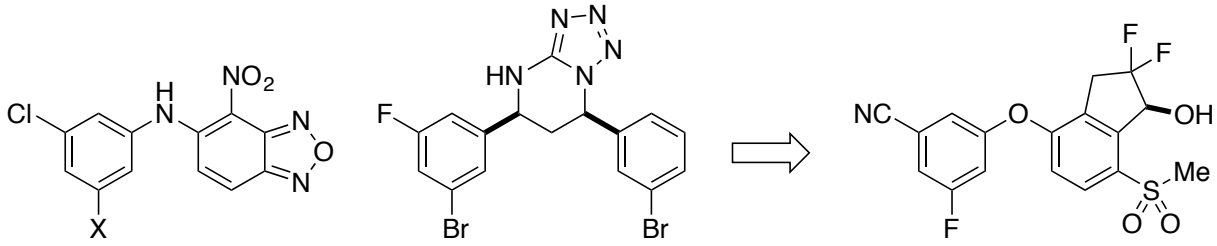
The hypoxia-inducible factor (HIF) family of transcription factors consists of HIF-1α[1], HIF-2α (EPAS1)[2,] and the less characterized HIF-3α[3]. Under normoxia, specific proline residues on the HIFα proteins are hydroxylated by the oxygen-dependent dioxygenase HIF-specific prolyl-hydroxylases (PHDs).[4,5] These post-translational modifications provide a mechanism to control transcriptional activity as they initiate the ubiquitin-proteasome degradation pathway by creating a substrate recognition site for von Hippel-Lindau protein (pVHL). pVHL is a tumor suppressor and part of an E3 ubiquitin-ligase complex that binds to the hydroxylated HIFα proteins, targeting them for proteasomal degradation. Under hypoxia, the PHD enzymes are inactive and, as a result, the HIFα proteins accumulate and translocate to the nucleus where they dimerize with the constituatively expressed aryl hydrocarbon receptor nuclear translocator (ARNT, also known as HIF-1β) to form an active transcription factor complex. Binding of the resulting HIFα-ARNT heterodimers to hypoxia-responsive elements (HRE) on target genes leads to the expression of hundreds of genes, many of which coordinately regulate anaerobic metabolism, angiogenesis, cell proliferation and survival, immune evasion,

extracellular matrix remodeling, pH homeostasis, amino acid and nucleotide metabolism, and genome stability.[6,7,8]

HIFα driven transcriptional activity has been implicated in many diseases including cancer[9], pulmonary arterial hypertension[10], iron overload[11] and inflammatory bowel disease[12]. Importantly, in clear cell renal cell carcinoma (ccRCC) HIF-2α activity has been demonstrated to be a key oncogenic driver. In ccRCC, *VHL* inactivation is found in more than 90% of patients, resulting in the accumulation and transcriptional activation of HIF-2α, even under normoxic conditions.[13] Several studies support the pathophysiological role of HIF-2α in ccRCC. Knockdown of HIF-2α expression in *VHL* defective ccRCC xenografts impedes tumor formation comparable to reintroduction of *VHL*[14] and overexpression of a stabilized variant of HIF-2α alone is adequate to overcome pVHL's tumor suppressive effect[15,16]. Significantly, the status of HIF-1α appears inconsequential in the course of ccRCC: HIF-1α is often deleted or mutated; and a stabilized variant of HIF-1α does not inhibit tumor suppression by pVHL.[17,18,19] This evidence implicates HIF-2α as the tumorigenic driver in ccRCC and suggests that HIF-2α antagonists could provide novel therapeutic intervention for its treatment.

The HIF-2α protein is a member of a larger family of transcription factors that contain a specific Helix-Loop-Helix-PAS-A-PAS-B fold (HLH-A-B). The pioneering work of Bruick and Gardner showed that the inner core of the PAS-B domain of HIF-2α possesses a water-filled hydrophobic cavity that can bind small molecules.[20] They also demonstrated that binding small molecule ligands in this pocket could disrupt the HIF-2α dimer complex with ARNT[21]. The ligands identified included two independent series; benzoxadiazole **1a** and tetrazole **2** (Figure 1)[22,23]. These analogs bound to the inner pocket with a Kd of 90 and 23 nM, respectively, based

on isothermal titration calorimetry analysis (ITC). Protein-inhibitor co-crystal structural determination of truncated HIF-2α and ARNT PAS-B domains[24] showed that the structurally distinct analogs both bound to the inner pocket of HIF-2α. Herein we describe the design and activity of specific, potent, orally bioavailable HIF-2α inhibitors that culminated in the discovery of PT2385; the first HIF-2α antagonist to enter clinical development.



1a: X = F, ITC K_d = 90 nM
cLogP = 3.99

1b: X = H, ITC K_d = 160 nM

2: ITC K_d = 23 nM
cLogP = 4.40

10i
(PT2385)

Figure 1. Literature HIF-2α inhibitors that formed the basis of SBDD efforts to identify PT2385

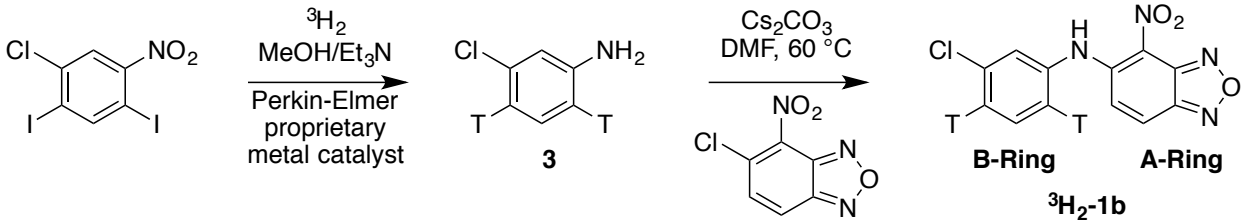
RESULTS AND DISCUSSION

Initial Inhibitor Design

To begin our own structure-based design effort to discover novel, potent and selective orally bioavailable HIF-2α antagonists it was necessary to develop a binding assay other than ITC, which is rather low throughput. We turned, instead, to a competitive binding assay with a radiolabeled ligand. Compound **1b**, a slightly less potent analog (160 nM) of benzoxadiazole **1a**, was labeled on the B-ring with two tritium atoms (Scheme 1) and a scintillation proximity assay (SPA) with the isolated PAS-B* domain of HIF-2α was developed and utilized to drive SAR. The HIF-2α PAS-B* domain is the R247E mutant. When combined with the ARNT PAS-B*

domain (E362R mutant), enhanced interfacial salt bridge interactions permit facile formation of the HIF-2α/ARNT heterodimer and enable crystallization studies where the wild-type fails.[20]

Scheme 1. Generation of radiolabeled HIF-2α inhibitor for the SPA Assay

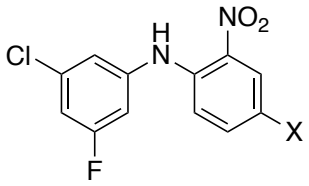


Although ligand binding is a necessary component to block the function of HIF-2α, it may not be sufficient. One can envision a scenario where a compound binds to the inner pocket of HIF-2α but does not sufficiently distort the protein to block dimerization with ARNT. Thus, functional assays were needed to establish that binding of compounds to the PAS-B domain of HIF-2α would block dimerization with ARNT and subsequent transcription of the downstream genes it regulates, thereby acting as true antagonists. For this, two cellular assays were utilized in the ccRCC cell line 786-O. 786-O is a VHL-mutant cell line with constitutively active HIF-2α and non-functional HIF-1α, thereby providing a well-defined cellular environment to evaluate specific HIF-2α activity. The first cell assay was a HIF-2α–driven HRE-dependent luciferase that provided good throughput for SAR support. The second cell assay was measurement of vascular endothelial growth factor A (VEGFA) secretion. VEGFA is a well-established target gene of HIF-2α in ccRCC and provided a physiological readout of cellular activity.

Analysis of the disclosed HIF-2α antagonists, **1a** and **2**, showed that the two aromatic rings were important for binding and occupied approximately the same space. Our starting point

for a structure based design effort focused on nitrobenzoxadiazole **1a**. Of the two hit classes it is less lipophilic with significantly lower molecular weight. Additionally, the highly-polarized nature of the nitrobenzoxadiazole heterocycle in **1a** lead us to our first hypothesis: that the low electron density of the nitrobenzoxadiazole was an important feature for binding by enhancing a potential n $\rightarrow \pi^*_{Ar}$ interaction[25] between a tyrosine oxygen lone pair and the benzoxadiazole.

Table 1. Replacements to the benzoxadiazole



	X	SPA IC_{50} (μM)	σ_p [a]
4a	SO_2CF_3	<0.005	0.96(78)
4b	SO_2CHF_2	0.016 ± 0.009	0.86(106)
4c	SO_2CH_2F	0.28 ± 0.11	-
4d	SO_2NHMe	4.2 ± 1.3	0.65(233)[b]
4e	CF_3	0.28 ± 0.10	0.54(70)
4f	CH(OH)Me	12.7 ± 4.6	-0.07(222)
1a	-	0.49 ± 0.16	-

[a]σ_p values as found in table 1 from reference 27. The number in parentheses denotes the line where the σ_p value can be found. [b]Data for $-SO_2NMe_2$.

Examination of the published protein co-crystal structure of **1a** in HIF-2α PAS-B domain[26] revealed an electrostatic contact of 3.32 Å between the phenolic oxygen of Tyr281 and the centroid of the benzene portion of the benzoxadiazole heterocycle which was well within the 2.8–3.8 Å distance reported for $n \rightarrow \pi^*_{Ar}$ interactions[25]. A variety of groups replacing the oxadiazole portion at the 4-position were tested and found to corroborate the initial hypothesis: the greater the electron deficiency[27] of the replacement, the better the binding (Table 1). *N*-(3-chloro-5-fluorophenyl)-2-nitro-4-((trifluoromethyl)sulfonyl)aniline **4a**, with the largest electron deficiency in this group, significantly improved binding affinity to < 5 nM. Other sulfone analogs with less fluorination (**4b** and **4c**), hence reduced electron deficiency, showed intermediate binding affinity between **4a** and **1a**. In addition, the methyl sulfonamide (**4d**), trifluoromethyl (**4e**) and alcohol (**4f**) replacements showed reduced affinity. Examination of the co-crystal structure of **4a** (Figure 2) supported the importance of the electrostatic interaction between Tyr281 and the antagonist (3.46 Å), and also revealed that the trifluoromethylsulfone moiety can twist out of the plane and fill a relatively small hydrophobic patch in the protein. This new interaction likely contributed to the high binding affinity of **4a**.

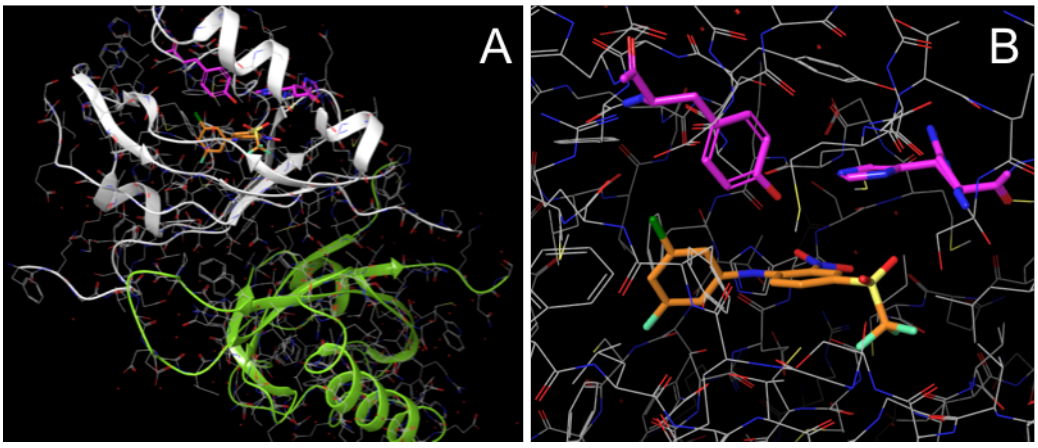
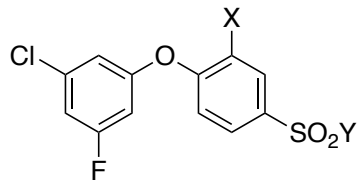


Figure 2. (A) X-ray crystal structure of **4a** (orange) in complex with the HIF-2α PAS-B* (white)/ARNT PAS-B* (green) dimer (PDB:6D0B). (B) Close up view of **4a** in the HIF-2α binding pocket with Tyr281 and His293 highlighted (magenta).

The increased affinity of **4a** afforded the opportunity to replace the metabolically problematic aniline moiety with an aryl ether (Table 2). In contrast to the reported SAR on **1a**[22], aryl ether replacement of the aniline was tolerated with only a modest loss in potency (**5a**). Evaluation of the SAR of the A-ring 2-position showed that the undesirable nitro moiety could be replaced. Binding affinity was retained with small electron-withdrawing groups at this position (**5b**, **5c**, **5d**, **5h**). Importantly, several of these analogs were active in cells with micromolar potency in the luciferase assay indicating functional activity. **5h** stood out, showing a nominal shift between the binding and cell assays. Larger, more hydrophilic analogs were detrimental to binding even though some were electron-withdrawing (compounds **5e**, **5f**, **5g**). Compound **5i** with one charged group was completely inactive. Modifications to examine lipophilicity included replacement of the trifluoromethylsulfone with a difluoromethylsulfone (**5j**) and methylsulfone (**5k**). While **5j** showed a comparable binding affinity to **5b**, the cLogP improved by more than one unit and the shift in the cell based assay was smaller. Despite further improvement in lipophilicity for **5k**, the decreased electron withdrawing potential of the methylsulfone proved deleterious to binding affinity.

Table 2. SAR for the replacement of the nitro group

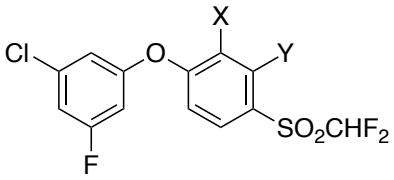


	X	Y	SPA IC_{50} (μM)	Luciferase EC_{50} (μM)	cLogP
5a	NO_2	CF_3	0.032 ± 0.002	-	5.03
5b	Br	CF_3	0.17 ± 0.07	3.7 ± 1.1	6.20
5c	Cl	CF_3	0.14 ± 0.06	3.4 ± 1.3	6.05
5d	CN	CF_3	0.034 ± 0.006	11.6 ± 3.4	5.00
5e	CO_2Me	CF_3	52.9 ± 15.3	-	5.29
5f	$CONH_2$	CF_3	22.6 ± 12.6	-	4.01
5g	CH_2OH	CF_3	1.2 ± 0.5	-	4.53
5h	CHF_2	CF_3	0.22 ± 0.04	0.24 ± 0.10	5.76
5i	CO_2H	CF_3	44.4 ± 7.3	-	4.88
5j	Br	CHF_2	0.18 ± 0.05	2.2 ± 0.4	5.03
5k	Br	Me	4.4 ± 0.4	-	4.09

Next, we turned to the 3-position of the A-ring as a variety of crystal structures, both apo form and those in complex with different ligands, indicated a degree of flexibility for His293 and Met252 sidechains. Based on this observation we hypothesized that installation of larger and possibly more hydrophilic substituents could be incorporated into our inhibitors. A series of tetra-substituted A ring analogs were thus prepared (Table 3). This area of the protein was not as tolerant as our structural analysis predicted, with many analogs resulting in weakly active compounds. Introduction of an amino methylene at the 3-position (**6a**) was poorly tolerated and acylation of the amino group (**6b**) ablated the remaining binding affinity. A very important

finding, however, was that benzyl alcohols **6c** and **6d** were active with improved potency to the unsubstituted compound **5j**. These derivatives have a smaller shift from binding to luciferase cell activity and have reduced lipophilicity. Interestingly, methylation of the hydroxyl (**6e**) dropped the binding affinity two orders of magnitude highlighting the importance of the alcohol moiety to binding. To get a better understanding of the interactions of the benzyl alcohol, compound **6c** was co-crystalized with HIF-2α and the key interactions are shown in Figure 3.

Table 3. SAR for the introduction of hydrophilic substituents



	X	Y	SPA IC_{50} (μM)	Luciferase EC_{50} (μM)	cLogP
6a	Br	CH_2NH_2	0.70 ± 0.10	-	3.99
6b	Br	CH_2NHAc	18.2 ± 9.4	-	3.84
6c	Br	CH_2OH	0.055 ± 0.023	0.33 ± 0.14	4.00
6d	Cl	CH_2OH	0.046 ± 0.018	0.38 ± 0.07	3.85
6e	Cl	CH_2OMe	4.2 ± 2.9	-	4.68

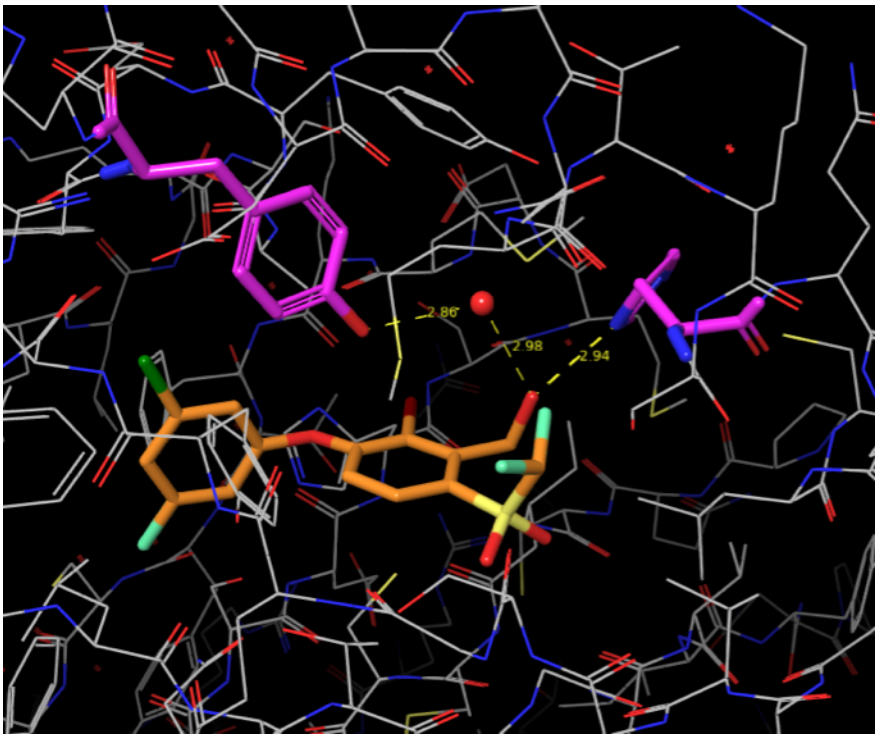
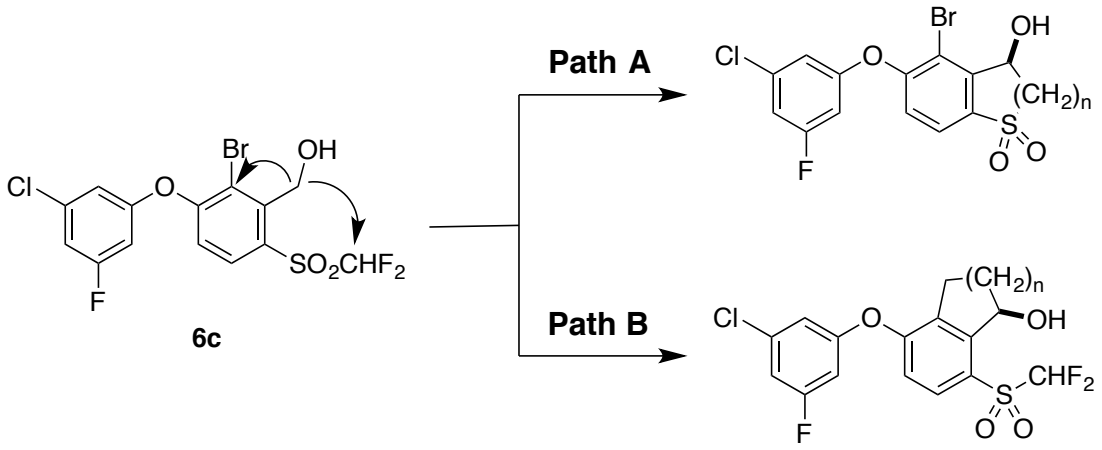


Figure 3. Close up view of X-ray crystal structure of **6c** (orange) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer (PDB:6CZW). Tyr281 and His293 are highlighted (magenta). Dotted lines indicate hydrogen bond interactions and the red sphere denotes a water molecule.

Compound **6c** bound to the inner cavity of HIF-2α as expected, however, the hydroxyl group participated in a unique H-bonding network between Tyr281, a water molecule, and His293. The other interesting observation was that the difluoromethyl group rotated 180 degrees away from the lipophilic patch discussed earlier. Initially, we thought that the difluoromethyl sulfone rotated in order to make potential dipole interactions with the surrounding environment much like a hydrogen bond.[28] However, a close analysis of the X-ray for **6c** showed potential contacts were too distant and that the most likely explanation for the differeing orientations of the sulfones in **4a** and **6c** is sterics. A consequence of the new sulfone orientation is a slight elongation (3.55 Å) of the Tyr281 contact to the aromatic system of the A-ring.

In addition to providing a lead with more favorable physical properties, the rigid hydrogen-binding network formed between alcohol **6c** and HIF-2α PAS-B domain may contribute to the observed enhancement in functional activity of the antagonist. Furthermore, the interactions of the primary alcohol inspired analog designs that constrained this moiety in the desired binding mode, thereby alleviating the entropic penalty incurred to adopt the preferred conformation. These designs led to two novel cyclic secondary alcohol scaffolds highlighted in Scheme 2. Cyclic sulfone derivatives arose from Path A whereas Path B yielded carbocyclic alcohol analogs. A consequence of the proposed inhibitor designs would be a strong dependence of potency on alcohol stereochemistry.

Scheme 2: Two paths (A and B) to constrain rotation of the benzyl alcohol

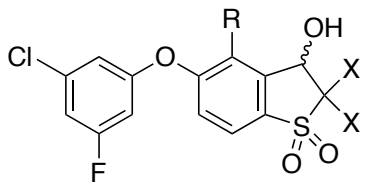


Path A: Development of SAR for the cyclic sulfone Scaffold

Evaluation of the initial 5-membered cyclic sulfone **7a** (a 2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide) proved disappointing with SPA potency 40-fold less than the parent benzyl alcohol **6c** (Table 4). Despite the discouraging start, our familiarity with the SAR of the earlier non-cyclized compounds suggested that modulation of the benzene by installation of electron withdrawing groups could increase potency. The first attempt at modulation was to install

geminal fluorine substitution alpha to the sulfone. Not only would such a modification impart decreased electron density at the benzene ring, it would be the most isoelectronic with benzyl alcohol **6c**. Gratifyingly, introduction of fluorine increased potency in dramatic fashion (**7b**). The magnitude of the increase, >100 fold in luciferase cell assay, suggested that the fluorine atoms were acting as more than just electron withdrawing groups. Comparing potency of earlier uncyclized analogs methyl sulfone **5k** and difluoromethylsulfone **5j** (Table 2), the increase in potency from fluorination was only 20-fold.

Table 4. Initial SAR of the cyclic sulfone scaffold



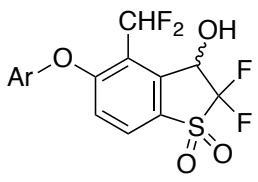
	R	X	SPA IC_{50} (μM)	Luciferase EC_{50} (μM)
7a	Br	H	2.4 ± 1.5	7.2 ± 3.8
7b	Br	F	<0.005	0.043 ± 0.011
7c	Br	Me	19.6 ± 3.9	-
7d	Cl	F	0.020 ± 0.005	0.11 ± 0.03
7e	Me	F	0.020 ± 0.013	0.34 ± 0.10
7f	CN	F	0.049 ± 0.017	9.2 ± 4.9
7g	H	F	1.1 ± 0.7	-
7h	CF_3	F	<0.005	0.10 ± 0.03
7i	CHF_2	F	<0.005	0.017 ± 0.023
7j	-	-	3.2 ± 1.8	-

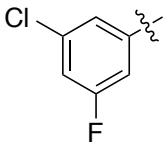
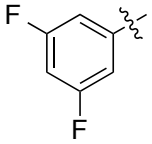
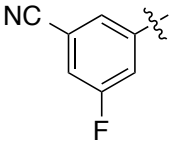
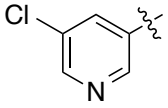
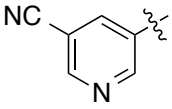
Recent literature on the impact of alpha fluorine atoms on neighboring alcohols suggest that in addition to influencing alcohol pK_A, the fluorine atoms may engage in intramolecular C−F···H−O electrostatic interactions (controversially, hydrogen bonds) that shield and restrict interactions with the larger environment.[29] Quantum chemical calculations of constrained 3- and

2-fluorocyclohexanol derivatives indicate a distinct preference for conformers of the alcohol O-H that locate the proton in the vicinity of the fluorine atom.[30] Experimentally, such speculation is furthered by the observation of ^{19}F coupling to the alcohol proton in ^{1}H NMR of these constrained fluorocyclohexanol derivatives.[30] In the hydrophobic binding pocket of the HIF-2α protein, the suggested electrostatic interactions imparted by fluorine could directly influence the localized solvent shell surrounding the hydroxyl moiety and reduce the desolvation penalty required for ligand binding and thereby enhance potency. Regardless of the exact contributions of the fluorine atoms, their positive impact was clear. Supporting electron withdrawing effects as the explanation for potency enhancement with fluorination, methylation ablated activity (**7c**) potentially suggesting additional detrimental steric interactions with the protein.

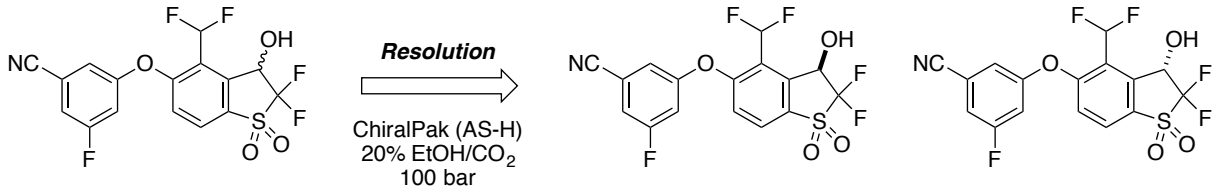
Exploration of the 2-position of the A-ring demonstrated several substituents were tolerated with $–CHF_2$ (**7i**) affording the best potency (Table 4). The impact of ring expansion to the six-membered cyclic sulfone ring was also examined and determined to be deleterious (**7j**). A focused evaluation of the B-ring SAR identified 3-cyano-5-fluorophenyl (**8b**) as providing the best balance of cellular activity and lipophilicity (Table 5). The dihalogenated B-rings in **7i** and **8a** showed excellent celluar activity, but with increased lipophilicity. The pyridine derivatives **8c** and **8d** reduced lipophilicity, however, cellular activity suffered. Separation of the enantiomers of the most promising cyclic sulfone, **8b**, confirmed our speculation that binding and cellular activity should reside in one stereoisomer (Scheme 3). X-ray crystal structure of the active enantiomer **9a** (Figure 4) recapitulated the binding features of benzyl alcohol **6c** (Figure 3). Interestingly, the phenol of Tyr281 achieved a closer contact with the aromatic system of the A-ring of **9a** than **6c**, realizing a distance of 3.30 Å to the centroid.

Table 5. SAR of the aryloxy moiety



	Ar	SPA IC_{50} (μM)	Luciferase EC_{50} (μM)	cLogP
7i		<0.005	0.017 ± 0.023	4.89
8a		0.011 ± 0.003	0.013 ± 0.002	4.32
8b		0.014 ± 0.003	0.032 ± 0.012	3.61
8c		0.35 ± 0.26	0.63 ± 0.31	3.34
8d		0.14 ± 0.07	0.18 ± 0.02	2.17

Scheme 3: Resolution of racemic **8b** and testing of both enantiomers



8b
SPA IC_{50} = 0.014 ± 0.003 μM
Luciferase EC_{50} = 0.032 ± 0.012 μM

9a (99% ee)
SPA IC_{50} = <0.005 μM
Luciferase EC_{50} = 0.010 ± 0.005 μM

9b (99% ee)
SPA IC_{50} = 1.7 ± 0.6 μM

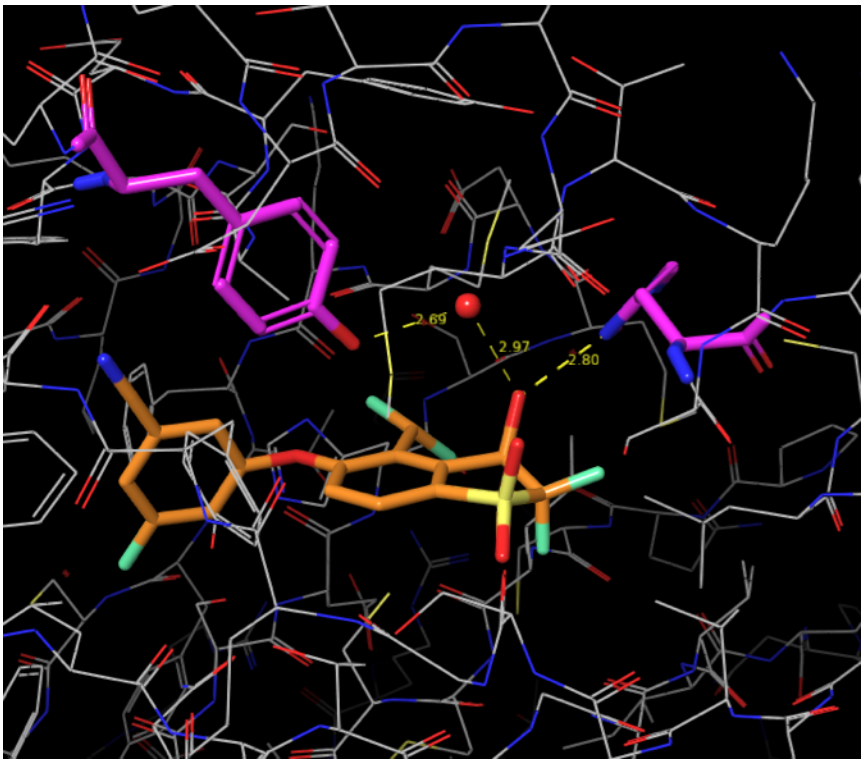


Figure 4. Close up view of X-ray crystal structure of **9a** (orange) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer (PDB:6D09). Tyr281 and His293 are highlighted (magenta). Dotted lines indicate hydrogen bond interactions and the red sphere denotes a water molecule.

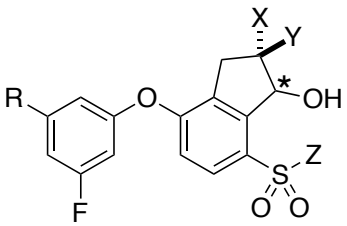
Path B: Development of SAR for the carbocyclic alcohol scaffold

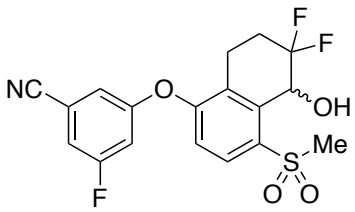
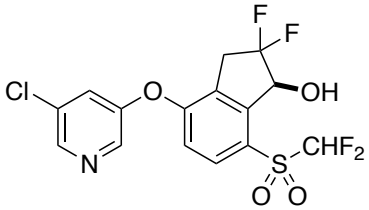
Additional efforts to constrain the benzyl alcohol of compound **6c** involved utilizing 5-member ring indane derivatives represented in Scheme 2 as Path B, where n=1. The initial evaluation of the unsubstituted indanol isomer (**10a**) demonstrated that this scaffold can achieve significant binding affinity and reasonable functional activity (Table 6). Evaluation of single enantiomers **10b** and **10c** showed activity residing in one stereoisomer as observed with the cyclic sulfone scaffold. Installation of a geminal difluoro group (**10d**) resulted in a nearly 10-fold improvement in potency. While not as dramatic as the >100-fold improvement observed in the cyclic sulfone series, fluorination improved the indanol series to pharmacologically relevant

potencies. The differing impact of fluorination between the cyclic sulfone and indanol scaffolds could reflect the possibility of dual roles in the cyclic sulfone scaffold and a singular effect in the indanol. In the cyclic sulfone scaffold, fluorination can enhance the electron-withdrawing capacity of the sulfone and alter the environment of the alcohol through electrostatic interactions with the adjacent fluorine. By contrast, the indanol (**10d**) already has fluorination at the sulfone moiety and the installation of fluorine adjacent to the alcohol primarily impacts the electrostatic interactions of the alcohol. Comparison of indanol **10a** and cyclic sulfone **7a** (Table 4) further illustrates this point. As observed in the cyclic sulfone scaffold, replacement of the chloro group with cyano (**10e**) on the B-ring was well tolerated for the indanol series.

Unlike the cyclic sulfone series where fluorination of the sulfone proved essential, imparting both electrostatic interactions with the alcohol and inductive effects on the phenyl ring, the potency enhancement of the difluoro-indanol allowed independent evaluation of the sulfone substitution. As expected, increased fluorination of the sulfone increased potency, with the trifluoromethyl sulfone (**10g**) exhibiting single-digit nanomolar potency in cells (Table 6). However, the increased fluorination also significantly increased the lipophilicity. It is important to highlight that whereas the methyl sulfone (**10i**) was the least potent in this sub-series, with an EC_{50} of 27 nM in cells, it demonstrated a desirable balance of properties with cLog P < 2. Monofluoro indanols were also investigated. The cis-fluorohydrin (**10k)** retained significant activity, whereas the trans-fluorohydrin (**10l**), with enhanced acidity of the alcohol and unable to engage in intramolecular C−F···H−O interactions, was significantly less potent. Finally, ring expansion to the six-membered ring (**10m**) resulted in a substantial loss of binding.

Table 6. SAR of the indanol scaffold



R	X	Y	Z	SPA IC_{50} (μM)	Luciferase EC_{50} (μM)	cLogP
(±)-10a	Cl	H	H	CHF_2	<0.005	0.18 ± 0.05	3.78
(*R*)-10b	Cl	H	H	CHF_2	<0.005	0.11 ± 0.01	3.78
(*S*)-10c	Cl	H	H	CHF_2	0.46 ± 0.08	2.9 ± 0.7	3.78
(±)-10d	Cl	F	F	CHF_2	<0.005	0.020 ± 0.003	4.06
(±)-10e	CN	F	F	CHF_2	0.010 ± 0.003	0.015 ± 0.001	2.78
(*S*)-10f	CN	F	F	CHF_2	<0.005	0.006 ± 0.001	2.78
(*S*)-10g	CN	F	F	CF_3	<0.005	<0.005	3.95
(*S*)-10h	CN	F	F	CH_2F	<0.005	0.009 ± 0.003	2.01
(*S*)-10i	CN	F	F	Me	0.012 ± 0.005	0.027 ± 0.006	1.84
(*S*)-10j	CN	F	F	Et	0.031 ± 0.015	0.088 ± 0.036	2.37
(1*S*,2*R*)-10k	CN	H	F	Me	0.041 ± 0.007	0.039 ± 0.021	1.39
(1*S*,2*S*)-10l	CN	F	H	Me	0.35 ± 0.03	0.49 ± 0.04	1.39
 **(±)-10m**	-	-	-	-	3.6 ± 1.3	-	2.40
 **(*S*)-10n**	-	-	-	-	0.060 ± 0.048	0.065 ± 0.031	2.42

X-ray co-crystal structure of **10i** (Figure 5) revealed an identical interaction paradigm with earlier alcohol analogs. Interestingly, the methyl sulfone moiety maintained a similar orientation as the difluoromethyl sulfone moiety in **6c** (Figure 3) and suggested that the original trifluoromethyl sulfone lead, **4a** (Figure 2), adopted the opposite orientation due to unfavorable contacts in this region. Lastly, Tyr281 maintains a contact with aromatic portion of the A-ring in **10i**, albeit elongated relative to cyclic sulfone **9a**, at 3.53 Å from the centroid.

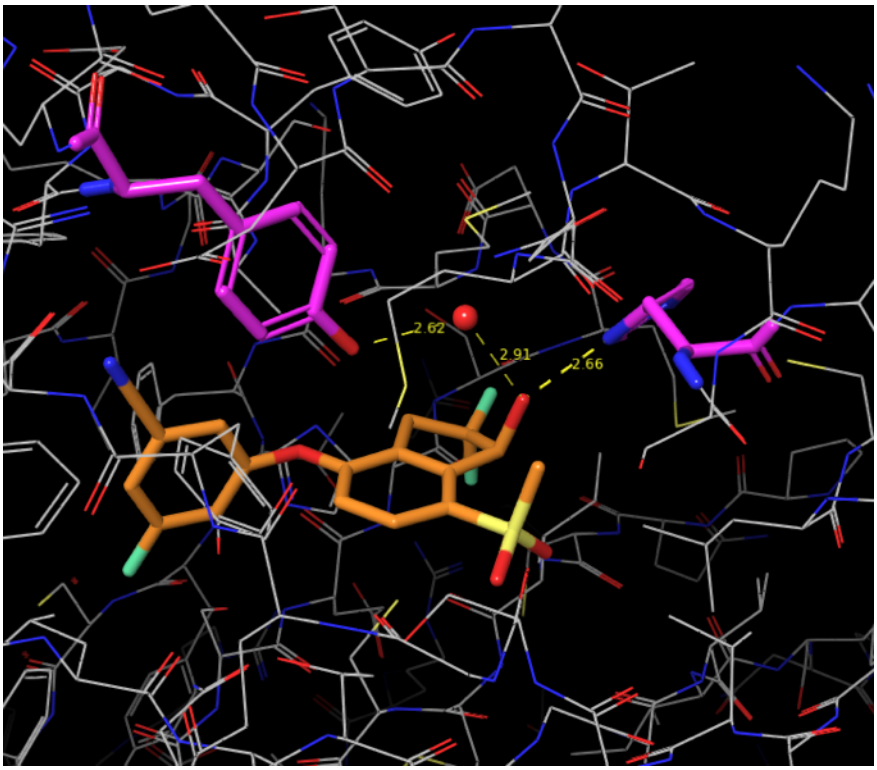


Figure 5. Close up view of X-ray crystal structure of **10i** (orange) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer (PDB:5TBM, pink). Tyr281 and His293 are highlighted (magenta). Dotted lines indicate hydrogen bond interactions and the red sphere denotes a water molecule.

Pharmacokinetic (PK), Pharmacodynamic (PD), and *In Vivo* Efficacy of Select Inhibitors

Based on potency and lipophilicity, four indanols and one cyclic sulfone were selected for further evaluation. Initial evaluation included potency in cellular VEGFA secretion assay, permeability, mouse microsomal stability, plasma protein binding and mouse pharmacokinetics (Table 7). While **10i** was the least potent compound in this group in the VEGFA secretion assay with an EC_{50} of 41 nM, the free-fraction adjusted cell EC_{50} was comparable to **9a**, **10f** and **10h** due to its lower lipophilicity and significantly decreased plasma protein binding. All five compounds exhibited good mouse oral bioavailability and low to medium *in vivo* clearance as predicted by high cell permeability and good microsomal stability.

Table 7. Functional cell activity and mouse PK parameters for select inhibitors

Compound	9a	10f	10h	10i	10n
VEGFA EC_{50} (nM)	16 ± 2	14 ± 4	20 ± 5	41 ± 12	37 ± 24
mouse PPB (%)	89	94	89	74	94
Free Fraction adjusted EC_{50} (nM)	145	233	182	158	617
12h plasma concentration (μM)	0.22	0.38	1.10	0.46	0.56
CL_{int} mouse (mL/min/kg)	5.9	32.2	26.9	19.9	20.1
P_{app} A→B (nm/s)	26	28.4	27.3	29.8	27.9
B→A/A→B ratio	0.82	0.63	1.04	0.91	0.83
CL[a] (mL/min/kg)	70.6	34.3	32.3	29.2	58.2
$AUC_{0\text{-}t}$[b] (hr*μM)	6.1	7.30	9.46	16.43	5.44
V_{SS}[a] (L/kg)	9.5	7.4	12.6	7.0	25
$t_{1/2}$[b] (h)	6.5	7.3	5.5	3.3	5.3
%F[b]	110	67	91	110	101

[a] 3 mg/kg intravenous dose (solution in 20% EtOH, 40% PEG400, 40% water) in male CD1 mice (n = 3/time point, 27 total). [b] 10 mg/kg oral dose (suspension in 10% EtOH, 30% PEG400, 60% (0.5% methylcellulose, 0.5% Tween 80 (aq)) in male CD1 mice (n = 3/time point, 24 total).

All analogs were progressed into pharmacokinetic/pharmacodynamic (PK/PD) study in the 786-O mouse xenograft model at an oral dose of 10 mg/kg on a twice daily schedule. Endpoints in the 36h PK/PD study were obtained 12h post final dose and included analysis of HIF-2α-ARNT transcriptional products VEGFA and cyclin D1 (CCND1) in excised tumors by qPCR and evaluation of circulating levels of human tumor-derived VEGFA in serum by ELISA. Plasma drug concentrations were determined by LC/MS/MS. Four of the analogs potently

inhibited HIF-2α-driven gene transcription in tumor as well as completely abolishing circulating human tumor-derived VEGFA (Figure 6). In contrast, **10n** had minimal to no effect on these endpoints in the experiment. Examination of the drug concentrations showed that the four active analogs all achieved trough (12 h) levels well-above the free-fraction adjusted VEGFA cell potency, but that **10n** did not.

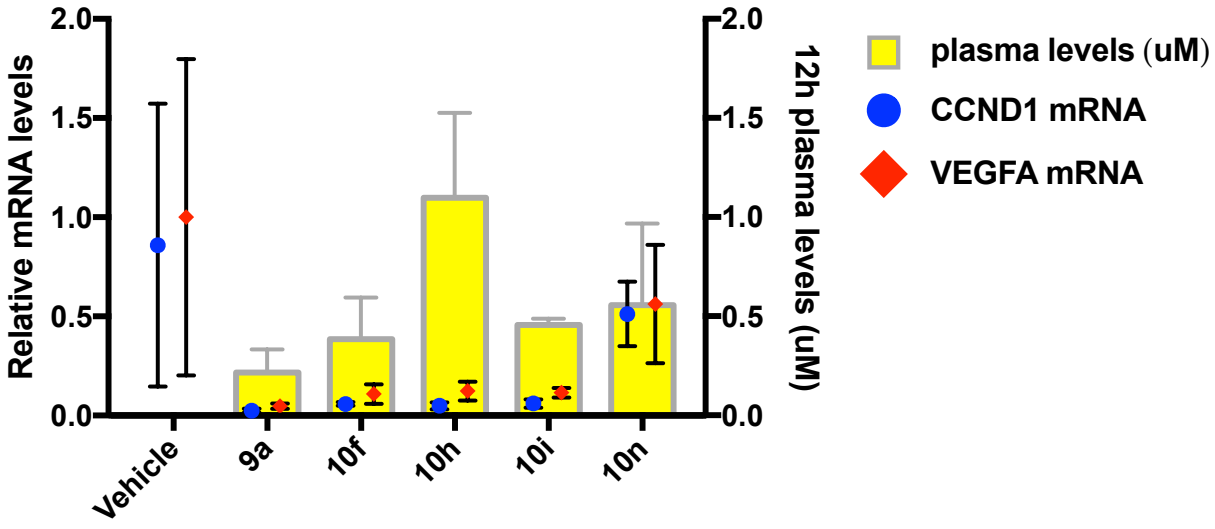


Figure 6. PK/PD evaluation of five leads in 786-O mouse xenograft (female SCID/beige mice, n=4) dosed at 10 mg/kg *p.o., b.i.d.* for three days to achieve steady-state exposure). Tumors were harvested 12 hours after administration of the final dose and total RNA was isolated from the tumor samples and used to make single-stranded cDNA. The resulting cDNA was used in quantitative PCR reactions; mRNA levels were normalized to internal control cyclophilin B mRNA levels in each sample.

All five analogs were also examined in 786-O mouse xenograft tumor growth study. In good agreement with the PK/PD, four analogs were efficacious with rapid regression of

established tumors, whereas **10n** was essentially inactive (Figure 7). Importantly, no morbidity or mortality was observed with treatment and all the leads showed a negligible impact on body weight (see Supporting Information).

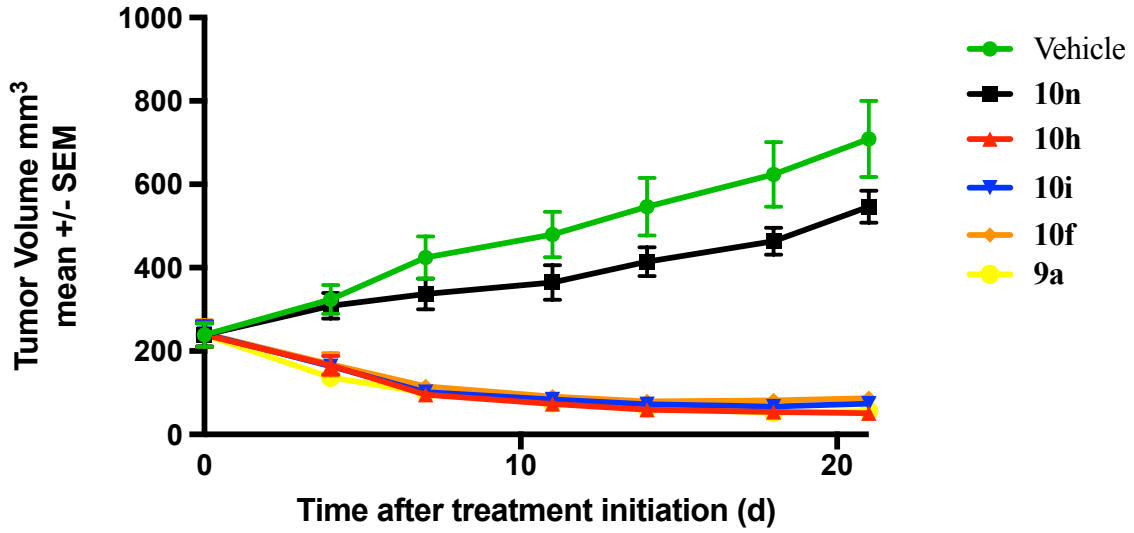


Figure 7. *In vivo* efficacy study of five leads in 786-O xenografts (female SCID/beige mice, n=8). Decrease in tumor volume in SCID mice with established sub-cutaneous 786-O tumors that were treated orally with twice-daily administration of Hif-2α antagonists (10 mg/kg, *p.o, b.i.d.*) for 21 days.

The four active analogs were evaluated in rat pharmacokinetics where **9a** and **10i** demonstrated exposure profiles suitable for advancement into higher species, while, in contrast, the profiles of **10f** and **10h** were deemed inadequate for progression. Both **9a** and **10i** performed well in dog pharmacokinetics (Table 8).

Table 8. Rat and dog PK parameters for select inhibitors

Species	Compound	CL[a] (mL/min/kg)	AUC_{0-t}[b] (hr*μM)	V_{SS}[a] (L/kg)	$t_{1/2}$[b] (h)	%F[b]
Rat	**9a**	27.2	5.49	3.5	3.7	36
	10f	57.7	0.39	5.55	5.4	6
	10h	57.6	2.14	6.15	2.9	32
	10i	34.6	5.12	6.24	3.3	40
Dog	**9a**	9.8	12.6	3.1	6.7	72
	10i	21.5	6.2	8.6	11.0	87

[a] 3 mg/kg intravenous dose (solution in 20% EtOH, 40% PEG400, 40% water) in male Sprague-Dawley rats (n = 3) or male beagles (n = 3). [b] 10 mg/kg oral dose (suspension in 10% EtOH, 30% PEG400, 60% (0.5% methylcellulose, 0.5% Tween 80 (aq)) in male Sprague-Dawley rats (n = 3) or male beagles (n = 3).

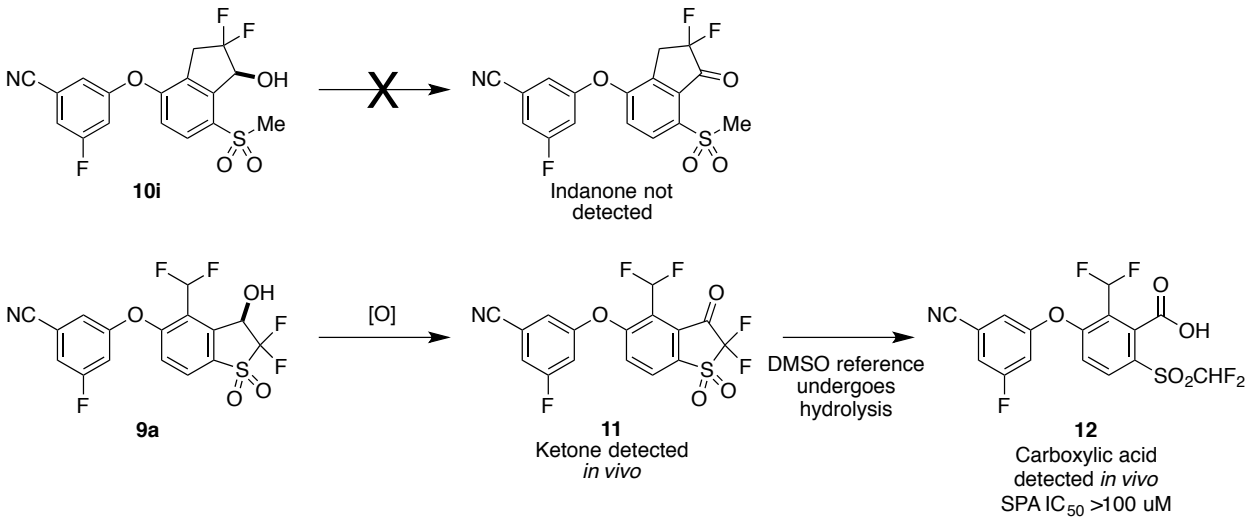
With two analogs (one indanol and one cyclic sulfone) demonstrating potent efficacy and favorable pharmacokinetics across multiple species, their profiles were examined more closely (Table 9). While **9a** showed a slight advantage in potency, solubility, and intrinsic clearance over **10i**, in many other regards the leads were quite comparable. CYP profiling did not show any liabilities for either lead. Permeability and plasma protein binding were also similar. At 10 μM concentration, neither lead showed a significant signal in the kinase or safety panels. Finally, hERG testing, also at 10 μM, suggested limited potential for QT prolongation for both compounds.

Table 9. Profile of Inhibitors 9a and 10i (mouse data omitted see Table 7)

Compound	**9a**	**10i**
Luciferase IC_{50}	10 ± 5 nM	27 ± 6 nM
VEGFA EC_{50}	16 ± 2 nM	41 ± 12 nM
thermodynamic solubility (μmol/L) (pH 7.4)	126	59
CL_{int} h (mL/min/kg)	< 3	4.7
CL_{int} r (mL/min/kg)	9.1	22.6
CL_{int} d (mL/min/kg)	< 5	< 5
CL_{int} monkey (mL/min/kg)	< 4	5.4
CYP(IC_{50}, μM)	1A2 > 50, 2B6 > 50, 2C8 > 50, 2C9 15.7, 2D6 > 50, 3A4 13.3	1A2 > 50, 2B6 > 50, 2C8 > 50, 2C9 23, 2C19 46, 2D6 > 50, 3A4 > 50
PPB h (%)	63	79
PPB r (%)	85	71
PPB d (%)	82	75
PPB monkey (%)	62	74
kinase selectivity (<70% activity remaining @ 10 μM)	0/40	0/40
hERG (% inhibition @10 μM)	17.0	8.2
Lead Profiling Screen®* (>50% inhibition @10 μM)	1/68	0/68

Next, the leads metabolism was examined with a focus on formation of ketone metabolites as the difluoro ketone species could be highly electrophilic and thus may represent a reactive metabolite. While the ketone or hydrate of **10i** was not observed in any matrix examined, significant quantities of carboxylic acid **12** ($AUC_{0\text{-}24h}$ **12**/$AUC_{0\text{-}24h}$ **9a** = 9.7, 10 mg/kg PO) were observed in plasma of rats treated with **9a** which was shown to arise from facile hydrolysis of the ketone **11**. (Scheme 4). In fact, quantification of ketone **11** in rat plasma was not done as analysis was complicated by the rapid hydrolysis of the ketone reference standard to carboxylic acid **12** on standing in DMSO at room temperature. This finding coupled with the lack of ketone formed from **10i** led to the removal of **9a** from consideration for advancement.

Scheme 4. Identification of ketone and carboxylic acid metabolites of **9a**



Based on potency, selectivity, pharmacokinetics, metabolite profile and efficacy **10i** (PT2385) was selected for further development and has progressed into clinical trials for the treatment of ccRCC and VHL Disease.[31,32,33]

Mechanism of Heterodimer Disruption

We have reported elsewhere on the mechanism of heterodimer disruption for **10i**[31], however, it is instructive to examine crystallographically the evolution of **10i** in a retrospective fashion (Figure 8). Such an analysis yields insights into the residue perturbations that appear to be essential for efficacious disruption. One of our earliest potent binders, **4a**, subtly changed HIF-2α upon complexation when compared to the apo form (Figure 8, A and B). Only Met252 showed a slight change in disposition to accommodate the nitro group of **4a**. Accordingly, **4a** and related analogs showed limited functional effects. A key breakthrough in overcoming limited functional activity was the discovery of **6c** (see Figure 8, C). The benzyl alcohol moiety engaged a unique hydrogen bonding network replacing the Tyr278 and His293 hydrogen bond with a water mediated hydrogen bond to Tyr281 (not shown) and a direct hydrogen bond to

His293. The consequence of this new hydrogen bond network was that His293 must rotate out of plane to accommodate interaction with the benzyl alcohol and Tyr278 must shift slightly to adapt to the water mediated hydrogen bond with Tyr281. Met252 showed little change in orientation when compared to the structure of **4a**. Cyclic sulfone **9a** maintained the alcohol hydrogen bonding interaction with His293, but further displaced Met252 and Tyr278 (Figure 8, D). Met252 nearly extended over the aromatic portion of the cyclic sulfone and the electron density for Tyr278 suggested two possible conformations. Interestingly, cyclization to indanol **10i** produced the most compelling changes in binding (Figure 8, E). The steric consequence of incorporating a new ring with geminal fluorination was profound perturbation of Met252. Electron density for Met252 indicates that it was splayed in linear fashion above the indane ring of **10i**. To accommodate the new orientation of Met252, Tyr278 shifted completely to the outside binding mode first observed in **9a**. The rotation of His293 deviated slightly from the structure of **6c** and **9a**, but maintained the hydrogen bond interaction with the alcohol moiety of **10i**.

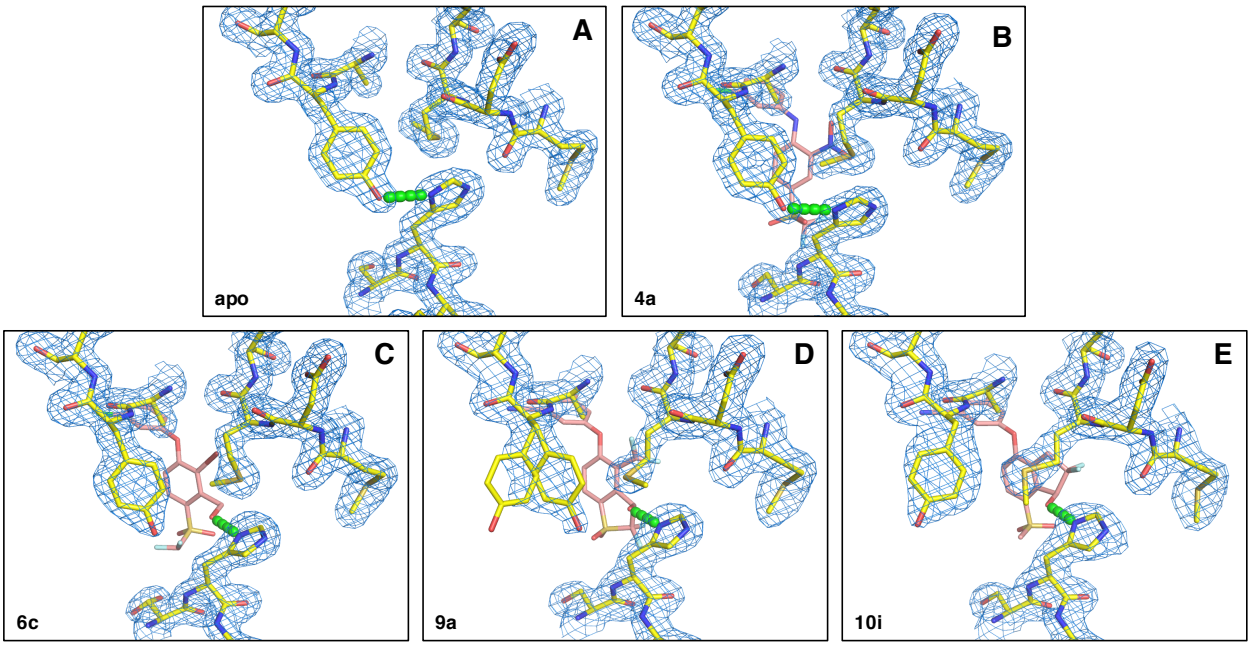


Figure 8. Structural evolution of **10i** highlighting the perturbation of Met252, Tyr278, and His293 by ligand binding. Dotted green lines denote hydrogen bond interactions. (A) X-ray crystal structure of apo HIF-2α PAS-B*/ARNT PAS-B* dimer (PDB:6D0C). (B) X-ray crystal structure of **4a** (PDB:6D0B, pink) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer. (C) X-ray crystal structure of **6c** (PDB:6CZW, pink) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer. (D) X-ray crystal structure of **9a** (PDB:6D09, pink) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer. (E) X-ray crystal structure of **10i** (PDB:5TBM, pink) in complex with the HIF-2α PAS-B*/ARNT PAS-B* dimer.

The discovery of the role of the alcohol moiety was crucial to developing functional HIF-2α antagonists. This moiety served to break the hydrogen bond between Tyr278 and His293 and, importantly, reorient Tyr278. It is believed that perturbation of Tyr278 is essential for functional activity. The structural evolution to **10i** showed increasing displacement of Tyr278. In these later examples, the perturbation of Met252 by the fortuitous incorporation of steric elements appeared to be important for enhancing the displacement of Tyr278. However, the exact nature of the small molecule antagonism of HIF-2α that causes the full suite of functional effects remains elusive. Some of the earlier less active analogs without the structural perturbations of **10i** can elicit functional effects in cell based assays of disruption.

In support of the importance of displacing Tyr278 are data from a resistant ccRCC patient-derived xenograft (PDX) tumor line where a F466L mutation in ARNT drives resistance to **10f**.[31,34] The mutant shows resistance to treatment with **10f** and suggests that the steric clash of Tyr278 with Phe466 of ARNT induced by binding of **10f** is responsible for functional activity (Figure 9).

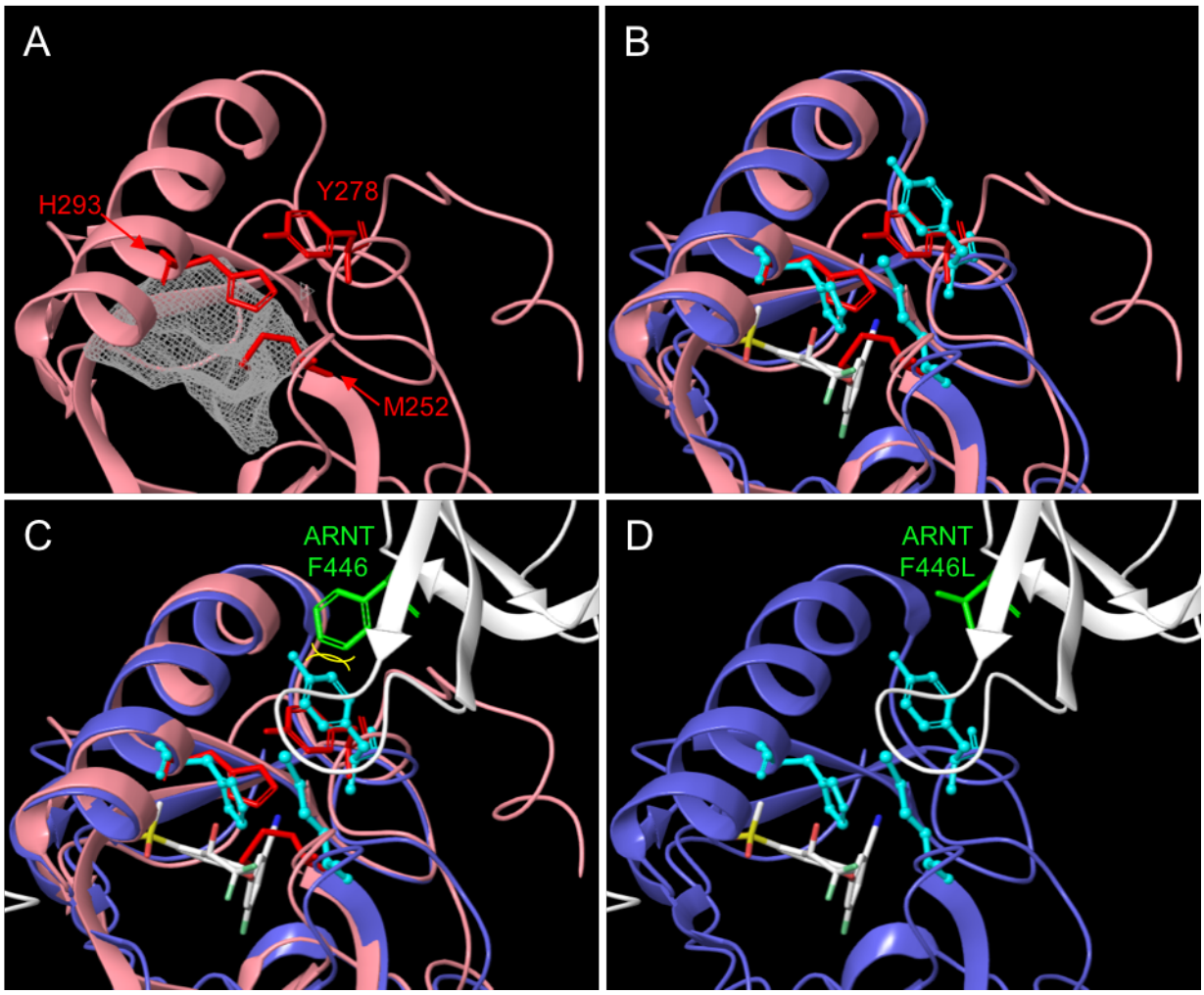


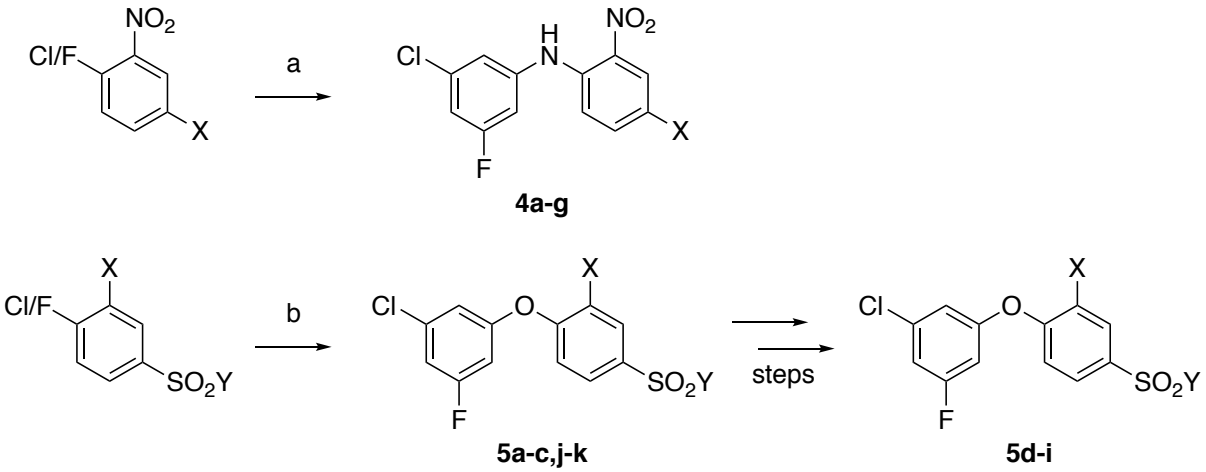
Figure 9. (A) The PAS-B domain from the apo crystal structure of HIF-2α:ARNT HLH-PAS-A-PAS-B heterodimer (PDB:4ZP4, pink). The inner cavity is represented in gray. The key residues perturbed by **10i** binding are highlighted in red. (B) Superposition of panel A PAS-B domain (pink) with the PAS-B domain of HIF2α PAS-B*:ARNT PAS-B* co-crystal with **10i** bound in the inner pocket (PDB:5TBM, blue). Key displaced residues are highlighted in cyan. (C) Addition of the ARNT PAS-B domain from the HIF-2α:ARNT HLH-PAS-A-PAS-B heterodimer (white) to panel B with ARNT:F446 highlighted in green. Displacement of the highlighted residues, particularly Y278 creates an unfavorable Van der Waals clash with ARNT:F446 resulting in dimer disruption. (D) PAS-B* domain of HIF-2α (blue) and the PAS-B

domain of ARNT (white) from panel C where F446 has been mutated to Leucine. The F446L mutation in ARNT has been shown to impart resistance to dimer disruption by compounds binding to the inner pocket.[34] The reduced size of F446L alleviates the deleterious steric clash and can now accommodate the displaced Y278 from HIF-2α.

Chemical Synthesis

The compounds described in Table 1 were prepared by S_NAr displacement of the appropriate chloro- or fluoro-nitro arene with 3-chloro-5-fluoroaniline (Scheme 5) under various conditions (see Experimental Section). Compounds in Table 2 were prepared similarly with the union of a phenol and a fluoro or chloroarene by S_NAr reaction forming the core of the molecule (Scheme 5). In some cases, additional steps were necessary to prepare the fluoro or chloroarene and/or to manipulate the intermediate diaryl ether to the final product (see Experimental Section).

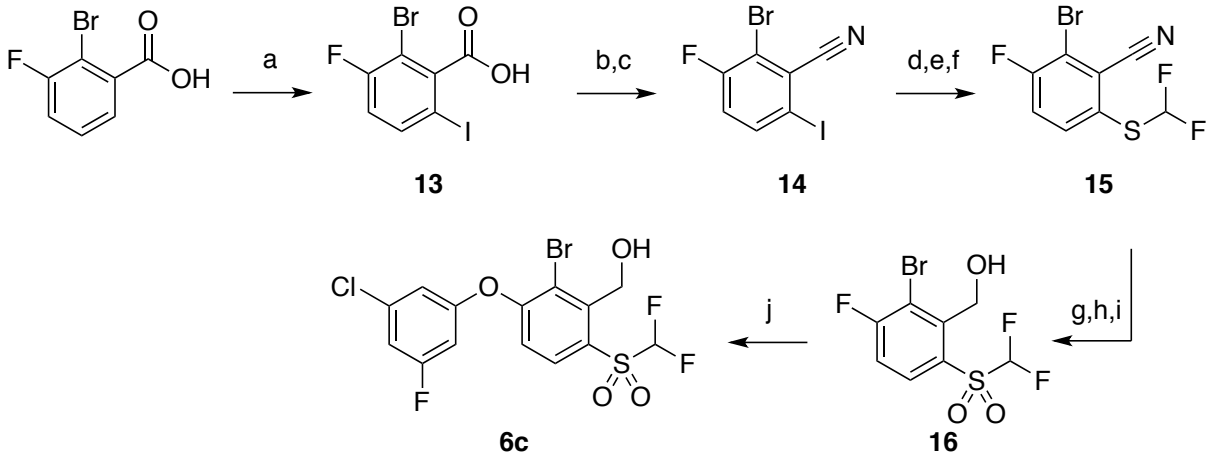
Scheme 5. Preparation of initial diaryl anilines and diaryl ethers[a]



[a]Reagents and conditions: (a) 3-chloro-5-fluoroaniline, base, solvent, various conditions, 13-32%; (b) 3-chloro-5-fluorophenol, base, solvent, various conditions, 66-94%.

The tetrasubstituted benzene derivatives highlighted in Table 3 exploited a common differentially halogenated benzoic acid starting material **13** (Scheme 6). This material was conveniently accessed by Pd-catalyzed proximal C-H activation of the commercial dihalogenated benzoic acid.[35] After condensation to nitrile **14**, differential halogenation enabled chemoselective installation of the sulfur moiety. Reduction of the nitrile and oxidation of the sulfide generated sulfone **16**. The synthesis of **6c** was completed following the union of difluoromethyl sulfone **16** with the phenol. Amino derivatives **6a** and **6b** were accessed by standard transformations on nitrile intermediate **15** and the chlorinated compounds **6d** and **6e** were prepared by their own unique synthesis (see Experimental Section).

Scheme 6. Preparation of **6c**[a]

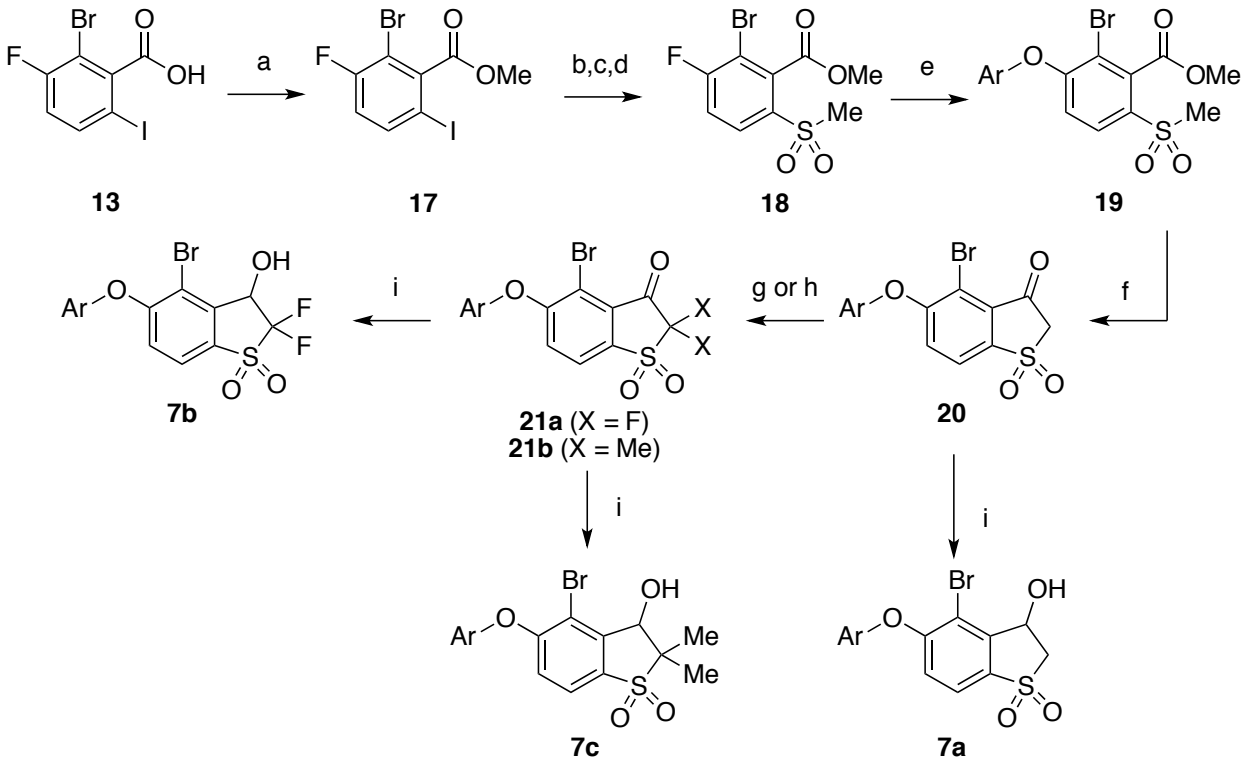


[a]Reagents and conditions: (a) $Pd(OAc)_2$, $PhI(OAc)_2$, I_2, DMF, 120 °C, 67%; (b) $SOCl_2$, cat DMF, THF, 0 °C → rt, then 0 °C, NH_4OH 94%; (c) Et_3N, $POCl_3$, 75 °C, 85%; (d) $Pd_2(dba)_3$, Xantphos, KSAc, toluene/acetone, 72 °C, 84%; (e) NH_4OH, THF; (f) KOH, CH_3CN/water, rt → -78 °C, then $BrCF_2P(O)(OEt)_2$, rt, 55% over 2 steps; (g) DIBAL, CH_2Cl_2, heptane, 0 °C → rt, then aq HCl, 48%; (h) $NaBH_4$, MeOH, 0 °C; (i) *m*-CPBA, CH_2Cl_2, 0 °C → rt, 62% over 2 steps; (j) 3-Cl-5-F-C_6H_3OH, K_2CO_3, DMF, 80 °C, 46%.

Access to the initial cyclic sulfones outlined in Table 4 utilized the same differentially halogenated benzoic acid described in Scheme 6. In this case (Scheme 7), elaboration to methyl sulfone **19** facilitated construction of the cyclic sulfone core **20** by sodium hydride mediated

cyclization. Subsequent fluorination or methylation of the resulting activated methylene was readily achieved and simple reduction with sodium borohydride afforded the racemic alcohol derivatives.

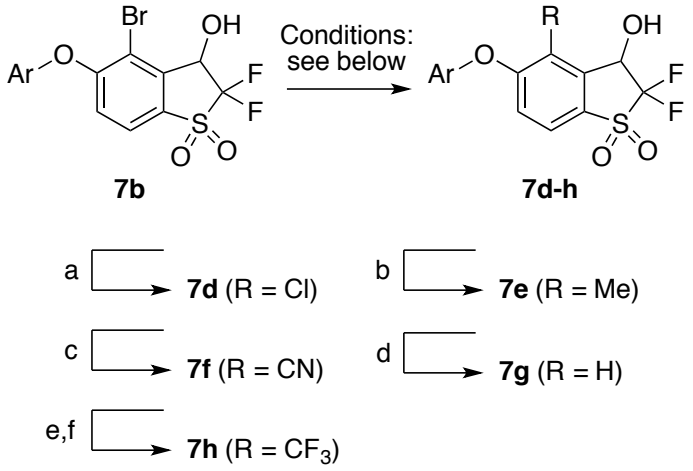
Scheme 7. Preparation of initial cyclic sulfone derivatives[a]



[a]Reagents and conditions: (a) K_2CO_3, MeI, DMF, rt, 90%; (b) $Pd_2(dba)_3$, Xantphos, KSAc, toluene/acetone, 70 °C, 66%; (c) Cs_2CO_3, MeI, MeOH, rt, 88%; (d) $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$, MeOH, H_2O, rt, 77%; (e) 3-Cl-5-F-C_6H_3OH, $NaHCO_3$, DMF, 90 °C, 91%; (f) 60% NaH, THF, 0 °C → rt, 70%; (g) F-TEDA-BF_4, Na_2CO_3, CH_3CN, rt, 81%; (h) MeI, K_2CO_3, DMF, rt,; (i) $NaBH_4$, MeOH, 0 °C, 70-72%, 47% over 2 steps for **7c**.

7b served as a versatile intermediate in the synthesis of most of the remaining derivatives in Table 4. As shown in Scheme 8, compounds **7d**, **7e**, **7f** and **7h** were prepared by replacement of the bromide in **7b** using Pd- or Cu-mediated coupling reactions. Reductive debromination of **7b** with borane dimethylsulfide complex and $LiBH_4$ led to analog **7g**.

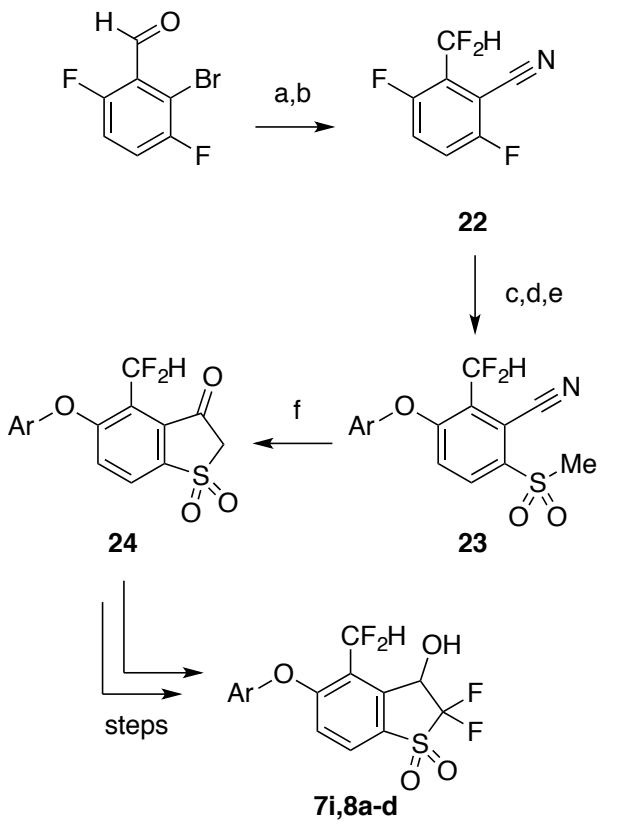
Scheme 8. Synthesis of **7d-7h**[a]



[a]Reagents and conditions (Ar = 3-Cl-5-F-C_6H_3): (a) CuCl, NMP, 170 °C, 50%; (b) $MeBF_3K$, $PdCl_2(dppf)$, Cs_2CO_3, dioxane/water, 100 °C, 28%; (c) CuCN, NMP, 160 °C, 17%; (d) BH_3•DMS, $LiBH_4$, toluene/THF, rt → 60 °C, 15%; (e) CuI, NMP, 180 °C, 56%; (f) [(phen)$CuCF_3$], DMF, 50 °C, 28%.

The difluoromethyl derivatives **7i** and **7j** required alternative synthetic routes to access (Scheme 9 and 10). The synthesis of **7i** was straightforward, but it is worth noting that during the intramolecular cyclization of **23**, the reaction of the methyl sulfone with the nitrile group resulted in a vinylogous sulfonamide intermediate that required hydrolysis to afford the desired ketone **24**. Preparation of the cyclic sulfones in Table 5 was readily achieved following Scheme 9 and varying the phenol component. The enantiomers of **8b** were resolved by preparative SFC chromatography (Scheme 3).

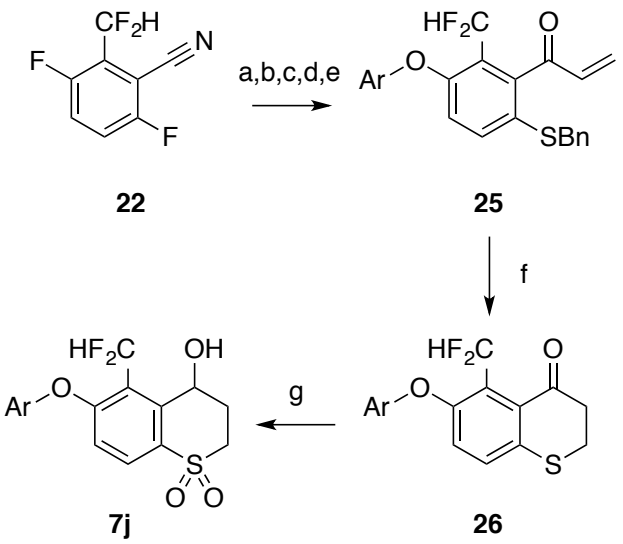
Scheme 9. Synthesis of **7i**, **8a-d**[a]



[a]Reagents and conditions: (a) DAST, CH_2Cl_2, 0 °C → rt, ; (b) CuCN, NMP, 180 °C, 67% over 2 steps; (c) NaSMe, CH_3CN, -30 °C, 91%; (d) $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$, CH_3CN/water, 56 °C, 71%; (e) ArOH, Cs_2CO_3, DMF, 45 °C, 96%; (f) 60% NaH, THF, then 4:1 MeOH/10% aq. HCl, rt, 99%.

Changing the sulfur source to benzyl mercaptan initiated the synthesis of the ring expanded thiochromane system in **7j** and elaboration to vinyl ketone **25** set up the cyclization step (Scheme 10). Aluminum chloride mediated deprotection of the benzyl group permited *in situ* cyclization of the liberated thiol onto the pendant vinyl ketone moiety in low yield. Reduction and oxidation under standard conditions completed the synthesis.

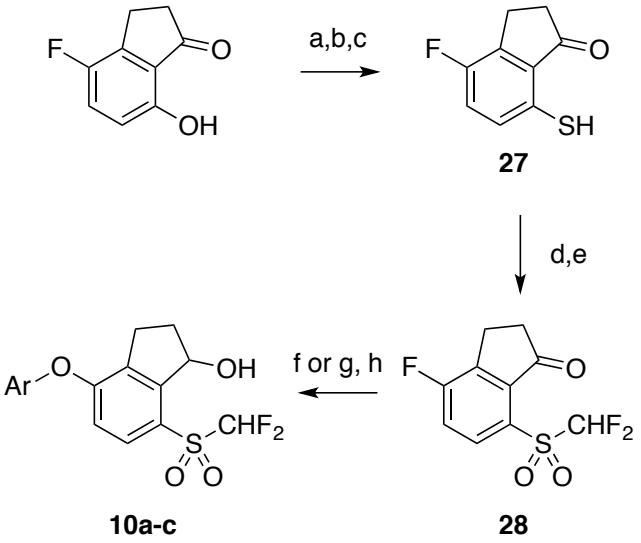
Scheme 10. Synthesis of **7j**[a]



[a]Reagents and conditions: (a) NaSBn, CH_3CN, -40 °C → 10 °C, 28%; (b) 3,5-$Cl_2C_6H_3OH$, $CsHCO_3$, DMF, 100 °C; (c) DIBAL-H, CH_2Cl_2, 0 °C, 18% over 2 steps; (d) VinylMgBr, THF, 0 °C, 85%; (e) Dess-Martin, CH_2Cl_2, rt; (f) $AlCl_3$, C_6H_6, rt, 20% over 2 steps; (g) $NaBH_4$, MeOH, 0 °C, workup, then mCPBA, CH_2Cl_2, rt, 60%.

The indanols compiled in Table 6 were readily assembled from a commercial phenol (Scheme 11). Newman-Kwart reaction transformed the phenol into thiol **27** which underwent base mediated difluoromethylation and ruthenium catalyzed oxidation to afford keto sulfone **28**. Surprisingly, the keto sulfone intermediate was a poor S_NAr substrate when reacted with various phenols. A competing reaction via the formation of a charge transfer complex between the electron deficient keto sulfone and electron rich phenoxide could explain this observation. The poor S_NAr reactivity of **28** was overcome by first reducing the ketone and then introducing the phenol. Reduction was either racemic with sodium borohydride or highly enantioselective when mediated by Noyori's asymmetric transfer hydrogenation catalysts.

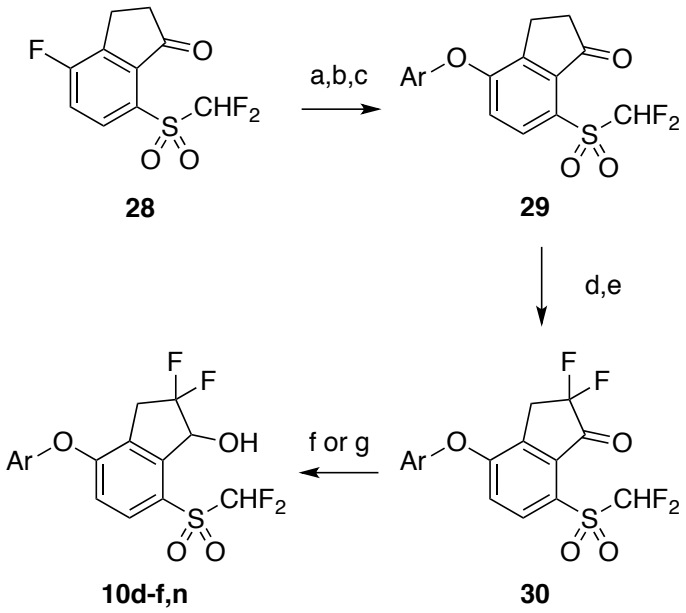
Scheme 11. Synthesis of initial indanol derivatives[a]



[a]Reagents and conditions: (a) $ClCSNMe_2$, DMF, rt, 73%; (b) Ph_2O, 220 °C, 95%; (c) NaOH, EtOH/water, 85 °C, 95%; (d) KOH, CH_3CN/water, rt → -78 °C, then $BrCF_2P(O)(OEt)_2$, rt, 84%; (e) $NaIO_4$, $RuCl_3$,CH_3CN/CCl_4/water, rt, 91%; (f) $NaBH_4$, MeOH, rt, 90%; (g) [(*R*,*R*) or (*S*,*S*)-Ts-DPEN]RuCl(*p*-cymene), HCO_2H, Et_3N, CH_2Cl_2, rt, 99%; (h) ArOH, $NaHCO_3$, NMP, 90 °C, 42%.

The installation of geminal fluorination adjacent to the alcohol took advantage of keto sulfone **28** (Scheme 12). Ketal protection followed by S_NAr reaction established the diaryl ether core. The ketal was then removed under acidic conditions and the resulting ketone condensed with butyl amine. Electrophilic fluorination of the intermediate imine and subsequent hydrolysis afforded ketone **30**.[36] As before, reduction to the alcohol can be either racemic or enantioselective.

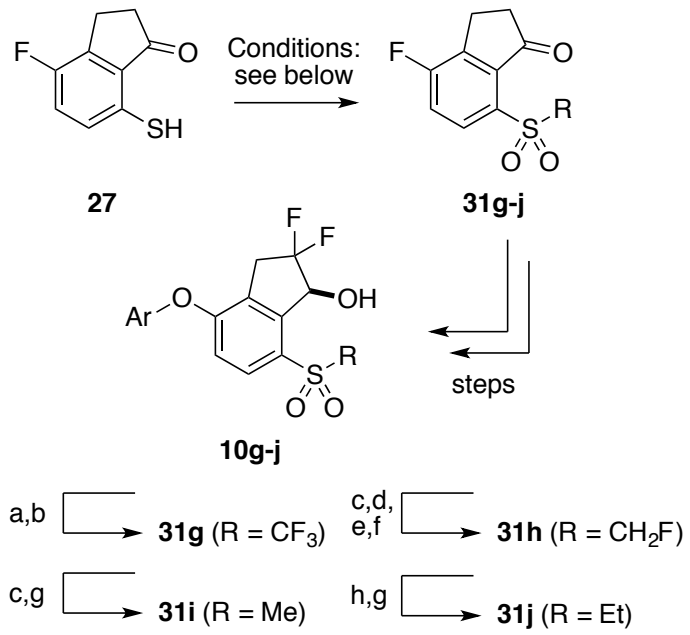
Scheme 12. Preparation of 2,2-difluoro indanes[a]



[a]Reagents and conditions: (a) $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, reflux, 90%; (b) ArOH, $CsHCO_3$, NMP, 110 °C, 69%; (c) PPTS, acetone/water, 85 °C, 95%; (d) $BuNH_2$, TFA, benzene, 90 °C; (e) F-TEDA-BF_4, Na_2SO_4, CH_3CN, 82 °C, then rt, aq HCl, 51% over 2 steps; (f) $NaBH_4$, MeOH, rt, 30%; (g) [(*R,R*)-Ts-DPEN]RuCl(*p*-cymene), HCO_2H, Et_3N, CH_2Cl_2, 4 °C, 83%.

Variation of the sulfone moiety described in Table 6 is shown in Scheme 13. Generally, a sequence of alkylation followed by oxidation afforded the desired intermediates. However, in the case of fluoromethyl sulfone derivative **31i**, it was necessary to generate an intermediate methyl sulfoxide that can then undergo antimony catalyzed conversion to the fluoromethyl thioether.[37]

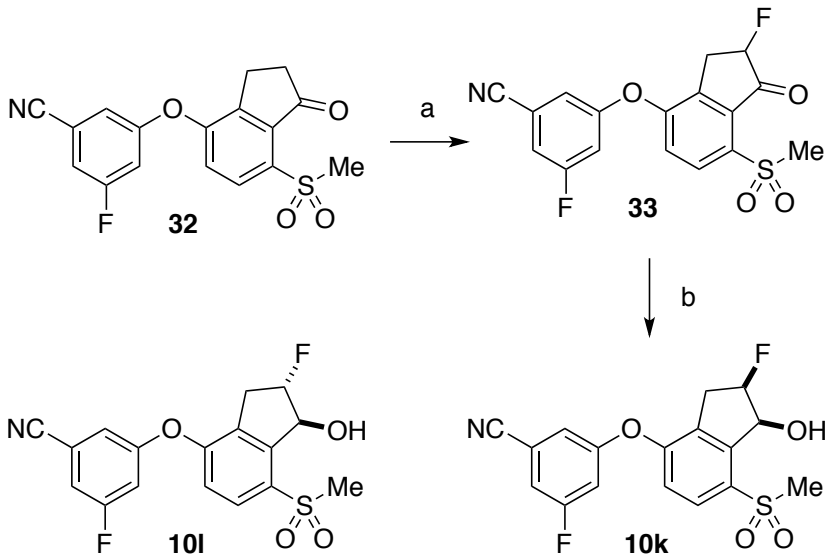
Scheme 13. Modification of the sulfone[a]



[a]Reagents and conditions: (a) Methyl viologen dichloride, CF_3I, Et_3N, DMF, -78 °C → rt, 30%; (b) $NaIO_4$, $RuCl_3$,CH_3CN/CCl_4/water, rt, 63%; (c) MeI, NaOH, EtOH/water, 0 °C; (d) *m*CPBA, CH_2Cl_2, rt, 80% over 2 steps; (e) DAST, $SbCl_3$, CH_2Cl_2, rt, 99%; (f) 6 eq *m*CPBA, CH_2Cl_2, rt; (g) $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$, MeOH/water, rt, 96%; (h) EtI, NaOH, EtOH/water, 0 °C.

Synthesis of the cis fluorohydrin **10k** was readily achieved by Noyori reduction of fluoroketone **33** (Scheme14). Selectivity for the *cis* isomer was excellent and constituted a dynamic kinetic resolution.[38] A small amount of the *trans* isomer **10l** was isolated as a minor product from this reaction.

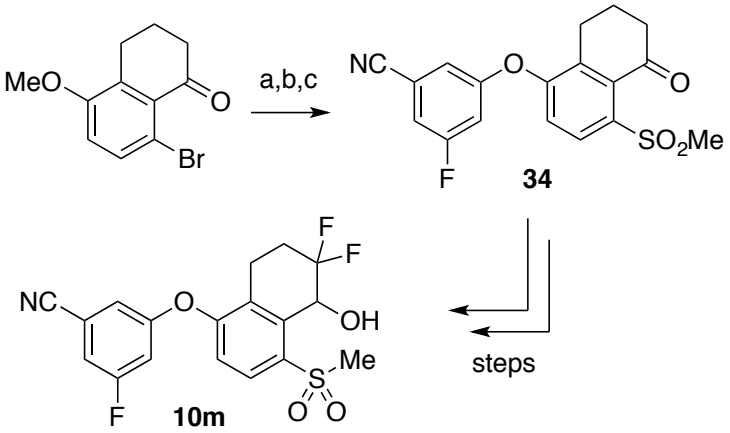
Scheme 14. Preparation of **10k** and **10l**[a]



[a]Reagents and conditions: (a) F-TEDA-BF_4, MeOH, reflux; (b) [(*R,R*)-Ts-DPEN]RuCl(*p*-cymene), HCO_2H, Et_3N, CH_2Cl_2, 4 °C, 83% over 2 steps.

Lastly, the ring expanded tetrahydronaphthalene derivative **10m** was prepared by a sequence of steps beginning with aluminum trichloride mediated demethylation of a methoxy tetralone (Scheme 15). The intermediate phenol was converted to the diaryl ether by S_NAr reaction with 3,5-difluorobenzonitrile and the bromide handle was then transformed into a methyl sulfone by exposure to copper iodide and the sodium salt of methyl sulfinic acid. Following standard procedures, tetralone **34** could be difluorinated adjacent to the ketone and elaborated into **10m**.

Scheme 15. Preparation of tetrahydronaphthalene derivative **10m** [a]



[a]Reagents and conditions: (a) $AlCl_3$, DCE, 85 °C, 40%; (b) 3,5-difluorobenzonitrile, $CsHCO_3$, NMP, 150 °C, μW; (c) $NaSO_2Me$, CuI, DMSO, 100 °C, 12% over 2 steps.

CONCLUSION

Beginning from benzoxadiazole **1** we employed a combination of structure based drug design and rational modification to discover potent, selective, orally bioavailable HIF-2α antagonists. During the optimization process several problematic features of the initial lead were addressed such as substitution of the benzoxadiazole with a sulfone moiety, exchange of the aniline linkage with an ether, and replacement of the nitro group with a myriad of suitable electron withdrawing groups. Crucial to further advancing the evolving series was the discovery of benzyl alcohol **6c**, which reduced the shift between enzyme and cellular based assays. In addition, the benzyl alcohol moiety uncovered a unique multi-component hydrogen-bonding network that improved functional activity through displacement of Tyr278. Constraining the benzyl alcohol moiety into a ring identified two novel scaffolds: the cyclic sulfone and the indanol. The introduction of fluorine atoms adjacent to the alcohol moiety proved essential to advancing these scaffolds towards drug candidates. These effects culminated in the selection of clinical candidate PT2385. PT2385 is the first HIF-2α antagonist to progress to clinical trials and it is currently under evaluation as a treatment for both ccRCC and VHL Disease.

EXPERIMENTAL SECTION

General Chemistry: All solvents and reagents were used as obtained. ^{1}H and ^{19}F NMR analysis of intermediates and exemplified compounds were performed on an Agilent Technologies 400/54 magnet system (operating at 399.85 MHz or 376.24 MHz). Vnmrj VERSION 3.2 software pulse sequences were selected from the default experiment set. Chemical shifts are expressed as δ units using trimethylsilane (TMS) as the external standard (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak).

High performance liquid chromatography (HPLC) coupled to a mass spectrometer (MS) was used to determine the purity of the compounds synthesized. The data confirmed that the target compounds generally had ≥ 95% of purity. Certain compounds, such as **5g** and **5i**, were prepared as part of a directed library synthesis and passed purity and mass check by LCMS; these inhibitors were not fully characterized. The following analytical method was used to determine chemical purity of final compounds: Agilent 1200 series high performance liquid chromatography (HPLC) system operating in reverse-phase mode coupled to an Agilent 6150 Quadrapole spectrometer using an ESI source, water with 0.1% formic acid (mobile phase A), acetonitrile with 0.1% formic acid (mobile phase B), Agilent ZORBAX Eclipse Plus C18, 1.8 µm, 2.1×50 mm, 40 °C column temperature, 5−95% mobile phase B in 4.0 min, 95% in 2.0 min, 700 µL/min flow rate, UV absorbance detection at 220 and 254 nm. Analyte ions were detected by mass spectrometry in both negative and positive modes (110 – 800 amu scan range, API-ES ionization).

For some compounds an additional longer method was also used to assay chemical purity: Agilent 1200 series high performance liquid chromatography (HPLC) system operating in reverse-phase mode, water with 0.1% formic acid (mobile phase A), acetonitrile with 0.1% formic acid (mobile phase B), Phenomenex Kinetex 2.6 µm C18 100 Å, 30x3.0 mm, 40 °C column temperature, 5−95% mobile phase B in 12.0 min, 95% in 2.0 min, 800 µL/min flow rate, UV absorbance detection at 214 and 254 nm.

Routine chromatographic purification was performed using Biotage Isolera One automated systems running Biotage Isolera One 2.0.6 software (Biotage LLC, Charlotte, NC). Flow rates were the default values specified for the particular column in use. Reverse phase chromatography was performed using elution gradients of water and acetonitrile on KP-C18-HS Flash+ columns (Biotage LLC) of various sizes. Normal phase chromatography was performed using elution gradients of various solvents (e.g. hexanes, ethyl acetate, methylene chloride, methanol, acetone, chloroform, MTBE, etc.). The columns were SNAP Cartridges containing KP-SIL (50 μm irregular particles) or SNAP Ultra (25μm spherical particles) of various sizes (Biotage LLC).

Enantiomeric excess was determined by Mosher ester analysis or with chiral HPLC. The chiral HPLC analysis was performed on an Agilent Technologies 1200 Series HPLC system. Analytes were detected by UV absorbance at 220 and 254 nm. A detailed description of the analytical method is provided below:

Column: Phenomenex Lux® 5 μm Cellulose-4 5.0 μm 1000 Å, 150×4.60 mm

Flow rate: 1.5 mL/min

Mobile phase A: 0.1% formic acid in water

Mobile phase B: 0.1% formic acid in acetonitrile

Strong needle wash: 90% acetonitrile, 10% water

Weak needle wash: 10% water, 90% acetonitrile

Injection volume: 2 μl.

Column temperature: 40° C.

Autosampler temperature: Room temperature

Run time: 5.0 min

Isocratic conditions: 60% mobile phase A and 40% mobile phase B

PAINS analysis (using http://zinc15.docking.org/patterns/home/) could not identify any known classes of assay interference compounds contained in any of the new compounds prepared and tested for

this manuscript (**4**-**10**, **12**). In addition, the final compounds **9a** and **10i** have kinase and Panlabs profiles that indicate no significant off-target activity.

The protocols and procedures involving the care and use of animals for this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of University of Texas Southwestern Medical Center.

cLogP values were determined using ChemDraw Professional version 17.1.0.105 (19).

F-TEDA-BF_4 is 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) and is commercially known as Selectfluor®, a trademark of Air Products and Chemicals.

$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, a triple salt, is commercially known as Oxone®.

Synthetic procedures and characterization data:

***N*-(3-Chlorophenyl-4,6-t2)-4-nitrobenzo[c][1,2,5]oxadiazol-5-amine ($^3H_2$-1b).** Step A: Preparation of 3-chlorobenzen-4,6-t_2-amine (**3**): Tritiation was carried out at PerkinElmer, Inc. Waltham, MA. 3-Chloro-4,6-diiodoaniline (100 mg, 0.264 mmol) was dissolved in methanol (3 mL) and triethylamine (0.1 mL) and submitted for overnight tritiation using 50 Ci of tritium gas at room temperature in the presence of a proprietary metal catalyst. Labile tritium was removed by dissolving the crude reaction mixture in methanol (3 mL) and bringing to dryness under vacuum. Labile removal was done in duplicate. The crude tritiated material was purified by preparative TLC (Silica gel, 1000 μm) using hexane:EtOAc:AcOH (85:14:1). The product band was eluted with EtOAc to give 3-chlorobenzen-4,6-t_2-amine (yield = 600 mCi, Radiochemical purity was >98%).

Step B: Preparation of *N*-(3-Chlorophenyl-4,6-t2)-4-nitrobenzo[c][1,2,5]oxadiazol-5-amine (**$^3H_2$-1b)**: A stirred mixture of 5-chloro-4-nitro-2,1,3-benzoxadiazole (20 mg, 0.10 mmol), 3-chlorobenzen-4,6-t_2-amine (600 mCi) and Cs_2CO_3 (65 mg, 0.20 mmol) in DMF (1 mL) was heated at 60 °C for 1 h. After cooling, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by preparative HPLC on an ACE-5 C18 Semi-prep column, 250 x 10 mm, 100Å.

Elution was carried out isocratically using 0.1% TFA in water:acetonitrile (35:65) to give **$^{3}H_2$-1b** (478 mCi, 80%). **1b** LCMS ESI (+) *m/z* 290.6, 292.6 (M+H). **$^{3}H_2$-1b** LCMS ESI (+) *m/z* 294.6, 296.6 (M+H).

***N*-(3-Chloro-5-fluorophenyl)-2-nitro-4-((trifluoromethyl)sulfonyl)aniline (4a).** 3-chloro-5-fluoroaniline (88.0 mg, 0.60 mmol) was added to 1-chloro-2-nitro-4-((trifluoromethyl)sulfonyl)benzene (58.0 mg, 0.20 mmol) in THF (2 mL) and stirred at 50 °C for 22 hours. The crude reaction mixture was purified directly by silica gel chromatography, eluting with a gradient of 5% to 40% EtOAc in hexane to give N-(3-chloro-5-fluorophenyl)-2-nitro-4-((trifluoromethyl)sulfonyl)aniline (25.0 mg, 31% yield) as solid. LCMS ESI (-) *m/z* 396.9, 398.9 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br s, 1H), 8.92 (d, 1H), 7.95-7.91 (m, 1H), 7.34 (d, 1H), 7.17-7.12 (m, 2H), 7.01-6.97 (m, 1H).

***N*-(3-Chloro-5-fluorophenyl)-4-((difluoromethyl)sulfonyl)-2-nitroaniline (4b).** Triethylamine (0.041 mL, 0.30 mmol) was added to 1-chloro-4-((difluoromethyl)sulfonyl)-2-nitrobenzene (40.0 mg, 0.15 mmol) and 3-chloro-5-fluoroaniline (32.0 mg, 0.22 mmol) in ethanol (1.0 mL) and stirred at room temperature for 3 days, then warmed to 50 °C for 14 hours. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and purified by reverse phase chromatography, eluting with a gradient of 20% to 100% acetonitrile in water to give N-(3-chloro-5-fluorophenyl)-4-((difluoromethyl)sulfonyl)-2-nitro-aniline (18.2 mg, 33% yield) as solid. LCMS ESI (+) *m/z* 381.0, 383.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (br s, 1H), 8.86 (d, 1H), 7.90 (dd, 1H), 7.34 (d, 1H), 7.17-7.15 (m, 1H), 7.12 (dt, 1H), 6.98 (dt, 1H), 6.22 (t, 1H).

***N*-(3-Chloro-5-fluorophenyl)-4-((fluoromethyl)sulfonyl)-2-nitroaniline (4c).** Triethylamine (0.019 mL, 0.14 mmol) was added to 1-fluoro-4-((fluoromethyl)sulfonyl)-2-nitrobenzene (25.0 mg, 0.11 mmol) and 3-chloro-5-fluoroaniline (20.0 mg, 0.14 mmol) in ethanol (0.5 mL) at room temperature and then stirred at reflux for 17 hours. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by reverse phase chromatography, eluting with a gradient of 20% to 100% acetonitrile in water to give N-(3-chloro-5-fluorophenyl)-4-((fluoromethyl)sulfonyl)-2-nitro-aniline (9.2 mg, 24% yield) as solid. LCMS ESI (+) *m/z* 363.0, 365.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ

9.85 (br s, 1H), 8.85 (d, 1H), 7.91 (dd, 1H), 7.35 (d, 1H), 7.15-7.13 (m, 1H), 7.10 (dt, 1H), 6.97 (dt, 1H), 5.15 (d, 2H).

4-((3-Chloro-5-fluorophenyl)amino)-*N*-methyl-3-nitrobenzenesulfonamide (4d). 3-Chloro-5-fluoroaniline (47 mg, 0.32 mmol) and 4-fluoro-*N*-methyl-3-nitrobenzenesulfonamide (50 mg, 0.21 mmol) were dissolved in 0.5 mL EtOH and treated with triethylamine (45 μL, 0.32 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was concentrated, solubilized with DMF, and purified by reverse phase chromatography, eluting with a gradient of 10% to 100% acetonitrile in water. 4-((3-Chloro-5-fluorophenyl)amino)-*N*-methyl-3-nitrobenzenesulfonamide was isolated as a yellow solid (10 mg, 13% yield). LCMS ESI (-) *m/z* 357.9, 359.9 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74-9.68 (br s, 1H), 8.74 (d, 1H), 7.86 (dd, 1H), 7.34 (d, 1H), 7.14-7.11 (m, 1H), 7.06 (dt, 1H), 6.95 (dt, 1H), 4.38 (q, 1H), 2.72 (d, 3H).

***N*-(3-Chloro-5-fluorophenyl)-2-nitro-4-(trifluoromethyl)aniline (4e).** A vial was charged with sodium bicarbonate (63 mg, 0.76 mmol), 3-chloro-5-fluoroaniline (100 mg, 0.69 mmol) and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (158 mg, 0.76 mmol). The resulting mixture was diluted with DMF (0.7 mL) and the sealed vial was heated at 110 °C for 1 h. The reaction mixture was poured into H_2O (50 mL) and extracted 3 x 20 mL Et_2O. The combined organics were washed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography on silica using a gradient of 0% to 20% EtOAc in hexane. *N*-(3-Chloro-5-fluorophenyl)-2-nitro-4-(trifluoromethyl)aniline was isolated as yellow solid (19 mg, 8.3%). LCMS ESI (-) *m/z* 332.9, 334.9 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.53 (s, 1H), 7.65 (d, 1H), 7.35 (d, 1H), 7.13-7.10 (m, 1H), 7.05-7.01 (m, 1H), 6.96-6.92 (m, 1H).

1-(4-((3-Chloro-5-fluorophenyl)amino)-3-nitrophenyl)ethan-1-ol (4f). Step A: Preparation of 1-(4-((3-chloro-5-fluorophenyl)amino)-3-nitrophenyl)ethan-1-one. A vial was charged with 3-chloro-5-fluoroaniline (200 mg, 1.37 mmol), DMF (1.5 mL), 1-(4-fluoro-3-nitrophenyl)ethanone (126 mg, 0.689 mmol), and pyridine (125 μL, 1.51 mmol). The sealed vial was heated at 60 °C for 72 hours. After

cooling, the reaction was poured into 50 mL of H_2O and extracted 3 x 30 mL Et_2O. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by silica gel chromatography using a gradient of 0% to 35% EtOAc in hexane. 1-(4-((3-Chloro-5-fluorophenyl)amino)-3-nitrophenyl)ethan-1-one was isolated as an orange solid (42 mg, 20% yield). LCMS ESI (-) *m/z* 307.0, 309.0 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78-9.72 (br s, 1H), 8.30 (d, 1H), 8.07 (dd , 1H), 7.30 (d, 1H), 7.14-7.11 (m, 1H), 7.03 (dt, 1H), 6.95 (dt, 1H), 2.60 (s, 3H).

Step B: Preparation of 1-(4-((3-chloro-5-fluorophenyl)amino)-3-nitrophenyl)ethan-1-ol. 1-(3-Nitro-4-((thiophen-3-ylmethyl)amino)phenyl)ethanone (27 mg, 0.087 mmol) was dissolved in 2 mL of MeOH and treated with sodium borohydride (8.3 mg, 0.22 mmol). The reaction mixture was quenched by the addition of 1 mL saturated aqueous NH_4Cl. Excess MeOH was removed by concentration under reduced pressure. The product residue was suspended in 30 mL water and extracted 3 x 15 mL EtOAc. The combined organics were washed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified by chromatography on silica gel using a gradient of 0% to 40% EtOAc in hexane. 1-(4-((3-Chloro-5-fluorophenyl)amino)-3-nitrophenyl)ethan-1-ol was isolated as an orange oil (15 mg, 54% yield). LCMS ESI (-) *m/z* 309.0, 311.0 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34-9.27 (br s, 1H), 8.21 (d, 1H), 7.53 (dd, 1H), 7.36 (d, 1H), 7.07-7.04 (br s, 1H), 6.92-6.87 (m, 2H), 4.90 (q, 1H), 1.94-1.82 (br, 1H), 1.51 (d, 3H).

1-(3-Chloro-5-fluorophenoxy)-2-nitro-4-((trifluoromethyl)sulfonyl)benzene (5a). A reaction vial containing 1-chloro-2-nitro-4-((trifluoromethyl)sulfonyl)benzene (50.0 mg, 0.173 mmol) and 3-chloro-5-fluorophenol (38.0 mg, 0.259 mmol) in benzene (2.0 mL) was treated with K_2CO_3 (36.0 mg, 0.259 mmol). The sealed vial was stirred at reflux for 15 h. The reaction mixture was cooled to room temperature, diluted with hexanes (3 mL), filtered through a cotton plug, rinsed with Et_2O (3 mL) and concentrated. The crude product was purified by reverse phase chromatography, eluting with a gradient of 20% to 100% acetonitrile in water to afford 1-(3-chloro-5-fluorophenoxy)-2-nitro-4-((trifluoromethyl)sulfonyl)benzene (50 mg, 72% yield) as a colorless oil. LCMS ESI (-) *m/z* 433.9, 435.8

(M+Cl). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, 1H), 8.15 (dd, 1H), 7.24 (d, 1H), 7.12 (ddd, 1H), 7.01-6.99 (m, 1H), 6.84 (dt, 1H).

2-Bromo-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (5b). Step A: Preparation of (3-bromo-4-fluorophenyl)(trifluoromethyl)sulfane: Trifluoromethyliodide (2.84 g, 14.5 mmol) was condensed into a solution of 3-bromo-4-fluorobenzenethiol (1.00 g, 4.83 mmol), methyl viologen dichloride (118 mg, 0.480 mmol) and Et_3N (1.68 mL, 12.1 mmol) in DMF (6.4 mL) at –78 °C. The tube was quickly capped with a threaded Teflon cap and tightly sealed. The reaction mixture was allowed to warm to room temperature and stirred for 39 h. The reaction mixture was cooled to –78 °C, opened carefully, and poured into brine (20 mL). The resulting mixture was extracted with Et_2O (5 x 40 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using a gradient of 1% to 20% EtOAc in hexane to afford (3-bromo-4-fluorophenyl)(trifluoromethyl)sulfane (1.2 g, 90% yield) as a clear, colorless oil.

Step B: Preparation of 2-bromo-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene: Sodium periodate (2.80 g, 13.1 mmol) was added all at once to (3-bromo-4-fluorophenyl)(trifluoromethyl)sulfane (1.20 g, 4.36 mmol) and $RuCl_3$ (22.6 mg, 0.11 mmol) in a mixture of ACN (10 mL), CCl_4 (10 mL), and water (20 mL) at room temperature and stirred for 2 h. The reaction mixture was extracted with EtOAc (3 x 50 mL), washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel with a gradient of 2% to 20% EtOAc in hexane to afford 2-bromo-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene (1.14 g, 85%) as a clear, colorless oil which became a white solid upon standing.

Step C: Preparation of 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (**5b**): Cesium carbonate (358 mg, 1.10 mmol) was added to a solution of 2-bromo-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene (307 mg, 1.00 mmol) and 3-chloro-5-fluorophenol (161 mg, 1.10 mmol) in NMP (3.0 mL) then warmed to 50 °C and stirred for 90 minutes.

The mixture was cooled to room temperature and purified directly by reverse phase chromatography with a gradient of 20% to 100% acetonitrile in water to afford 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (389 mg, 90% yield) as a white solid. LCMS ESI (-) *m/z* 430.8/432.8 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 1H), 7.93 (m, 1H), 7.08–7.02 (m, 2H), 6.93–6.91 (m, 1H), 6.78–6.74 (m, 1H).

2-Chloro-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (5c). Step A: Preparation of 2-chloro-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene: Trifluoromethyliodide (2.17 g, 11.1 mmol) was condensed into a solution of 3-chloro-4-fluorobenzenethiol (0.60 g, 3.7 mmol), methyl viologen dichloride (95 mg, 0.37 mmol) and Et_3N (1.3 mL, 9.2 mmol) in DMF (5.0 mL) at –78 °C. The tube was sealed with a threaded Teflon cap. The reaction mixture was allowed to warm to room temperature and was stirred for 60 h. The reaction mixture was cooled to –78 °C, opened carefully, and poured into brine (20 mL). The mixture was extracted with Et_2O (5 x 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* using a low temperature water bath. The crude product was purified by chromatography on silica gel with a gradient of 1% to 10% EtOAc in hexane to afford (3-chloro-4-fluorophenyl)(trifluoromethyl)sulfane (600 mg) as a clear, colorless oil which was used in the next reaction immediately. Sodium periodate (1.80 g, 8.40 mmol) was added to (3-chloro-4-fluorophenyl)(trifluoromethyl)sulfane (600 mg, 2.60 mmol) and $RuCl_3$ (14 mg, 0.065 mmol) in a mixture of acetonitrile (6 mL), CCl_4 (6 mL), and water (12 mL) at room temperature and stirred for 2 h. The reaction mixture was filtered and the filter cake was rinsed with CH_2Cl_2 (30 mL). The filtrate was extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel eluting with a gradient of 1% to 20% EtOAc in hexane to afford 2-chloro-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene (530 mg, 55% yield) as a clear, colorless oil which turned into a white solid upon cooling to –78 °C.

Step B: Preparation of 2-chloro-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (**5c**): Cesium carbonate (41.0 mg, 0.126 mmol) was added to 2-chloro-

1-fluoro-4-((trifluoromethyl)sulfonyl)benzene (30.0 mg, 0.110 mmol) and 3-fluoro-5-chlorophenol (18.0 mg, 0.130 mmol) in NMP (0.5 mL), warmed to 50 °C and stirred for 90 minutes. After cooling to room temperature, the mixture was purified directly by reverse phase chromatography with a gradient of 3% to 100% acetonitrile in water to afford 2-chloro-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (41.6 mg, 94% yield) as a clear oil. LCMS ESI (-) *m/z* 386.9, 388.9 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H), 7.91-7.87 (m, 1H), 7.11 (d, 1H), 7.04 (ddd, 1H), 6.93-6.91 (m, 1H), 6.76 (dt, 1H).

2-(3-Chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzonitrile (5d). Preparation of 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzonitrile (**5d**): $Pd(PPh_3)_4$ (14 mg, 0.013 mmol) was added to a mixture of $Zn(CN)_2$ (8.8 mg, 0.080 mmol) and 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (**5b**) (54 mg, 0.13 mmol) in NMP (1.0 mL) under nitrogen, then evacuated and back-filled with nitrogen five times. The reaction mixture was heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water (5 mL), extracted with Et_2O (4 x 10 mL), washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel eluting with a gradient of 1% to 24% EtOAc in hexane to afford 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzonitrile **5d** (28 mg, 60%) as a clear oil. LCMS ESI (-) *m/z* 379 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 1H), 8.13 (m, 1H), 7.16–7.13 (m, 1H), 7.11 (d, 1H), 7.03–7.01 (m, 1H), 6.88–6.85 (m, 1H).

Methyl 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoate (5e). Preparation of methyl 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoate (**5e**): Triethylamine (106 µL, 0.761 mmol) was added dropwise to a mixture of 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((trifluoromethyl)sulfonyl)benzene (**5b**) (110 mg, 0.250 mmol), $Pd(OAc)_2$ (5.7 mg, 0.025 mmol) and 1,3-bis(diphenylphosphino)propane (11 mg, 0.025 mmol) in DMF (1.5 mL) and MeOH (1.0 mL) that had been saturated with carbon monoxide. The reaction mixture was then warmed to 80 °C under a balloon of carbon monoxide for 3.5 h. The reaction mixture was cooled to room temperature and directly purified

by reverse phase chromatography with a gradient of 20% to 100% acetonitrile in water to afford methyl 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoate (47 mg, 45% yield) as a clear, colorless oil. LCMS ESI (-) *m/z* 411 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, 1H), 8.10–8.07 (m, 1H), 7.14 (d, 1H), 7.03–7.00 (m, 1H), 6.91–6.90 (m, 1H), 6.77–6.73 (m, 1H), 3.94 (s, 3H).

2-(3-Chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzamide (5f). Step A: Preparation of 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoic acid: Lithium hydroxide monohydrate (46 mg, 1.09 mmol) was added all at once to a solution of methyl 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoate (**5e**) (45 mg, 0.11 mmol) in 4:1 THF/water (1.2 mL) and stirred at room temperature for 6 h. The mixture was diluted with 4 N HCl (4 mL), extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification was achieved by reverse phase chromatography with a gradient of 20% to 100% acetonitrile in water to afford 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoic acid (27.8 mg, 64% yield) as a sticky white foam. LCMS ESI (-) m/z 396.9, 398.9 (M-H).

Step B: Preparation of 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzamide (**5f**): *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, (HATU) (42 mg, 0.11 mmol) was added all at once to a solution of 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoic acid (22 mg, 0.055 mmol), NH_4Cl (6.0 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (29 μL, 0.17 mmol) in DMF (0.5 mL) at room temperature then stirred for 16 h in a sealed reaction vial. The mixture was directly purified by reverse phase chromatography with a gradient of 20% to 100% acetonitrile in water to afford 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzamide (15 mg, 70% yield). LCMS ESI (+) *m/z* 398.0, 400.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, 1H), 8.07–8.04 (m, 1H), 7.21 (br s, 1H), 7.15–7.12 (m, 1H), 7.05 (d, 1H), 7.02–7.01 (m, 1H), 6.86–6.83 (m, 1H), 6.01 (br s, 1H).

(2-(3-Chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)phenyl)methanol (5g). DIBAL-H (1.0 M in heptanes, 174 μL, 0.174 mmol) was added dropwise to methyl 2-(3-chloro-5-fluorophenoxy)-

5-((trifluoromethyl)sulfonyl)benzoate (**5e**) (24.0 mg, 0.0583 mmol) dissolved in CH_2Cl_2 (0.5 mL) at 0 °C and stirred for 1 h. Excess DIBAL-H was quenched by the careful addition of acetone (0.5 mL). The mixture was diluted with water (2 mL), extracted with dichloromethane (3 x 5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on silica gel with a gradient of 20% to 55% EtOAc in hexane to afford (2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)phenyl)methanol (16.0 mg, 72% yield) as a clear oil. LCMS ESI (-) *m/z* 383 (M-H).

1-(3-Chloro-5-fluorophenoxy)-2-(difluoromethyl)-4-((trifluoromethyl)sulfonyl)benzene (5h). Step A: Preparation of 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzaldehyde: Dess-Martin periodinane (20 mg, 0.050 mmol) was added to (2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)phenyl)methanol (12 mg, 0.030 mmol) dissolved in ice cold CH_2Cl_2 (0.5 mL) and stirred for 40 minutes. The reaction was quenched with 1:1 saturated $NaHCO_3$:$Na_2S_2O_3$ aqueous solution (2 mL), extracted with CH_2Cl_2 (2 x 5 mL), dried (Na_2SO_4), filtered. and concentrated. The crude was purified by chromatography on silica gel with a gradient of 7% to 60% EtOAc in hexane to afford 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzaldehyde (11 mg, 92% yield) as a clear oil.

Step B: Preparation of 1-(3-chloro-5-fluorophenoxy)-2-(difluoromethyl)-4-((trifluoromethyl)sulfonyl)benzene (**5h**): (Diethylamino)sulfur trifluoride (10 mg, 0.080 mmol) was added to 2-(3-chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzaldehyde (5.0 mg, 0.010 mmol) in dichloromethane (0.2 mL) at room temperature and stirred for 4.5 days in a sealed flask. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), extracted with MTBE (3 x 3 mL), washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on silica gel with a gradient of 2% to 20% EtOAc in hexane to afford 1-(3-chloro-5-fluorophenoxy)-2-(difluoromethyl)-4-((trifluoromethyl)sulfonyl)benzene (4.0 mg, 75% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35–8.34 (m, 1H), 8.09–8.05 (m, 1H), 7.17–6.90 (m, 4H), 6.82–6.78 (m, 1H).

2-(3-Chloro-5-fluorophenoxy)-5-((trifluoromethyl)sulfonyl)benzoic acid (5i). See Step A in the synthesis of **5f**.

2-Bromo-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)benzene (5j). Step A: Preparation of (3-bromo-4-fluorophenyl)(difluoromethyl)sulfane: Diethyl (bromodifluoromethyl)phosphonate (2.58 g, 9.66 mmol) was added to a degassed mixture of 3-bromo-4-fluorobenzenethiol (1.00 g, 4.83 mmol) and KOH (5.42 g, 96.6 mmol) in acetonitrile (24 mL) and water (24 mL) at –78 °C under nitrogen. The cooling bath was removed immediately and the mixture was stirred at room temperature for 30 minutes. The reaction was diluted with water (20 mL), extracted with MTBE (4 x 50 mL), washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Crude (3-bromo-4-fluorophenyl)(difluoromethyl)sulfane (1.24 g) was used directly in the following reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.80 (m, 1H), 7.54–7.50 (m, 1H), 7.15 (t, 1H), 6.80 (t, 1H).

Step B: Preparation of 2-bromo-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene: Sodium periodate (2.58 g, 12.1 mmol) was added all at once to a stirred solution of (3-bromo-4-fluorophenyl)(difluoromethyl)sulfane (1.24 g, 4.83 mmol) and $RuCl_3$ (25 mg, 0.12 mmol) in a mixture of acetonitrile (10 mL), CCl_4 (10 mL), and water (20 mL) at room temperature and stirred for 2 h. The reaction mixture was filtered and the filter cake was washed with dichloromethane. The filtrate was washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel with a gradient of 5% to 40% EtOAc in hexanes to afford 2-bromo-1-fluoro-4-((trifluoromethyl)sulfonyl)benzene (1.16 g, 83% yield over 2 steps) as a clear, colorless oil which became a white solid upon standing.

Step C: Preparation of 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)benzene (**5j**): Cesium carbonate (358 mg, 1.10 mmol) was added to a mixture of 2-bromo-4-((difluoromethyl)sulfonyl)-1-fluorobenzene (289 mg, 1.00 mmol) and 3-chloro-5-fluorophenol (161 mg, 1.10 mmol) in NMP (3.0 mL) and stirred at 50 °C for 2.75 h. The mixture was cooled to room temperature and purified directly by reverse phase chromatography with a gradient of

20% to 100% acetonitrile in water to afford 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)benzene (369 mg, 89% yield) as a white solid. LCMS ESI (-) *m/z* 413 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, 1H), 7.89–7.87 (m, 1H), 7.07 (d, 1H), 7.04–7.00 (m, 1H), 6.90–6.89 (m, 1H), 6.75–6.72 (m, 1H), 6.21 (t, 1H).

2-Bromo-1-(3-chloro-5-fluorophenoxy)-4-(methylsulfonyl)benzene (5k). Step A: Preparation of 2-bromo-1-fluoro-4-(methylsulfonyl)benzene: *N*-Bromosuccinimide (579 mg, 3.25 mmol) was added in two equal portions over 30 minutes at room temperature to 1-fluoro-4-(methylsulfonyl)benzene (515 mg, 2.96 mmol) in concentrated H_2SO_4 (3.0 mL) and stirred for 6 h. The mixture was carefully poured onto ice and water (10 mL), extracted with CH_2Cl_2 (4 x 15 mL), washed with 3 N NaOH (10 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel with a gradient of 6% to 50% EtOAc in hexanes to afford 2-bromo-1-fluoro-4-(methylsulfonyl)benzene (530 mg, 71% yield) as a white solid.

Step B: Preparation of 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-(methylsulfonyl)benzene (**5k**): Cesium carbonate (176 mg, 0.540 mmol) was added to a mixture of 2-bromo-1-fluoro-4-(methylsulfonyl)benzene (114 mg, 0.450 mmol) and 3-chloro-5-fluorophenol (79 mg, 0.54 mmol) in NMP (2.0 mL) and heated at 50 °C for 20 h. The crude reaction mixture was purified by reverse phase chromatography with a gradient of 20% to 100% acetonitrile in water to afford 2-bromo-1-(3-chloro-5-fluorophenoxy)-4-(methylsulfonyl)benzene (113 mg, 66% yield) as a white solid. LCMS ESI (+) *m/z* 379.0, 380.9, 382.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H), 7.88 (dd, 1H), 7.10 (d, 1H), 6.96 (ddd, 1H), 6.83-6.81 (m, 1H), 6.67 (dt, 1H), 3.10 (s, 3H).

(2-Bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanamine (6a). Step A: Preparation of t-butyl (2-bromo-6-((difluoromethyl)thio)-3-fluorobenzyl)carbamate. A solution of 2-bromo-6-((difluoromethyl)thio)-3-fluorobenzonitrile (**15**) (45 mg, 0.16 mmol) in tetrahydrofuran (1 mL) was treated with borane dimethylsulfide complex (47 µL, 0.48 mmol) and stirred at 60 °C for 4 h. The reaction mixture was quenched by the addition of 1 mL of MeOH and 0.8 mL of 4 M HCl in dioxane. The resulting mixture stirred for 15 minutes at room temperature and 30 minutes at

50 °C. The reaction mixture was quenched by the addition of 2 mL of saturated $NaHCO_3$ and then concentrated under reduced pressure. The residue was solubilized with 10 mL of 1:1 CH_2Cl_2/water. The biphasic mixture was treated with t-butoxycarbonyl t-butyl carbonate (35 mg, 0.16 mmol) and stirred for 1 h. The reaction mixture was extracted with 3 x 15 mL 30% isopropyl alcohol in $CHCl_3$. The combined organics were rinsed with 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 5% to 30% EtOAc in hexane to give t-butyl (2-bromo-6-((difluoromethyl)thio)-3-fluorobenzyl)carbamate (56 mg, 91% yield). LCMS ESI (+) *m/z* 286, 288 (M+H-CO_2-C_4H_8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, 1H), 7.12 (dd, 1H), 6.82 (t, 1H), 4.96 (br s, 1H), 4.80 (d, 2H), 1.43 (br s, 9H).

Step B: Preparation of t-butyl-(2-bromo-6-((difluoromethyl)sulfonyl)-3-fluorobenzyl)carbamate. A procedure similar to Step I in the synthesis of **6c** was followed. LCMS ESI (+) *m/z* 362, 364 (M+H-C_4H_8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, 1H), 7.33 (dd, 1H), 6.80 (t, 1H), 5.30-5.10 (br, 1H), 4.91 (d, 2H), 1.43 (s, 9H).

Step C: Preparation of t-butyl-(2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)benzyl)carbamate: A procedure similar to Step J in the synthesis of **6c** was followed. Purification was achieved by chromatography on silica using a gradient of 5% to 30% EtOAc in hexane. t-butyl-(2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)benzyl)carbamate was isolated as a clear film (51 mg, 51% yield). LCMS ESI (+) *m/z* 488, 490, 492 (M+H-C_4H_8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1H), 7.02 (m, 1H), 6.99 (d, 1H), 6.90-6.88 (m, 1H), 6.73 (m, 1H), 6.62 (br t, 1H), 5.22 (br s, 1H), 4.95 (d, 2H), 1.45 (s, 9H).

Step D: Preparation of (2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanamine **(6a)**. A solution of t-butyl (2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)benzyl)carbamate (49 mg, 0.090 mmol) in dichloromethane (1 mL) at 25 °C was treated with 0.5 mL of TFA. The reaction mixture was left to stir for 1 h. Volatiles were removed by concentration under reduced pressure. The residue was solubilized with 15 mL of 30% isopropyl alcohol/$CHCl_3$ and poured into 10 mL of saturated aqueous $NaHCO_3$. The organic phase was

separated and the aqueous extracted further with 3 x 10 mL 30% isopropyl alcohol/$CHCl_3$. The combined organics were washed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. (2-Bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanamine **(6a)** was isolated as a clear film (35 mg, 87% yield) and used without further purification. LCMS ESI (+) *m/z* 444, 446, 448 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1H), 7.02 (m, 1H), 6.97 (d, 1H), 6.89 (m, 1H), 6.73 (m, 1H), 6.66 (t, 1H), 4.45 (br s, 2H).

***N*-(2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)benzyl)acetamide (6b).** A solution of (2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanamine (**6a**) (15 mg, 0.034 mmol) and triethylamine (9.6 µL, 0.070 mmol) in dichloromethane (1 mL) at 25 °C was treated with acetic anhydride (4.0 µL, 0.040 mmol) and stirred at 25 °C until complete by LCMS (~1 h). The reaction mixture was poured into 10 mL of saturated aqueous $NaHCO_3$ and extracted with 3 x 10 mL 30% isopropyl alcohol/$CHCl_3$. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. *N*-(2-Bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)benzyl)acetamide (**6b**) was isolated as a white solid (16.7 mg, 99% yield) and used without further purification. LCMS ESI (+) *m/z* 486, 488, 490 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1H), 7.03 (m, 1H), 6.99 (d, 1H), 6.90 (m, 1H), 6.74 (m, 1H), 6.66 (t, 1H), 6.11 (br s, 1H), 5.05 (d, 2H), 2.00 (s, 3H).

(2-Bromo-3-(3-chloro-5-fluorophenoxy)-6-(difluoromethyl)sulfonyl)phenyl)methanol (6c). Step A: Preparation of 2-bromo-3-fluoro-6-iodobenzoic acid **(13)**: 2-Bromo-3- fluoro-benzoic acid (7.5 g, 34 mmol) was combined with palladium (II) acetate (0.38 g, 1.7 mmol), iodine (8.7 g, 34 mmol), diacetoxy iodobenzene (11 g, 34 mmol) and DMF (165 mL). The resulting suspension was heated at 120 °C for 28 h then stirred at ambient temperature for 40 h. The reaction was concentrated to remove most of the DMF then the residue was poured into 0.1 M HCl (resultant pH <3) and extracted with Et_2O. Solid $Na_2S_2O_3$ was added to dissipate some of the iodine color. After separation, the aqueous layer was washed three times with Et_2O (100 mL each). The combined organic layers were washed with 1 M $Na_2S_2O_3$ to remove the remaining purple color. The organic layer was washed with brine, dried over

Na_2SO_4, and concentrated *in vacuo*. The crude product solidified after standing under vacuum to afford 2-bromo-3-fluoro-6-iodobenzoic acid **(13)** (8.0 g, 67%) and was used without further purification. LCMS ESI (+) *m/z* 344.8, 346.8 (M+H).

Step B: Preparation of 2-bromo-3-fluoro-6-iodobenzamide: 2-Bromo-3-fluoro- 6-iodobenzoic acid **(13)** (2.33 g, 6.76 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. The solution was treated with DMF (10 drops) followed by dropwise addition of thionyl chloride (1.0 mL, 10 mmol) then stirred for 10 minutes. The reaction was warmed to ambient temperature and stirred for 2 h. The mixture was recooled to 0 °C and treated with concentrated ammonium hydroxide (5 mL) and the mixture allowed to warm to ambient temperature and stirred overnight. The mixture was concentrated *in vacuo* then dissolved in saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 2-bromo-3-fluoro-6-iodobenzamide as a white solid (2.20 g, 94%) that was used without further purification. LCMS ESI (+) *m/z* 343.8, 345.8 (M + H).

Step C: Preparation of 2-bromo-3-fluoro-6-iodobenzonitrile **(14)**: 2-Bromo-3-fluoro-6-iodobenzamide (10.0 g, 29.1 mmol) was suspended in phosphorus oxychloride (41 mL), treated with triethylamine (12.2 mL, 87.2 mmol), then the mixture was heated to 75 °C for 3 h. The reaction was stirred overnight at ambient temperature. The mixture was concentrated *in vacuo* to remove excess $POCl_3$ then the residue was treated with ice and water. The mixture was stirred until the ice melted and the beige solid was collected by filtration, washed with water and air-dried to afford 2-bromo-3-fluoro-6-iodobenzonitrile **(14)** (8.04 g, 85%). Used without further purification.

Step D: Preparation of *S*-(3-bromo-2-cyano-4-fluorophenyl) ethanethioate: To a mixture of 2-bromo-3-fluoro-6-iodo-benzonitrile **(14)** (1.00 g, 3.07 mmol), $Pd_2(dba)_3$ (140 mg, 0.150 mmol), potassium ethanethiolate (350 mg, 3.07 mmol), and xantphos (178 mg, 0.310 mmol) under argon was added degassed Toluene (8 mL) and Acetone (4 mL). The mixture was flushed with nitrogen, sealed, and heated at 72 °C overnight. The reaction mixture was concentrated under reduced pressure and dissolved in DCM, filtered through a pad of silica gel with 50% EtOAc/hexane. The filtrate was concentrated. The

residue was purified by flash column chromatography with a gradient of 0% to 15% EtOAc in hexanes to afford *S*-(3-bromo-2-cyano-4-fluorophenyl) ethanethioate as a light yellow solid (712 mg, 84%). LCMS ESI (+) *m/z* 273.9, 275.9 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.48 (m, 1H), 7.41-7.34 (m, 1H), 2.52 (s, 3H).

Step E: Preparation of 2-bromo-3-fluoro-6-mercaptobenzonitrile: To a solution of *S*-(3-bromo-2-cyano-4-fluorophenyl) ethanethioate (710 mg, 2.59 mmol) in THF (12.0 mL) under N_2 was added concentrated ammonium hydroxide (3.0 mL). The reaction was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure. 1 N HCl was added to adjust pH of the aqueous layer to about 2. The mixture was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 2-bromo-3-fluoro-6-mercaptobenzonitrile as a yellow solid (607 mg, 100%) that was used without further purification. LCMS ESI (-) *m/z* 229.9, 231.9 (M-H).

Step F: Preparation of 2-bromo-6-((difluoromethyl)thio)-3-fluorobenzonitrile (**15**): To a mixture of 2-bromo-3-fluoro-6-mercaptobenzonitrile (605 mg, 2.61 mmol) and potassium hydroxide (2.92 g, 52.1 mmol) in acetonitrile (20.0 mL) and water (4.0 mL) at -78 °C was added bromodifluoromethyl diethylphosphonate (0.930 mL, 5.21 mmol). The reaction was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was diluted with brine (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification by chromatography on silica gel using a gradient of 0% to 30% EtOAc in hexanes gave 2-bromo-6-((difluoromethyl)thio)-3-fluorobenzonitrile (**15**) (410 mg 55% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, 1H), 7.39 (dd, 1H), 6.93 (t, 1H).

Step G: Preparation of 2-bromo-6-((difluoromethyl)thio)-3-fluorobenzaldehyde: A solution of 2-bromo-6-(difluoromethylsulfanyl)-3-fluoro-benzonitrile **(15)** (300 mg, 1.06 mmol) in DCM (7 mL) at 0 °C was treated with DIBAL-H (1.0 M solution in heptane, 1.49 mL, 1.49 mmol) and allowed to warm to room temperature over 1 h. The reaction mixture was quenched by the addition of 10% HCl (2 mL). The

resulting mixture was stirred vigorously for 30 minutes. Then the sample was treated with 20% aqueous potassium sodium tartrate (2 mL) and stirred vigorously for another 30 minutes. The reaction mixture was made basic with 10% aqueous NaOH and extracted with 3 x 20 mL DCM. The combined organics were rinsed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by chromatography on silica gel using a gradient of 0% to 20% EtOAc in hexanes to give 2-bromo-6-((difluoromethyl)thio)-3-fluorobenzaldehyde as a solid (146 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.66 (dd, 1H), 7.34 (dd, 1H), 6.92 (t, 1H).

Step H: Preparation of (2-bromo-6-((difluoromethyl)thio)-3-fluorophenyl)methanol: A solution of 2-bromo-6-(difluoromethylsulfanyl)-3-fluoro-benzaldehyde (145 mg, 0.51 mmol) in methanol (3.4 mL) at 25 °C was treated with sodium borohydride (28.9 mg, 0.76 mmol) and stirred at 25 °C for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL). MeOH was removed by concentration under reduced pressure. The reaction mixture was poured into water (20 mL) and extracted with 3 x 20 mL EtOAc. The combined organics were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated to dryness. The resulting (2-bromo-6-((difluoromethyl)thio)-3-fluorophenyl)methanol was used without further purification. LCMS ESI (+) *m/z* 268.9, 270.9 (M – OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, 1H), 7.15 (dd, 1H), 6.88 (t, 1H), 5.12 (dd, 2H), 2.15 (t, 1H).

Step I: Preparation of 2-bromo-6-((difluoromethyl)sulfonyl)-3-fluorophenyl)methanol (**16**): A solution of (2-bromo-6-((difluoromethyl)thio)-3-fluorophenyl)methanol (142 mg, 0.50 mmol) in DCM (5 mL) at 0 °C was treated with 3-chloroperbenzoic acid (267 mg, 1.19 mmol) and stirred overnight at room temperature. The reaction mixture was poured into 1 M NaOH (10 mL) and extracted with 3 x 20 mL DCM. The combined organics were washed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica gel using a gradient of 5% to 30% EtOAc in hexanes to give 2-bromo-6-((difluoromethyl)sulfonyl)-3-fluorophenyl)methanol (**16**) as a solid (99 mg, 62% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, 1H), 7.36 (dd, 1H), 6.48 (t, 1H), 5.20 (dd, 2H), 2.67 (t, 1H).

Step J: Preparation of (2-bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanol (**6c**): A solution of 3-chloro-5-fluoro-phenol (15.9 mg, 0.11 mmol) and 2-bromo-6-((difluoromethyl)sulfonyl)-3-fluorophenyl)methanol **(16)** (34.7 mg, 0.11 mmol) in DMF (0.5 mL) at room temperature was treated with potassium carbonate (15.0 mg, 0.11 mmol) and stirred at 80 °C for 1 h. The reaction mixture was purified directly by reverse phase chromatography using a gradient of 40% to 80% acetonitrile in water. (2-Bromo-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanol (**6c**)was isolated as a white solid (22.3 mg, 46%). LCMS ESI (+) *m/z* 461.8, 463.8, 465.8 ($M + NH_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H), 7.04-6.99 (m, 2H), 6.90 (m, 1H), 6.73 (m, 1H), 6.48 (t, 1H), 5.25 (d, 2H), 2.69 (t, 1H).

(2-Chloro-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanol (6d). Step A: Preparation of 2-chloro-3-fluoro-6-sulfanyl-benzonitrile: A flask containing a solution of 2-chloro-3,6-difluoro-benzonitrile (2.00 g, 11.5 mmol) in DMF (10 mL) was sparged with nitrogen, cooled in ice, and treated with sodium sulfide (944 mg, 12.1 mmol). The yellow suspension was stirred and slowly allowed to warm to ambient temperature. After 45 minutes, the reaction mixture was diluted with 1 M NaOH, washed with 2 portions of DCM, acidified to pH 2 with concentrated HCl, and extracted with 2 portions of DCM. The DCM was washed with two portions of brine, dried over $MgSO_4$, filtered, and evaporated to yield 2-chloro-3-fluoro-6-sulfanyl-benzonitrile (1.44 g, 67% yield) as a waxy pale yellow solid. LCMS ESI (-) *m/z* 185.9, 187.9 (M-H).

Step B: Preparation of 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzonitrile: Bromodifluoromethyl diethylphosphonate (384 mg, 1.44 mmol) was added to a degassed frozen slurry of 2-chloro-3-fluoro-6-sulfanyl-benzonitrile (180 mg, 0.957 mmol) and potassium hydroxide (807 mg, 14.4 mmol) in acetonitrile (4 mL) and water (4 mL) cooled in dry ice/acetone under nitrogen. The mixture was allowed to warm to ambient temperature. After 20 minutes, the reaction mixture was partitioned between MTBE and brine. The MTBE was washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. The crude was purified by chromatography on silica gel with a gradient of 10% to 60%

EtOAc in hexane to give 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzonitrile (77 mg, 34% yield) as a colorless oil. LCMS ESI (+) *m/z* 237.9, 239.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, 1H), 7.43 (t, 1H), 6.93 (t, 1H).

Step C: Preparation of 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzaldehyde: Diisobutylaluminum hydride solution (1.0 M in heptane, 1.18 mL, 1.18 mmol) was added to an ice cold solution of 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzonitrile (200 mg, 0.837 mmol) in dichloromethane (5 mL). After 1 h, the reaction mixture was treated with methanol (2 mL), then 10% HCl (2 mL). The reaction mixture was stirred for 1 h. The mixture was then concentrated and the aqueous residue was partitioned between EtOAc and water. The EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford a pale yellow oil. The crude was purified by chromatography on silica gel with a 10% to 60% EtOAc in hexane gradient to give 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzaldehyde (124 mg, 61% yield) as a colorless glass. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.61 (dd, 1H), 7.38 (t, 1H), 6.93 (t, 1H).

Step D: Preparation of [2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-phenyl]methanol: Sodium borohydride (29 mg, 0.77 mmol) was added to an ice cold solution of 2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-benzaldehyde (124 mg, 0.52 mmol) in methanol (10 mL). The reaction mixture was allowed to slowly warm to ambient temperature. After 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl and concentrated. The aqueous slurry was partitioned between EtOAc and water. The EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield [2-chloro-6-(difluoromethylsulfanyl)-3-fluoro-phenyl]methanol (110 mg, 88 % yield) as a colorless oil. LCMS ESI (+) *m/z* 266.0, 268.0 (M+Na). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, 1H), 7.18 (t, 1H), 6.87 (t, 1H), 5.08 (s, 2H), 2.16 (br s, 1H).

Step E: Preparation of [2-chloro-6-(difluoromethylsulfonyl)-3-fluoro-phenyl]methanol: 3-Chloroperbenzoic acid (235 mg, 1.36 mmol) was added to a solution of [2-chloro-6-

(difluoromethylsulfanyl)-3-fluoro-phenyl]methanol (110 mg, 0.451 mmol) in DCM (10 mL). The vial was sealed and heated at 45 °C. After 4.5 h, the reaction mixture was concentrated, diluted with EtOAc, washed twice with a mixture of saturated aqueous $NaHCO_3$ and 1 M sodium thiosulfate, then with water and brine, dried over $MgSO_4$, filtered, and evaporated to afford a colorless oil that solidified. The crude was purified by chromatography on silica gel with a 10% to 80% EtOAc in hexane gradient to give [2-chloro-6-(difluoromethylsulfonyl)-3-fluoro-phenyl]methanol (94 mg, 76% yield) as a waxy white solid. LCMS ESI (-) *m/z* 318.9, 320.9 (M-H+HCO_2H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.05 (m, 1H), 7.39 (t, 1H), 6.49 (dt, 1H), 5.16 (d, 2H), 2.85 (t, 1H).

Step F: Preparation of (2-chloro-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanol **(6d)**: 3-Chloro-5-fluoro-phenol (0.004 mL, 0.04 mmol) was added to a solution of [2-chloro-6-(difluoromethylsulfonyl)-3-fluoro-phenyl]methanol (10 mg, 0.040 mmol) and $NaHCO_3$ (6.1 mg, 0.070 mmol) in DMF (0.5 mL) in a vial. The vial was sealed and heated at 80 °C. After 3 h, the reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel with a gradient of 10% to 60% EtOAc in hexane to give (2-chloro-3-(3-chloro-5-fluorophenoxy)-6-((difluoromethyl)sulfonyl)phenyl)methanol (8.8 mg, 60% yield) as a white solid. LCMS ESI (-) *m/z* 444.9, 446.8 (M-H+HCO_2H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H), 7.06 (d, 1H), 7.04-7.01 (m, 1H), 6.91-6.88 (m, 1H), 6.76-6.71 (m, 1H), 6.47 (t, 1H), 5.21 (d, 2H), 2.69 (t, 1H).

2-Chloro-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)-3-(methoxymethyl)benzene (6e). Step A: Preparation of [2-chloro-3-(3-chloro-5-fluoro-phenoxy)-6-(difluoromethylsulfonyl)phenyl]methyl methanesulfonate: Methanesulfonyl chloride (0.0039 mL, 0.050 mmol) was added to an ice cold solution of [2-chloro-3-(3-chloro-5-fluoro-phenoxy)-6-(difluoromethylsulfonyl)phenyl]methanol (**6d**) (16.9 mg, 0.0423 mmol) and triethylamine (0.010 mL, 0.11 mmol) in DCM (2 mL). The mixture was allowed to slowly warm to ambient temperature. After 2 h,

the reaction mixture was diluted with DCM, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to afford [2-chloro-3-(3-chloro-5-fluoro-phenoxy)-6-(difluoromethylsulfonyl)phenyl]methyl methanesulfonate as a colorless film that was used immediately in the next step without further purification.

Step B: Preparation of 2-chloro-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)-3-(methoxymethyl)benzene **(6e)**: A solution of 25% sodium methoxide in methanol (0.01 mL, 0.04 mmol) was added to a solution of [2-chloro-3-(3-chloro-5-fluoro-phenoxy)-6-(difluoromethylsulfonyl)phenyl]methyl methanesulfonate (20 mg, 0.04 mmol) in methanol (1 mL). The mixture was heated at 50 °C for 30 minutes. Another equivalent of 25% sodium methoxide in methanol was added. After 2 h, the reaction mixture was evaporated and the residue was partitioned between EtOAc and dilute brine. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel with a gradient of 10% to 60% EtOAc in hexane. 2-Chloro-1-(3-chloro-5-fluorophenoxy)-4-((difluoromethyl)sulfonyl)-3-(methoxymethyl)benzene was obtained as a colorless film (0.9 mg, 5% yield). LCMS ESI (+) *m/z* 414.9, 416.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H), 7.06 (d, 1H), 7.04-7.01 (m, 1H), 6.91-6.88 (m, 1H), 6.76-6.71 (m, 1H), 6.47 (t, 1H), 5.21 (d, 2H), 2.69 (t, 1H).

4-Bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7a). Step A: Preparation of methyl 2-bromo-3-fluoro-6-iodobenzoate **(17)**: 2-Bromo-3-fluoro-6-iodo-benzoic acid **(13)** (0.81 g, 2.3 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), then treated with potassium carbonate (0.97 g, 7.0 mmol) and iodomethane (0.44 mL, 7.0 mmol). The mixture was stirred at ambient temperature for 60 h. The suspension was dissolved in diethyl ether and water and separated. The organic layer was washed five times with water, then with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 2-bromo-3-fluoro-6-iodobenzoate **(17)** as a white solid (0.76 g, 90% yield). LCMS ESI (+) *m/z* 358.8, 360.8 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, 1H), 6.92 (dd, 1H), 4.00 (s, 3H).

Step B: Preparation of methyl 6-(acetylthio)-2-bromo-3-fluorobenzoate: Methyl 2-bromo-3-fluoro-6-iodobenzoate **(17)** (1.26 g, 3.51 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 243 mg, 0.42 mmol) were suspended in 2:1 toluene/acetone (17 mL). The mixture was sparged with argon, then treated with tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3, 192 mg, 0.21 mmol) and potassium ethanethioate (500 mg, 4.38 mmol). The reaction mixture was sealed in a tube, stirred vigorously, and heated at 70 °C for 2 h. The reaction was cooled, diluted with DCM, treated with Celite, then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to an orange oil. The crude mixture was chromatographed on silica gel eluting with a gradient ethyl acetate in hexane. Methyl 6-(acetylthio)-2-bromo-3-fluorobenzoate was obtained as a yellow oil (0.71 g, 66%). LCMS ESI (+) *m/z* 306.9, 308.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 1H), 7.25-7.21 (m, 1H), 3.95 (s, 3H), 2.41 (s, 3H).

Step C: Preparation of methyl 2-bromo-3-fluoro-6-(methylthio)benzoate: Methyl 6-(acetylthio)-2-bromo-3-fluorobenzoate (1.21 g, 3.93 mmol) was dissolved in methanol (12 mL) and degassed with argon for 5 minutes. The solution was treated with cesium carbonate (1.66 g, 5.09 mmol), then the solution was stirred at ambient temperature for 55 minutes. The reaction mixture was treated with iodomethane (1.22 mL, 20 mmol) and stirred overnight under argon. The reaction mixture was concentrated *in vacuo* and redissolved in diethyl ether and water. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo*. Methyl 2-bromo-3-fluoro-6-(methylthio)benzoate was obtained as a yellow oil (0.97 g, 88%). LCMS ESI (+) *m/z* 296.0, 297.9 (M+NH_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 1H), 7.16-7.11 (m, 1H), 3.98 (s, 3H), 2.45 (s, 3H).

Step D: Preparation of methyl 2-bromo-3-fluoro-6-(methylsulfonyl)benzoate **(18)**: A solution of methyl 2-bromo-3-fluoro-6-(methylthio)benzoate (3.57 g, 12.8 mmol) in methanol (63 mL) was added dropwise to a solution of Oxone® (23.6 g, 38.4 mmol) in water (63 mL). The reaction mixture was stirred at ambient temperature for 20 h, and then heated at 60° C. for 6 h. The reaction mixture was concentrated

in vacuo. The residue was diluted with water and ethyl acetate and the layers separated. The aqueous layer was washed with a second portion of ethyl acetate and then the combined organics were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellowish solid (3.7 g). The crude material was chromatographed on silica gel with a gradient of ethyl acetate in hexane to give methyl 2-bromo-3-fluoro-6-(methylsulfonyl)benzoate **(18)** as a white solid (3.07 g, 77%). LCMS ESI (+) *m/z* 327.9, 329.9 ($M+NH_4$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.04-8.01 (m, 1H), 7.37-7.33 (m, 1H), 4.02 (s, 3H), 3.17 (s, 3H).

Step E: Preparation of methyl 2-bromo-3-(3-chloro-5-fluoro-phenoxy)-6-methylsulfonyl-benzoate **(19)**: Methyl 2-bromo-3-fluoro-6-methylsulfonyl-benzoate **(18)** (400 mg, 1.29 mmol) was combined with 3-chloro-5-fluoro-phenol (245 mg, 1.67 mmol) and *N*,*N*-dimethylformamide (3.0 mL). The solution was treated in a single portion with sodium bicarbonate (216 mg, 2.57 mmol) and the reaction mixture was heated at 90 °C for 24 h. The reaction mixture was cooled to room temperature, then purified directly by reverse phase chromatography, eluting with a gradient of 20% to 100% acetonitrile in water to afford methyl 2-bromo-3-(3-chloro-5-fluoro-phenoxy)-6-methylsulfonyl-benzoate **(19)** (510 mg, 91% yield). LCMS ESI (+) *m/z* 434.8, 436.8, 438.8 (M+H).

Step F: Preparation of 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-1,1-dioxo-benzothiophen-3-one **(20)**: Sodium hydride (60% in mineral oil, 140 mg, 3.5 mmol) was washed three times with hexane, then resuspended in tetrahydrofuran (3.0 mL). The suspension was cooled to 0° C. and treated dropwise with a solution of methyl 2-bromo-3-(3-chloro-5-fluoro-phenoxy)-6-methylsulfonyl-benzoate **(19)** (510 mg, 1.17 mmol) dissolved in tetrahydrofuran (7.0 mL). After the addition, the reaction mixture was warmed to ambient temperature and stirred for 1 h. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. Ethyl acetate and some water were added, the solids were resolubilized, then the pH of the aqueous was adjusted to 3-4 with 10% aqueous $KHSO_4$. After separation, the aqueous layer was washed twice with ethyl acetate. The combined organics were washed twice with water, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-1,1-dioxo-

benzothiophen-3-one **(20)** (333 mg, 70% yield). LCMS ESI (−) *m/z* 402.8, 404.8, 406.8 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.44 (d, 1H), 6.98 (dt, 1H), 6.80 (m, 1H), 6.67 (dt, 1H), 4.20 (s, 2H).

Step I: Preparation of 4-bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,3-dihydrobenzo[b]thiophene 1,1-dioxide **(7a)**: A solution of 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-1,1-dioxo-benzothiophen-3-one **(20)** (31 mg, 0.080 mmol) in methanol (1.5 mL) and dichloromethane (0.75 mL) at 0 °C was treated with sodium borohydride (1.5 mg, 0.040 mmol) and stirred at 0 °C for 45 minutes. The reaction mixture was quenched by the addition of water (1 mL). Volatiles were removed by concentration under reduced pressure. The reaction mixture was poured into 10 mL water and extracted with 3×15 mL EtOAc. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica gel using a gradient of 20% to 70% EtOAc in hexane to give 4-bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,3-dihydrobenzo[b]thiophene 1,1-dioxide **(7a)** as a clear thin film (22 mg, 71%). LCMS ESI (+) *m/z* 423.8, 425.8, 427.8 ($M+NH_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 1H), 7.19 (d, 1H), 6.98-6.94 (ddd, 1H), 6.82-6.80 (m, 1H), 6.67 (dt, 1H), 5.60 (td, 1H), 3.80 (dd, 1H), 3.68 (dd, 1H), 2.89 (d, 1H).

4-Bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7b). Step A: Preparation of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluorobenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **(21a)**: A solution of 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-1,1-dioxo-benzothiophen-3-one **(20)** (200 mg, 0.490 mmol) in acetonitrile (7.4 mL) at 25 °C was sparged with nitrogen for 3 minutes and then treated with sodium carbonate (115 mg, 1.08 mmol). The resulting suspension was stirred for 1.5 h. Selectfluor® (384 mg, 1.08 mmol) was added and the reaction mixture left to stir at 25 °C for 2 h. Volatiles were removed by concentration under reduced pressure. The reaction mixture was suspended in 30 mL water and extracted with 3 x 20 mL 30%IPA/$CHCl_3$. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica gel using a gradient of 10% to 30% EtOAc in hexanes to afford 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-

difluorobenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **(21a)** as a white solid (176.5 mg, 81%). LCMS ESI (−) *m/z* 440.8/442.8/444.8 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H), 7.50 (d, 1H), 7.05 (ddd, 1H), 6.89-6.86 (m, 1H), 6.73 (dt, 1H).

Step B: Preparation of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)**: A solution of 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-2,2-difluoro-1,1-dioxo-benzo[b]thiophen-3-one **(21a)** (18.0 mg, 0.041 mmol) in methanol (2.0 mL) at 0 °C was treated with sodium borohydride (1.5 mg, 0.040 mmol) and stirred at 0 °C for 30 minutes. The reaction mixture was quenched by the addition of 0.5 mL water. Volatiles were removed by concentration under reduced pressure. The mixture was poured into 10 mL water and extracted with 3 × 20 mL EtOAc. The combined organics were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 10% to 30% EtOAc in hexanes to afford 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** as a white solid (13.0 mg, 72%). LCMS ESI (+) *m/z* 424.7, 426.8, 428.8 (M-OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 1H), 7.22 (d, 1H), 7.01 (dt, 1H), 6.87-6.85 (m, 1H), 6.71 (dt, 1H), 5.38 (d, 1H), 2.98 (br s, 1H).

4-Bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,2-dimethyl-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7c). Step A: Preparation of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-dimethylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **(21b)**: Iodomethane (31 μL, 0.49 mmol) was added to a mixture of 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-1,1-dioxo-benzothiophen-3-one (40 mg, 0.10 mmol) and potassium carbonate (41 mg, 0.30 mmol) in *N*,*N*-dimethylformamide (1.0 mL) at room temperature and then stirred for 2 h. The reaction mixture was diluted with water (5 mL), and extracted with ethyl acetate (3 ×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-dimethylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **(21b)** was used directly in the next reaction without purification. LCMS ESI (+) *m/z* 433, 435, 437 (M+H).

Step B: Preparation of 4-bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,2-dimethyl-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7c)**: Sodium borohydride (4.0 mg, 0.10 mmol) was added all at once to 4-bromo-5-(3-chloro-5-fluoro-phenoxy)-2,2-dimethyl-1,1-dioxo-benzothiophen-3-one **(21b)** (43 mg, 0.10 mmol) in methanol (2.0 mL) at room temperature and stirred for 10 minutes. The reaction was quenched with saturated aqueous ammonium chloride (2.0 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using a gradient of 5% to 45% ethyl acetate in hexane as eluent affording 4-bromo-5-(3-chloro-5-fluorophenoxy)-3-hydroxy-2,2-dimethyl-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7c)** (20 mg, 47% yield over 2 steps). LCMS ESI (+) *m/z* 451.8/453.8/455.8 ($M + NH_4$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (dd, 1H), 7.16 (d, 1H), 6.98-6.95 (m, 1H), 6.83-6.82 (m, 1H), 6.66 (dt, 1H), 1.65 (s, 3H), 1.40 (s, 3H).

4-Chloro-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7d). A solution of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** (5.8 mg, 0.013 mmol) in 1-methyl-2-pyrrolidone (0.5 mL) was treated with copper(I) chloride (13 mg, 0.13 mmol) and stirred at 170 °C by microwave irradiation for 30 minutes. The reaction mixture was poured into 30 mL water and extracted with 3 × 10 mL Et_2O. The combined organics were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 0% 10% EtOAc in CH_2Cl_2 to afford 4-chloro-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7d)** as a white solid (2.6 mg, 50%). LCMS ESI (−) *m/z* 396.9, 398.9, 400.8 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 1H), 7.26 (d, 1H), 7.01 (ddd, 1H), 6.87-6.85 (m, 1H), 6.71 (dt, 1H), 5.44 (dd, 1H), 2.94 (d, 1H).

5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-methyl-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7e). A solution of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** (10.6 mg, 0.024 mmol) and

potassium methyltrifluoroborate (4.4 mg, 0.036 mmol) in 1,4-dioxane (0.5 mL) and water (50 μL) was sparged with nitrogen for 3 minutes. The reaction mixture was then treated sequentially with cesium carbonate (39 mg, 0.12 mmol) and dichloro[1;1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct ($Pd(dppf)Cl_2$ CH_2Cl_2, 1.9 mg, 10 mol %) under continuous nitrogen stream. The vessel was sealed and heated to 100 °C overnight. The reaction mixture was poured into 20 mL water and extracted with 3 × 10 mL EtOAc. The combined organics were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 10% to 15% EtOAc in hexane to afford 5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-methyl-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7e)** as a white solid (2.5 mg, 28%). LCMS ESI (−) *m/z* 376.9, 378.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H), 7.16 (d, 1H), 6.95 (ddd, 1H), 6.80-6.78 (m, 1H), 6.64 (dt, 1H), 5.30 (dd, 1H), 2.72 (dd, 1H), 2.43 (s, 3H).

5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile 1,1-dioxide (7f). A solution of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** (18.9 mg, 0.0443 mmol) in 1-methyl-2-pyrrolidone (0.25 mL) was treated with copper (I) cyanide (4.6 mg, 0.050 mmol) and heated at 160 °C by microwave irradiation for 30 minutes. The reaction mixture was poured into 30 mL water and extracted with 3 × 10 mL Et_2O. The combined organics were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 10% to 30% EtOAc in hexane to afford 5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene-4-carbonitrile 1,1-dioxide **(7f)** as a white solid (2.9 mg, 17%). LCMS ESI (−) *m/z* 387.9/389.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 1H), 7.19 (d, 1H), 7.12 (ddd, 1H), 6.99-6.97 (m, 1H), 6.83 (dt, 1H), 5.58-5.51 (m, 1H), 3.51 (br d, 1H).

5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7g).: A solution of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** (12 mg, 0.028 mmol) in toluene (0.4 mL) at 25 °C was treated

with borane dimethylsulfide complex (0.15 mL, 1.58 mmol) and stirred at 25 °C overnight. Lithium borohydride solution (1.0 M in tetrahydrofuran, 0.27 mL, 0.27 mmol) was added. The resulting mixture was heated to 60 °C for 1 day. Volatiles were removed by concentration under reduced pressure. The remaining residue was solubilized with 30 mL of 3% aqueous HCl and extracted with 3×15 mL EtOAc. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Repeated purifications (3×) by chromatography on silica using a gradient of 10% to 15% EtOAc in hexane afforded 5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7g)** as a thin film (1.6 mg, 15%). LCMS ESI (−) *m/z* 362.9/364.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 1H), 7.27-7.23 (m, 2H), 7.01 (dt, 1H), 6.90-6.88 (m, 1H), 6.72 (dt, 1H), 5.35 (q, 1H), 2.79 (dd, 1H).

5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-(trifluoromethyl)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7h). Step A: Preparation of 5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-iodo-2,3-dihydrobenzo[b]thiophene 1,1-dioxide: A solution of 4-bromo-5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7b)** (32.4 mg, 0.0759 mmol) in 1-methyl-2-pyrrolidone (1.5 mL) was treated with copper (I) iodide (208 mg, 1.09 mmol) and heated at 180 °C by microwave irradiation for 1 h. The reaction mixture was poured into 30 mL water and extracted with 3×10 mL Et_2O. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 5% to 20% EtOAc in hexane to afford 5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-iodo-2,3-dihydrobenzo[b]thiophene 1,1-dioxide as a beige solid (20 mg, 56%). LCMS ESI (−) *m/z* 488.7, 490.7 (M−H).

Step B: Preparation of 5-(3-chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-(trifluoromethyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide **(7h)**: A solution of 5-(3-chloro-5-fluoro-phenoxy)-2,2-difluoro-4-iodo-1,1-dioxo-3H-benzothiophen-3-ol (20 mg, 0.041 mmol) in *N*,*N*-dimethylformamide (0.8 mL) was sparged with nitrogen for 3 minutes, treated with (1,10-

phenanthroline)(trifluoromethyl)copper(I) (19 mg, 0.06 mmol) under a stream of nitrogen, sealed, and stirred overnight at 50 °C. After cooling, the reaction mixture was diluted with Et_2O and filtered through a pad of Celite. The Celite pad was washed with Et_2O. The combined filtrate was washed sequentially with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by flash column chromatography on silica gel using a gradient of 10% to 20% EtOAc in hexane to afford 5-(3-Chloro-5-fluorophenoxy)-2,2-difluoro-3-hydroxy-4-(trifluoromethyl)-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide **(7h)** as a thin film (4.9 mg, 28%). LCMS ESI (−) *m/z* 430.8, 432.8 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, 1H), 7.29 (d, 1H), 7.04 (ddd, 1H), 6.91-6.89 (m, 1H), 6.74 (dt, 1H), 5.58 (d, 1H), 3.16 (br s, 1H).

5-(3-Chloro-5-fluorophenoxy)-4-(difluoromethyl)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (7i). For detailed synthetic procedures see the synthesis of **8b**. **7i** was prepared analogously to **8b**, substituting 3-chloro-5-fluorophenol for 3-fluoro-5-hydroxy-benzonitrile in Step E. LCMS ESI (−) *m/z* 412.9, 414.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.25 (t, 1H), 7.21-7.17 (m, 1H), 7.06 (ddd, 1H), 6.92-6.89 (m, 1H), 6.75 (dt, 1H), 5.67 (dd, 1H), 3.10 (dd, 1H).

5-(Difluoromethyl)-6-(3,5-difluorophenoxy)-4-hydroxythiochromane 1,1-dioxide (7j). Step A: Preparation of 6-(benzylthio)-2-(difluoromethyl)-3-fluorobenzonitrile: A solution of 2-(difluoromethyl)-3,6-difluoro-benzonitrile **(22)** (1.50 g, 7.93 mmol) in acetonitrile (40 mL, previously sparged with nitrogen for 5 minutes) at – 40 °C was treated with sodium phenylmethanethiolate (1.16 g, 7.90 mmol) in 2 portions over 10 minutes. The resulting suspension was stirred initially at – 40 °C and then allowed to slowly warm towards room temperature (the reaction remained immersed in the acetone bath during this time). The reaction was quenched when the temperature reached 10 °C. The reaction mixture was poured into 300 mL water and extracted with 3×100 mL Et_2O. The combined organics were washed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved using reverse phase chromatography with a gradient of 40% to 95% acetonitrile in water to

afford 6-(benzylthio)-2-(difluoromethyl)-3-fluorobenzonitrile as an off-white solid (650 mg, 28%). LCMS ESI (−) *m/z* 292.0 (M−H).

Step B: Preparation of 6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)benzonitrile: A solution of 6-(benzylthio)-2-(difluoromethyl)-3-fluorobenzonitrile (800 mg, 2.73 mmol) and cesium hydrogen carbonate (582 mg, 3.00 mmol) in *N*,*N*-dimethylformamide (6.8 mL) was treated with 3,5-difluorophenol (355 mg, 2.73 mmol) and stirred at 100 °C for 2 h. The reaction mixture was poured into 70 mL water and extracted with 3×30 mL Et_2O. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The product residue was used without further purification. LCMS ESI (+) *m/z* 421.0 ($M+NH_4$).

Step C: Preparation of 6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)benzaldehyde: A solution of 6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)benzonitrile (550 mg, 1.36 mmol) in dichloromethane (9 mL) at 0 °C was treated with diisobutylaluminum hydride (1.0 M in heptane, 2.05 mL, 2.05 mmol) and stirred at 0 °C. for 1 h. Additional diisobutylaluminum hydride (1.0 M in heptane, 600 μL, 0.600 mmol) was added. After stirring for an additional 30 minutes, the reaction mixture was quenched by the addition of 8.5 mL 10% aqueous HCl. The resulting mixture was stirred vigorously for 1 hour. Then the sample was treated with 8.5 mL 20% aqueous potassium sodium tartrate and stirred vigorously an additional hour. The reaction mixture was basified with 10% aqueous NaOH and extracted with 3×20 mL CH_2Cl_2. The combined organics were rinsed with 20 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 20% to 60% CH_2Cl_2 in hexane to afford 6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)benzaldehyde as a solid (100 mg, 18%). LCMS ESI (−) *m/z* 404.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (m, 1H), 7.51 (d, 1H), 7.32-7.20 (m, 5H), 7.19 (t, 1H), 7.08 (d, 1H), 6.61 (tt, 1H), 6.51-6.44 (m, 2H), 4.11 (s, 2H).

Step D: Preparation of 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-ol: A solution of 6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)benzaldehyde (91 mg, 0.22 mmol) in tetrahydrofuran (2.2 mL) at 0 °C was treated with vinylmagnesium bromide (1.0 M in tetrahydrofuran, 220 μL, 0.22 mmol) and stirred at 0 °C for 30 minutes. The reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl. The reaction mixture warmed to room temperature and was then poured into 10 mL of water and extracted with 3×15 mL EtOAc. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 30% to 70% CH_2Cl_2 in hexane to afford 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-ol as a yellow solid (83 mg, 85%). LCMS ESI (−) *m/z* 433.0 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H), 7.40-7.07 (m, 6H), 6.93 (d, 1H), 6.57 (tt, 1H), 6.51-6.44 (m, 2H), 6.08-5.90 (m, 2H), 5.27-4.98 (m, 2H), 3.99 (dd, 2H), 2.23 (br, 1H).

Step E: Preparation of 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-one **(25)**: A solution of 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-ol (83 mg, 0.19 mmol) in dichloromethane (1.9 mL) at 25 °C was treated with Dess-Martin periodinane (101 mg, 0.24 mmol) and stirred at 25 °C for 3 h. The reaction mixture was diluted with water (2 mL) and treated with sodium thiosulfate pentahydrate (130 mg, 0.53 mmol). The resulting mixture was stirred for 30 minutes and was then poured into 20 mL of water and extracted with 3×10 mL CH_2Cl_2. The combined organics were rinsed with 10 mL of brine, dried with $MgSO_4$, filtered, and concentrated to dryness to afford 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-one **(25)**. The product residue was used without further purification. LCMS ESI (+) *m/z* 432.9 (M+H).

Step F: Preparation of 5-(difluoromethyl)-6-(3,5-difluorophenoxy)thiochroman-4-one **(26)**: A vigorously stirred solution of 1-(6-(benzylthio)-2-(difluoromethyl)-3-(3,5-difluorophenoxy)phenyl)prop-2-en-1-one **(25)** (21 mg, 0.050 mmol) in benzene (0.5 mL) at 25 °C was treated with aluminum chloride

(10.8 mg, 0.081 mmol). After 1 h, the reaction was quenched by the addition of ice chips. The reaction mixture was then diluted with 10 mL CH_2Cl_2, poured into 10 mL 1 M HCl and extracted with 3×10 mL CH_2Cl_2. The combined organic extracts were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 5% to 25% EtOAc in hexane to afford 5-(difluoromethyl)-6-(3,5-difluorophenoxy)thiochroman-4-one **(26)** as a thin film (3.3 mg, 20% over 2 steps). LCMS ESI (−) *m/z* 340.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 1H), 7.36 (t, 1H), 7.09 (d, 1H), 6.54 (tt, 1H), 6.50-6.43 (m, 2H), 3.29-3.20 (m, 2H), 3.12-3.03 (m, 2H).

Step G: Preparation of 5-(difluoromethyl)-6-(3,5-difluorophenoxy)thiochroman-4-ol **(7j)**: A solution of 5-(difluoromethyl)-6-(3,5-difluorophenoxy)thiochroman-4-one **(26)** (3.3 mg, 0.0096 mmol) in methanol (1 mL) at 25 °C. was treated with sodium borohydride (0.36 mg, 0.0095 mmol) and stirred at 25 °C for 1 h. The reaction mixture was quenched by the addition of 0.25 mL of saturated NH_4Cl. Volatiles were removed by concentration under reduced pressure. The residue was poured into 10 mL water and extracted with 3×10 mL EtOAc. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. The intermediate product residue was dissolved in dichloromethane (1 mL) and treated with 3-chloroperbenzoic acid (˜70% by wt, 5.9 mg, 0.024 mmol). The reaction mixture stirred at 25 °C for 1.5 h and was then poured into 10 mL of 1:1 mixture of 1 M NaOH and 20% $Na_2S_2O_3$ and extracted with 3×10 mL CH_2Cl_2. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a gradient of 25% to 75% EtOAc in hexane to afford 5-(difluoromethyl)-6-(3,5-difluorophenoxy)thiochroman-4-ol **(7j)** as a white solid (2.2 mg, 60%). LCMS ESI (+) *m/z* 394.0 ($M+NH_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, 1H), 7.31 (t, 1H), 7.10 (d, 1H), 6.71 (tt, 1H), 6.61-6.54 (m, 2H), 5.52-5.48 (m, 1H), 4.05 (td, 1H), 3.32 (ddd, 1H), 2.84-2.74 (m, 1H), 2.73-2.64 (m, 2H).

4-(Difluoromethyl)-5-(3,5-difluorophenoxy)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (8a). For detailed synthetic procedures see the synthesis of **8b**.

8a was prepared analogously to **8b**, substituting 3,5-difluorophenol for 3-fluoro-5-hydroxy-benzonitrile in Step E. LCMS ESI (−) *m/z* 396.9 (M−H).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.25 (t, 1H), 7.23-7.19 (m, 1H), 6.78 (tt, 1H), 6.68-6.61 (m, 2H), 5.67 (dd, 1H), 3.09 (dd, 1H).

3-((4-(difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile (8b). Step A: Preparation of 2-bromo-3-(difluoromethyl)-1,4-difluorobenzene: A solution of 2-bromo-3,6-difluorobenzaldehyde (40.0 g, 181 mmol) dissolved in dichloromethane (800 mL) was cooled to 0 °C, then treated with (diethylamino)sulfur trifluoride (DAST, 70.0 g, 454 mmol). After the addition, the reaction mixture was warmed to ambient temperature and stirred for 4 h. Saturated aqueous sodium bicarbonate solution was added slowly until the pH was 8-9. The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2-bromo-3-(difluoromethyl)-1,4-difluorobenzene (44.0 g, quant.) as a solid which was used immediately in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.22 (m, 1H), 7.17-7.10 (m, 1H), 7.04 (t, 1H).

Step B: Preparation of 2-(difluoromethyl)-3,6-difluorobenzonitrile **(22)**: A suspension of 2-bromo-3-(difluoromethyl)-1,4-difluorobenzene (44.0 g, 181 mmol) and copper (I) cyanide (21.1 g, 235 mmol) in 1-methyl-2-pyrrolidinone (400 mL) was heated at 180 °C for 2 h. After cooling to ambient temperature, the reaction mixture was poured into water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate, filtered and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexane to give 2-(difluoromethyl)-3,6-difluorobenzonitrile **(22)** as a solid (23 g, 67% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.35 (m, 2H), 6.98 (t, 1H).

Step C: Preparation of 2-(difluoromethyl)-3-fluoro-6-(methylthio)benzonitrile: A solution of 2-(difluoromethyl)-3,6-difluorobenzonitrile **(22)** (31.3 g, 65.5 mmol) in acetonitrile (500 mL) was cooled to – 30 °C, then treated with sodium sulfide (12.8 g, 174 mmol). After addition of the solid, the reaction

mixture was stirred for 7 h while maintaining the temperature between – 30 °C and – 40 °C. A mixture of water (200 mL) and methyl t-butyl ether (500 mL) were added and the reaction mixture was warmed to ambient temperature. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2-(difluoromethyl)-3-fluoro-6-methylsulfanyl-benzonitrile as a yellow solid (36.3 g, 91%). LCMS ESI (+) *m/z* 218.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.44 (m, 1H), 7.36-7.32 (m, 1H), 6.99 (t, 1H), 2.58 (s, 3H).

Step D: Preparation of 2-(difluoromethyl)-3-fluoro-6-(methylsulfonyl)benzonitrile: A slurry of 2-(difluoromethyl)-3-fluoro-6-methylsulfanyl-benzonitrile (36.3 g, 167 mmol) in acetonitrile (350 mL) and water (175 mL) was treated with Oxone® (257 g, 418 mmol), then the mixture was heated at 56 °C for 4 h. After cooling to ambient temperature, the remaining solids were removed by filtration and washed with dichloromethane (300 mL). The filtrate was concentrated *in vacuo* to remove volatile solvents. The resulting aqueous solution was extracted with dichloromethane (400 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting solid was suspended in 4:1 hexane:methyl t-butyl ether (200 mL) and stirred for 10 minutes at ambient temperature. The undissolved solid was collected by filtration and air-dried to give 2-(difluoromethyl)-3-fluoro-6-(methylsulfonyl)benzonitrile (29.9 g, 71%). LCMS ESI (+) *m/z* 250.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41-8.37 (m, 1H), 7.66-7.61 (m, 1H), 7.11 (t, 1H), 3.34 (s, 3H).

Step E: Preparation of 3-(3-cyano-5-fluorophenoxy)-2-(difluoromethyl)-6-(methylsulfonyl)benzonitrile **(23)**: A suspension of 2-(difluoromethyl)-3-fluoro-6-(methylsulfonyl)benzonitrile (9.52 g, 38.2 mmol), 3-fluoro-5-hydroxy-benzonitrile (5.23 g, 38.2 mmol), and cesium carbonate (7.77 g, 40.1 mmol) in *N*,*N*-dimethylformamide (76 mL) was heated at 45 °C for 3 h. Additional cesium carbonate (0.46 g, 1.4 mmol) was added and the reaction mixture was heated at 45 °C for 3 h, then stirred at ambient temperature for 54 h. The reaction mixture was vigorously stirred while water (800 mL) was added. The resulting suspension was stirred for 30 minutes, then the solids were collected by filtration, washed with water (1.2 L), and dried under high vacuum to give 3-(3-cyano-5-

fluorophenoxy)-2-(difluoromethyl)-6-(methylsulfonyl)benzonitrile **(23)** as a white solid (13.3 g, 96%). LCMS ESI (+) *m/z* 383.9 ($M+NH_4$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, 1H), 7.86-7.82 (m, 1H), 7.72-7.62 (m, 3H), 7.49 (t, 1H), 3.44 (s, 3H).

Step F: Preparation of 3-((4-((difluoromethyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(24)**: A solution of 3-(3-cyano-5-fluorophenoxy)-2-(difluoromethyl)-6-(methylsulfonyl)benzonitrile **(23)** (13.3 g, 36.1 mmol) was dissolved in tetrahydrofuran (380 mL) and treated with sodium hydride (60% in mineral oil, 2.26 g, 56.0 mmol) in two equal portions at five minute intervals. The resulting suspension was stirred at ambient temperature for 60 minutes. The reaction mixture was quenched by addition of a mixture of 4:1 methanol:10% aqueous HCl (200 mL) and the resulting suspension was stirred for 1 h. The mixture was concentrated to remove volatile solvents, then the remaining aqueous slurry was diluted with additional water (800 mL) and stirred for an additional 30 minutes. The solids were recovered by filtration and washed with water and the resulting beige solid was dried under high vacuum in the presence of solid NaOH. 3-((4-(Difluoromethyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(24)** was obtained as a beige solid (13.3 g, quant.) and was used without further purification. LCMS ESI (−) *m/z* 365.9 (M−H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 1H), 7.79 (d, 1H), 7.76 (t, 1H), 7.76-7.72 (m, 1H), 7.56-7.50 (m, 2H), 4.72 (s, 2H).

Step G: Preparation of 3-((4-(difluoromethyl)-2,2-difluoro-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(11)**: A solution of 3-((4-(difluoromethyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(24)** (1.40 g, 3.82 mmol) dissolved in acetonitrile (38 mL) was treated at ambient temperature with sodium carbonate (890 mg, 8.40 mmol) followed by Selectfluor® (2.98 g, 8.42 mmol). The reaction mixture was stirred at ambient temperature for 90 minutes. The reaction mixture was concentrated *in vacuo* to remove volatile solvents, then the residue was diluted with water (100 mL) and extracted three times with ethyl acetate (50 mL portions). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 3-((4-(difluoromethyl)-2,2-difluoro-1,1-dioxido-3-oxo-2,3-

dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(11)** as a solid (1.48 g, quant.). LCMS ESI (+) *m/z* 403.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6, sample exists as hydrate): δ 8.81 (s, 2H), 8.29 (d, 1H), 7.80-7.76 (in, 1H), 7.74 (t, 1H), 7.57-7.50 (m, 3H).

Step H: Preparation of 3-((4-(difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(8b)** : A solution of 3-((4-(difluoromethyl)-2,2-difluoro-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(11)** (1.48 g, 3.67 mmol) in methanol (37 mL) was cooled to 0 °C, then treated with sodium borohydride (139 mg, 3.7 mmol) and stirred for 1 h. The reaction was quenched by addition of water (0.5 mL) and saturated NH_4Cl (0.25 mL). The reaction mixture was concentrated *in vacuo* to remove volatile solvents, then diluted with 0.5 M NaOH (10 mL). The aqueous was extracted three times with ethyl acetate and the combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was chromatographed on SiO_2 eluting with a gradient of ethyl acetate/hexane to give 3-((4-(difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(8b)** as a white solid (1.24 g, 83%). LCMS ESI (−) *m/z* 403.9 (M−H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H), 7.33-7.30 (m, 1H), 7.23 (t, 1H), 7.22-7.18 (m, 2H), 7.10-7.06 (m, 1H), 5.69-5.65 (m, 1H), 3.23 (d, 1H).

5-((5-Chloropyridin-3-yl)oxy)-4-(difluoromethyl)-2,2-difluoro-3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (8c). For detailed synthetic procedures see the synthesis of **8b**. **8c** was prepared analogously to **8b**, substituting 3-chloro-5-hydroxypyridine for 3-fluoro-5-hydroxy-benzonitrile in Step E. LCMS ESI (+) *m/z* 397.9, 399.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, 1H), 8.38 (d, 1H), 7.96 (d, 1H), 7.46 (t, 1H), 7.29 (t, 1H), 7.16-7.13 (m, 1H), 5.67 (dd, 1H), 3.24 (dd, 1H).

5-((4-(Difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)oxy)nicotinonitrile (8d). For detailed synthetic procedures see the synthesis of **8b**. **8d** was prepared analogously to **8b**, substituting 3-cyano-5-hydroxypyridine for 3-fluoro-5-hydroxy-benzonitrile in Step E.

LCMS ESI (+) *m/z* 388.9 (M+H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.81 (d, 1H), 8.71 (d, 1H), 8.08 (d, 1H), 8.04 (dd, 1H), 7.42 (d, 1H), 7.38 (t, 1H), 5.69 (d, 1H).

(*R*)-3-((4-(difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)oxy)-5-fluorobenzonitrile (9a) and **(*S*)-3-((4-(difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)oxy)-5-fluorobenzonitrile (9b).** (±)3-((4-(Difluoromethyl)-2,2-difluoro-3-hydroxy-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile **(8b)** was resolved using preparative SFC chromatography under the following conditions: ChiralPak AS(-H) (2×15 cm) column, 20% ethanol with carbon dioxide at 100 bar, 60 mL/min flow rate, injection volume was 0.5 mL of a 20 mg/mL solution in ethanol, peak detection at 220 nm. Compound **9a** was recovered as the first peak (1.50 minutes) to elute from the column and compound **9b** as the second peak (1.84 minutes) to elute from the column. LCMS ESI (-) *m/z* 403.9 (M-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 1H), 7.33-7.30 (m, 1H), 7.23 (t, 1H), 7.22-7.18 (m, 2H), 7.10-7.06 (m, 1H), 5.69-5.65 (m, 1H), 3.23 (d, 1H).

4-(3-chloro-5-fluorophenoxy)-7-((difluoromethyl)sulfonyl)-2,3-dihydro-1*H*-inden-1-ol (10a). Step A: Preparation of *O*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate: A mixture of 4-fluoro-7-hydroxy-indan-1-one (17.0 g, 102 mmol), DMF (340 mL), *N*,*N*-dimethylcarbamothioyl chloride (37.9 g, 307 mmol), and 1,4-diazabicyclo[2.2.2]octane (34.4 g, 307 mmol) was stirred at ambient temperature for 2 h. The reaction was poured into cold water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated. The resulting solid was recrystallized from 1:1 hexane:EtOAc (240 mL) to give *O*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate as a white solid (12.0 g). The mother liquid was concentrated and purified by flash chromatography on silica gel with a gradient of 0% to 1% EtOAc in dichloromethane to give a solid, which was triturated with 4:1 hexane:EtOAc to give additional *O*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate (6.9 g, combined yield 18.9 g, 73%). LCMS ESI (+) *m/z* 254 (M+H). ^{1}H NMR

(400 MHz, CDCl3): δ 7.30- 7.28 (m, 1H), 7.02 -7.00 (m, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 3.15-3.12 (m, 2H), 2.71-2.68 (m, 2H).

Step B: Preparation of *S*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate: A mixture of *O*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate (18.9 g, 74.6 mmol) and diphenyl ether (200 mL) was heated at 220 °C under nitrogen for 30 minutes. After cooling, the reaction mixture was diluted with hexane. The mixture was passed through a short silica gel pad eluting with hexane to remove diphenyl ether. Further elution with EtOAc afforded the crude product, which was purified by chromatography on silica gel using a gradient of 15% to 40% EtOAc in hexane to afford *S*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate (18.0 g, 95%) as a solid. LCMS ESI (+) *m/z* 254 (M+H). ^{1}H NMR (400 MHz, CDCl3): δ 7.49-7.46 (m, 1H), 7.25- 7.21 (m, 1H), 3.26-2.95 (m, 8H), 2.79-2.72 (m, 2H).

Step C: Preparation of 4-fluoro-7-sulfanyl-indan-1-one **(27)**: A stirred mixture of *S*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate (25.0 g, 98.7 mmol), 95% ethanol (490 mL) and 3 N NaOH (173 mL, 691 mmol) was heated under nitrogen at reflux for 30 minutes. After cooling, the reaction mixture was cooled to 0 °C using an ice bath. 3 N HCl was added dropwise to adjust the pH to 4-5. Most of the ethanol was evaporated under reduced pressure. The precipitated solid was collected by filtration, washed with water, and dried to give 4-fluoro-7-sulfanyl-indan-1-one **(27)** (17.0 g, 95%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.10 (m, 2H); 3.09-3.03 (m, 2H), 2.79-2.76 (m, 2H).

Step D: Preparation of 7-(difluoromethylsulfanyl)-4-fluoro-indan-1-one: To a stirred solution of 4-fluoro-7-sulfanyl-indan-1-one **(27)** (crude from Step C, 17.0 g, 93.3 mmol) in acetonitrile (490 mL) was added a solution of KOH (104.7 g, 1866 mmol) in water (490 mL). The reaction mixture was purged with nitrogen and then cooled to - 78 °C. Bromodifluoromethyl diethylphosphonate (33.2 mL, 187 mmol) was added all at once. The resulting mixture was allowed to warm to ambient temperature and vigorously

stirred for 2 h. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by passing through a short silica gel pad eluting with 10% EtOAc in hexane to give 7-(difluoromethylsulfanyl)-4-fluoro-indan-1-one (18.3 g, 84%), which was used in the next step without further purification. LCMS ESI (+) *m/z* 233 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 1H), 7.28-7.23 (m, 1H), 7.07 (t, 1H), 3.16- 3.13 (m, 2H), 2.79-2.76 (m, 2H).

Step E: Preparation of 7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydro-1*H*-inden-1-one **(28)**: Sodium periodate (41.9 g, 196 mmol) was added to 7-(difluoromethylsulfanyl)-4-fluoro-indan-1-one (18.2 g, 78.4 mmol) and ruthenium(III) chloride (0.41 g, 2.0 mmol) in a mixture of acetonitrile (392 mL), carbon tetrachloride (392 mL), and water (392 mL). The reaction mixture was stirred at ambient temperature for 5 h. Solids were removed by filtration through Celite and rinsed with CH_2Cl_2. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was passed through a short silica gel pad eluting with 30% EtOAc in hexane to give 7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydro-1*H*-inden-1-one **(28)** (18.8 g, 91%) as a white solid. LCMS ESI (+) *m/z* 265 (M+H). ^{1}H NMR (400 MHz, CDCl3): δ 8.28-8.27 (m, 1H), 7.51-7.47 (m, 1H), 7.10 (t, 1H), 3.28-3.24 (m, 2H), 2.90-2.87 (m, 2H).

Step F: Preparation of 7-(difluoromethylsulfonyl)-4-fluoro-indan-1-ol: To a stirred solution of 7-(difluoromethyl)sulfonyl-4-fluoro-2,3-dihydro-1*H*-inden-1-one **(28)** (110 mg, 0.42 mmol) in methanol (4 mL) was added sodium borohydride (24 mg, 0.62 mmol). The reaction mixture was stirred at ambient temperature for 1 h. Saturated aqueous NH_4Cl solution was added dropwise. The mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated *in vacuo* to give 7-(difluoromethylsulfonyl)-4-fluoro-indan-1-ol (100 mg, 90%), which was used in the next step without further purification. LCMS ESI (+) *m/z* 267.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87

(dd, 1H), 7.22 (t, 1H), 6.35 (t, 1H), 5.66-5.61 (m, 1H), 3.23 (dt, 1H), 3.14 (dd, 1H), 2.99 (ddd, 1H), 2.51-2.40 (m, 1H), 2.32-2.24 (m, 1H).

Step G: Preparation of 4-(3-chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-1-ol **(10a)**: A solution of 3-chloro-5-fluoro-phenol (24 mg, 0.17 mmol) and 7-(difluoromethylsulfonyl)-4-fluoro-indan-1-ol (40 mg, 0.15 mmol) in NMP (1 mL) at ambient temperature was treated with $NaHCO_3$ (37 mg, 0.45 mmol). The reaction mixture was stirred at 90 °C under nitrogen for 4 h. After cooling, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried and concentrated. The residue was purified by reverse phase chromatography with a gradient of 10% to 60% acetonitrile in water to give 4-(3-chloro-5-fluoro-phenoxy)-7-(difluoromethylsulfonyl)indan-1-ol **(10a)** (25 mg, 42%). For products using a chiral alcohol starting material, the *ee* was determined to be 98% by ^{19}F NMR analysis of the corresponding Mosher ester. LCMS ESI (+) *m/z* 409.9, 411.9 ($M+NH_4$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, 1H), 7.00-6.89 (m, 3H), 6.73-6.71 (m, 1H), 6.35 (t, 1H), 5.66-5.65 (m, 1H), 3.19-3.13 (m, 2H), 2.96-2.90 (m, 1H), 2.50-2.40 (m, 1H), 2.30-2.24 (m, 1H).

(*R*)-4-(3-chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-1-ol (10b). Step A: Preparation of (*R*)-7-(difluoromethylsulfonyl)-4-fluoro-indan-1-ol: A pear-shaped flask was charged with 7-(difluoromethylsulfonyl)-4-fluoro-indan-1-one **(28)** (992 mg, 3.75 mmol), formic acid (0.178 mL, 4.69 mmol), triethylamine (0.576 mL, 4.13 mmol), and dichloromethane (25 mL). The reaction mixture was backfilled with nitrogen. RuCl(p-cymene)[(*R*,*R*)-Ts-DPEN] (48 mg, 0.080 mmol) was added in one portion, and the reaction mixture was stirred at ambient temperature overnight. The reaction was concentrated under reduced pressure. The residue was purified by chromatography on silica gel using a gradient of 5% to 20% EtOAc in hexanes to give (1*R*)-7-(difluoromethylsulfonyl)-4-fluoro-indan-1-ol (990 mg, 99%) as a solid. The *ee* was determined to be 98% by ^{19}F NMR analysis of the corresponding Mosher ester. LCMS ESI (+) *m/z* 267 (M+H). ESI (-) *m/z* 311 ($M-H+HCO_2H$).

Step B: Preparation of (*R*)-4-(3-chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-1-ol **(10b)**: Same procedure and characterization for compound **10a** Step G, except using (*R*)-7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydro-1*H*-inden-1-ol as the aryl fluoride component.

(*S*)-4-(3-chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-1-ol (10c). Step A: Preparation of (*S*)-7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydro-1*H*-inden-1-ol: As described in the synthesis of **10b** Step A, except that the antipode of the catalyst is used: RuCl(p-cymene)[(*S*,*S*)-Ts-DPEN].

Step B: Preparation of (*S*)-4-(3-chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-1-ol **(10c)**: Same procedure and characterization for compound **10a** Step G, except using (*S*)-7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydro-1*H*-inden-1-ol as the aryl fluoride component. The *ee* was determined to be 96% by ^{19}F NMR analysis of the corresponding Mosher ester.

4-(3-Chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-2,3-dihydro-1*H*-inden-1-ol (10d). Prepared analogously to the procedure for compound **10f** substituting 3-chloro-5-fluorophenol for 3-fluoro-5-hydroxy-benzonitrile in Step B and the final reduction was racemic with sodium borohydride. Step F: Preparation of 4-(3-chloro-5-fluoro-phenoxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-indan-1-ol **(10d)**: To a solution of 4-(3-chloro-5-fluoro-phenoxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-indan-1-one (analogous product from **10f** Step E) in methanol (4 mL) was added sodium borohydride (100 mg, 2.64 mmol). The reaction was stirred at room temperature for 20 minutes. The reaction mixture was poured into brine, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The residue was purified twice by preparative TLC with 15% EtOAc/hexane to give 4-(3-Chloro-5-fluorophenoxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-2,3-dihydro-1*H*-inden-1-ol **10d** (14 mg, 30% from Step E). LCMS ESI (+) *m/z* 429, 431 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H), 7.06-7.03 (m, 1H), 6.98 (d, 1H), 6.94-6.92 (m, 1H), 6.78-6.74 (m, 1H), 6.42 (t, 1H), 5.50 (d, 1H), 3.61-3.43 (m, 2H), 3.24 (s, 1H).

3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10e). Prepared analogously to the procedure for compound **10d** using intermediate **(30)** (from **10f** Step E) instead of 4-(3-chloro-5-fluoro-phenoxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-indan-1-one. LCMS ESI (+) *m/z* 437 ($M+NH_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H), 7.33-7.29 (m, 1H), 7.23-7.21 (m, 1H), 7.13-7.09 (m, 1H), 7.00 (d, 1H), 6.43 (t, 1H), 5.51 (d, 1H), 3.60-3.43 (m, 2H), 3.30 (br s, 1H).

(*S*)-3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10f). Step A: Preparation of 7-(difluoromethylsulfonyl)-4-fluoro-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolane]: A mixture of 7-(difluoromethylsulfonyl)-4-fluoro-indan-1-one **(28)** (740 mg, 2.80 mmol), *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol), and ethylene glycol (5 mL) in benzene (50mL) was refluxed overnight with removal of water by a Dean-Stark trap. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel eluting with a gradient of 0% to 60% EtOAc in hexane to give 7'-(difluoromethylsulfonyl)-4'-fluoro-spiro[1,3-dioxolane-2,1'-indane] (780 mg, 90%) as a white solid. LCMS ESI (+) *m/z* 309 (M+H). ^{1}H NMR (400 MHz, CDCl3): δ 8.09-8.05 (m, 1H), 7.28-7.23 (m, 1H), 6.85 (t, 1H), 4.38-4.35 (m, 2H), 4.11-4.07 (m, 2H), 3.03-3.00 (m, 2H), 2.32-2.28 (m, 2H).

Step B: Preparation of 3-((7-(difluoromethylsulfonyl)-2,3- dihydrospiro[indene-1,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile: A mixture of 3-fluoro-5-hydroxy-benzonitrile (1.33 g, 9.70 mmol), 7'-(difluoromethylsulfonyl)-4'-fluorospiro[1,3-dioxolane-2,1'-indane] (1.00 g, 3.24 mmol), and cesium bicarbonate (1.26 g, 6.49 mmol) in 1-methyl-2-pyrrolidone (1.8 mL) was heated under nitrogen at 110 °C by microwave irradiation for 1 hour and 5 minutes. The reaction was repeated ten times. The reaction mixtures were combined, diluted with EtOAc, and washed twice with 1 N NaOH. The combined aqueous layer was extracted with EtOAc. The EtOAc extracts were combined and washed with brine, dried over Na_2SO_4, filtered, and concentrated to about 100 mL to give a suspension. The suspension was

filtered to give 3-((7-(difluoromethylsulfonyl)-2,3- dihydrospiro[indene-1,2'-[1,3]dioxolan]-4-yl)oxy)-5-fluorobenzonitrile as an off-white solid (6.25 g). The filtrate was diluted with EtOAc, washed with brine (3X), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 0% to 40% EtOAc in hexane to give additional 3-((7-(difluoromethylsulfonyl)-2,2-difluoro-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolan]-4- yl)oxy)-5-fluorobenzonitrile (3.3 g, 69% combined yield) as a white solid. LCMS ESI (+) *m/z* 425.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, 1H), 7.25-7.22 (m, 1H), 7.16-7.15 (m, 1H), 7.05-7.00 (m, 2H), 6.78 (t, 1H), 4.40-4.36 (m, 2H), 4.12-4.09 (m, 2H), 2.96-2.92 (m, 2H), 2.32-2.29 (m, 2H).

Step C: Preparation of 3-((7-(difluoromethylsulfonyl)-1-oxo-2,3- dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile **(29)**: A mixture of 3-((7- (difluoromethylsulfonyl)-2,3-dihydrospiro[indene-1,2'-[1,3]dioxolan]-4-yl)oxy)-5- fluorobenzonitrile (10.9 g, 25.6 mmol) and pyridinium p-toluenesulfonate (667 mg, 2.66 mmol) in acetone (100 mL) and water (15 mL) was heated at 82 °C for 5 h and then 75 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was filtered and washed with water. The solid obtained was briefly dried under vacuum at 50 °C and then triturated with EtOAc/hexane to give 3-((7- (difluoromethylsulfonyl)-1-oxo-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile (8.0 g). Chromatography of the mother liquor on silica gel eluting with a gradient of 0% to 80% EtOAc in hexane provided additional 3-((7-(difluoromethylsulfonyl)-1-oxo-2,3- dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile **(29)** (1.3 g, combined 9.3 g, 95%). LCMS ESI (+) *m/z* 381.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, 1H), 7.33-7.31 (m, 1H), 7.24-7.23 (m, 1H), 7.17-7.15 (d, 1H), 7.14-7.10 (m, 1H), 7.13 (t, 1H), 3.23-3.20 (m, 2H), 2.92-2.89 (m, 2H).

Step D: Preparation of (*E*, *Z*)-3-((1-(butylimino)-7- (difluoromethylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile: A mixture of 3-((7-(difluoromethylsulfonyl)-1-oxo-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile **(29)** (1.42 g, 3.72 mmol), butylamine (6.0 mL) and 5 drops of

trifluoroacetic acid (~ 0.1 mL) in benzene (40 mL) was refluxed overnight with removal of water using a Dean-Stark trap. The reaction mixture was concentrated under reduced pressure, diluted with methyl t-butyl ether, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used in the next step without further purification.

Step E: Preparation of 3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-oxo- 2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile (**30**): A mixture of (*E*, *Z*)-3-((1-(butylimino)-7-(difluoromethylsulfonyl)-2,3-dihydro-1H-inden-4-yl)oxy)-5-fluorobenzonitrile (1.29 g, 2.96 mmol, crude from step D), Selectfluor® (2.62 g, 7.40 mmol) and sodium sulfate (4.00 g, 28.2 mmol) in CH_3CN (12 mL) under N_2 was heated at 82 °C for 4 h. After cooling to room temperature, concentrated HCl (37%, 3 mL) was added. The mixture was stirred at room temperature for 15 minutes and then concentrated under reduced pressure. The residue was diluted with methyl t-butyl ether, washed with half saturated aqueous $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, and triturated with EtOAc/hexane to give 3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-oxo-2,3-dihydro-1H-inden-4- yl)oxy)-5-fluorobenzonitrile as an off-white solid (0.5 g). The mother liquor was purified by chromatography on silica gel eluting with a gradient of 5% to 40% EtOAc in hexane to give additional 3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-oxo-2,3-dihydro-1H-inden-4-yl)oxy)-5- fluorobenzonitrile **(30)** (0.13 g, 51% combined yield). LCMS ESI (+) *m/z* 418 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H), 7.40-7.38 (m, 1H), 7.28-7.16 (m, 3H), 6.93 (t, 1H), 3.69-3.63 (m, 2H).

Step F: Preparation of (*S*)-3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **(10f)**: An ice cold solution of RuCl(p-cymene)[(*R,R*)-Ts-DPEN] (0.6 mg) in dichloromethane (0.2 mL) was added by syringe under nitrogen to an ice cold solution of 3-[7-(difluoromethylsulfonyl)-2,2-difluoro-1-oxo-indan-4-yl]oxy-5-fluoro-benzonitrile **(30)** (28 mg, 0.067 mmol), triethylamine (18.7 µL, 0.13 mmol) and formic acid (7.6 µL, 0.2 mmol) in dichloromethane (0.5 mL) and then placed in a refrigerator at 4 °C overnight. The reaction mixture was directly purified on preparative TLC with 40% EtOAc in hexane to give (*S*)-3-((7-(difluoromethylsulfonyl)-2,2-difluoro-1-

hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **10f** (23.4 mg, 83% yield). The *ee* was determined to be greater than 95% by ^{19}F NMR analysis of the corresponding Mosher ester. LCMS ESI (+) *m/z* 420 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H), 7.33-6.98 (m, 4H), 6.44 (t, 1H), 5.51 (d, 1H), 3.61-3.45 (m, 2H).

(*S*)-3-((2,2-difluoro-1-hydroxy-7-(trifluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10g). Step A: 4-Fluoro-7-(trifluoromethylsulfanyl)indan-1-one: Methyl viologen dichloride hydrate (22.6 mg, 0.0879 mmol) and 4-fluoro-7-sulfanyl-indan-1-one (320 mg, 1.76 mmol) were dissolved in DMF (3 mL) in a vial. The solution was cooled in dry ice/acetone and trifluoromethyl iodide gas (688 mg, 3.5 mmol) was condensed into the cooled solution. Triethylamine (0.340 mL, 2.46 mmol) was added and the vial was sealed. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was partitioned between EtOAc and water. The EtOAc was washed with water, brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel eluting with a 10% to 60% EtOAc in hexane gradient to give 4-fluoro-7-(trifluoromethylsulfanyl)indan-1-one (130 mg, 30% yield) as a colorless glass. LCMS ESI (+) *m/z* 251.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, 1H), 7.29 (t, 1H), 3.13-3.13 (m, 2H), 2.80-2.76 (m, 2H).

Step B: 4-Fluoro-7-(trifluoromethylsulfonyl)indan-1-one **(31g)**: Sodium periodate (458 mg, 2.14 mmol) was added to a mixture of 4-fluoro-7-(trifluoromethylsulfanyl)indan-1-one (130 mg, 0.52 mmol) and ruthenium(III) chloride (4.4 mg, 0.02 mmol) in carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (4 mL). The mixture was stirred at ambient temperature for 2 h. The reaction mixture was partitioned between dichloromethane and water. The dichloromethane was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel eluting with a 10% to 60% EtOAc in hexane gradient to give 4-fluoro-7-(trifluoromethylsulfonyl)indan-1-one **(31g)**

(127 mg, 87% yield) as a white solid. LCMS ESI (+) *m/z* 283.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, 1H), 7.50 (t, 1H), 3.26-3.22 (m, 2H), 2.89-2.85 (m, 2H).

Step C: (*S*)-3-((2,2-Difluoro-1-hydroxy-7-(trifluoromethylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **(10g):** Prepared analogously to **10f** Step G substituting **31g** for **30**. LCMS ESI (-) *m/z* 435.9 (M-H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H), 7.35-7.31 (m, 1H), 7.26-7.23 (m, 1H), 7.15-7.11 (m, 1H), 6.99 (d, 1H), 5.46-5.39 (m, 1H), 3.63-3.41 (m, 2H), 3.36 (d, 1H). ^{19}F NMR ($CDCl_3$) showed an e.e. of 93 % based on the Mosher ester analysis of the trifluoromethyl resonance.

(*S*)-3-((2,2-Difluoro-7-((fluoromethyl)sulfonyl)-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10h). Step A: Preparation of 4-fluoro-7-(methylthio)-2,3-dihydro-1*H*-inden-1-one: A stirred mixture of *S*-(7-fluoro-3-oxo-indan-4-yl)-*N*,*N*-dimethylcarbamothioate (product of **10a** Step B, 50.4 g, 199 mmol), 95% ethanol (690 mL) and 3 N NaOH solution (398 mL, 1.6 mol) was heated at reflux for 30 minutes. After cooling, the reaction mixture was cooled to 0 °C using an ice bath. Iodomethane (16.1 mL, 259 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 h and concentrated under reduced pressure to remove EtOH. The residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated. The crude was used in the next step without further purification. LCMS ESI (+) *m/z* 197.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t, 1H), 7.04 (dd, 1H), 3.14-3.10 (m, 2H), 2.75-2.71 (m, 2H), 2.48 (s, 3H).

Step B: 4-Fluoro-7-methylsulfinyl-indan-1-one: 3-Chloroperbenzoic acid (37 mg, 0.15 mmol) was added to an ice-cold solution of 4-fluoro-7-methylsulfanyl-indan-1-one (30 mg, 0.15 mmol) in dichloromethane (5 mL). After 5 minutes, the reaction mixture was concentrated, diluted with EtOAc, washed twice with a mixture of saturated aqueous $NaHCO_3$ and 1M sodium thiosulfate, water, brine, dried over $MgSO_4$, filtered, and evaporated to afford 4-fluoro-7-methylsulfinyl-indan-1-one (26 mg, 80%

yield) as a white solid. LCMS ESI (+) *m/z* 213.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, 1H), 7.47 (t, 1H), 3.28-3.23 (m, 2H), 2.82 (s, 3H), 2.79-2.75 (m, 2H).

Step C: 4-Fluoro-7-(fluoromethylsulfanyl)indan-1-one: Diethylaminosulfur trifluoride (DAST, 5.50 mL, 41.9 mmol) was added dropwise to an ice-cold solution of 4-fluoro-7-methylsulfinyl-indan-1-one (1.48 g, 6.98 mmol) and antimony trichloride (0.80 g, 3.5 mmol) in dichloromethane (140 mL). The mixture was stirred at ambient temperature. After 3 h, the reaction mixture was quenched with dropwise addition of saturated aqueous $NaHCO_3$. The mixture was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and evaporated to yield 4-fluoro-7-(fluoromethylsulfanyl)indan-1-one (1.55 g, 99% yield). LCMS ESI (+) *m/z* 195.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, 1H), 7.24 (t, 1H), 5.83 (d, 2H), 3.15-3.11 (m, 2H), 2.76-2.72 (m, 2H).

Step D: 4-Fluoro-7-(fluoromethylsulfonyl)indan-1-one **(31h)**: 3-Chloroperbenzoic acid (5.35 g, 21.7 mmol) was added to a solution of 4-fluoro-7-(fluoromethylsulfanyl)indan-1-one (1.55 g, 7.24 mmol) in dichloromethane (145 mL). After 4.5 h, additional 3-chloroperbenzoic acid (5.35 g, 21.7 mmol) was added. After 6.5 h, the reaction mixture was concentrated, diluted with EtOAc, washed with 2 portions of a mixture of 1 M $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and evaporated to afford a tan solid. The crude was purified by chromatography on silica gel eluting with a 20% to 80% EtOAc in hexane gradient to give 4-fluoro-7-(fluoromethylsulfonyl)indan-1-one **(31h)** (0.700 g, 39% yield) as a white solid. LCMS ESI (+) *m/z* 247.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, 1H), 7.46 (t, 1H), 5.69 (d, 2H), 3.26-3.22 (m, 2H), 2.89-2.85 (m, 2H).

Step E: (*S*)-3-((2,2-Difluoro-7-((fluoromethyl)sulfonyl)-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **(10h)**: Prepared analogously to **10f** Step G substituting **31h** for **30**. LCMS ESI (-) *m/z* 445.9 (M-H+HCO_2H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.30-7.26 (m, 1H), 7.20-7.19 (m, 1H), 7.10-7.07 (m, 1H), 7.00 (d, 1H), 5.59-5.13 (m, 3H), 3.58-3.38 (m, 1H). ^{19}F NMR ($CDCl_3$) showed an e.e. of 89% based on the Mosher ester analysis of the trifluoromethyl resonance.

(*S*)-3-((2,2-Difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10i). Step A: Preparation of 4-fluoro-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-1-one **(31i)**: A solution of Oxone® (117 g, 191 mmol) in water (580 mL) was added dropwise to a suspension of 4-fluoro-7-(methylthio)-2,3-dihydro-1*H*-inden-1-one (crude from Step A for **10h**, 17.0 g, 86.6 mmol) in methanol (580 mL) at ambient temperature. The temperature slightly increased during the addition. The reaction mixture was stirred at ambient temperature for 5 h. Residual solids were removed by filtration and washed with EtOAc. The organics were removed from the filtrate *in vacuo*. The residue was extracted with EtOAc (3x). The aqueous layer was further extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting solid was triturated with EtOAc/hexane (1:5) to give 4-fluoro-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-1-one as a white solid (16.8 g). The mother liquor was concentrated and purified by chromatography on silica gel using a gradient of 10% to 80% EtOAc in hexane to afford additional 4-fluoro-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-1-one **(31i)** (2.30 g, combined 19.1 g, 96%). LCMS ESI (+) *m/z* 229 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, 1H), 7.41 (t, 1H), 3.42 (s, 3H), 3.25-3.20 (m, 2H), 2.89-2.84 (m, 2H).

Step B: (*S*)-3-((2,2-Difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **(10i)**: Prepared analogously to **10f** Step G substituting **31i** for **30**. Enantiomeric excess (98%) was determined by chiral HPLC as described in the general chemistry section. Retention time for (*S*)-enantiomer:1.93 minutes; retention time for (*R*)-enantiomer: 2.32 minutes. LCMS ESI (-) *m/z* 428 (M-H+HCO_2H). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1 H), 7.27–7.24 (m, 1 H), 7.15–7.14 (m, 1 H), 7.07–7.03 (m, 1 H), 7.00 (d, 1 H), 5.63–5.58 (m, 1 H), 3.56–3.35 (m, 3 H), 3.24 (s, 3 H).

(*S*)-3-((7-(ethylsulfonyl)-2,2-difluoro-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (10j). Step A: Preparation of 7-(ethylthio)-4-fluoro-2,3-dihydro-1*H*-inden-1-one **(31j)**: The ethyl group was installed in an identical procedure to Step A for the synthesis of **10h**, except

that iodoethane was used as the alkylating agent instead of iodomethane. LCMS ESI (+) *m/z* 211.1 (M+H).

Step B: (*S*)-3-((7-(Ethylsulfonyl)-2,2-difluoro-1-hydroxy-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile **(10j)**: Prepared analogously to **10f** Step G substituting **31j** for **30**. Enantiomeric excess (96%) was determined by chiral HPLC as described in the general chemistry section. Retention time for (*S*)-enantiomer: 2.101 minutes; retention time for (*R*)-enantiomer: 2.31 minutes. LC-MS ESI (-) *m/z* 442 (M-H+HCO_2H). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.27–7.24 (m, 1H), 7.16–7.14 (m, 1H), 7.07–7.04 (m, 1H), 6.99 (d, 1H), 5.55–5.51 (m, 1H), 3.61–3.27 (m, 5H), 1.35 (t, 3H).

3-Fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile (10k) and **3-fluoro-5-(((1*S*,2*S*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile (10l).** Step A: Preparation of 3-fluoro-5-((2-fluoro-7-(methylsulfonyl)-1-oxo-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile **(33)**: Selectfluor® (18.1 g, 51.0 mmol) was added to a solution of 3-fluoro-5-(7-methylsulfonyl-1-oxo-indan-4-yl)oxy-benzonitrile (intermediate from the synthesis of **10i**, 11.0 g, 31.9 mmol) in methanol (300 mL) at room temperature and then warmed to reflux for 24 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ethyl acetate then the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with 1 N HCl and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 3-fluoro-5-(2-fluoro-7-methylsulfonyl-1-oxo-indan-4-yl)oxy-benzonitrile **(33)** as a light yellow foam which was used without further purification. LC-MS ESI (+) *m/z* 364 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H), 7.32-7.28 (m, 1H), 7.23-7.19 (m, 2H), 7.10 (dt, 1H), 5.42 (ddd, 1H), 3.72 (ddd, 1H), 3.45 (s, 3H), 3.20 (ddd, 1H).

Step B: Preparation of 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile (**10k**): RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] (203 mg, 0.320 mmol) was added to an ice-cold solution of 3-fluoro-5-(2-fluoro-7-methylsulfonyl-1-oxo-indan-4-yl)oxy-benzonitrile

(33) (11.6 g, 31.8 mmol), triethylamine (8.90 mL, 63.7 mmol) and formic acid (3.60 mL, 95.5 mmol) in dichloromethane (200 mL). The reaction flask was sealed with a septum equipped with a limp balloon and placed in a 4 °C refrigerator overnight. The reaction mixture was poured into saturated $NaHCO_3$, extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* until ~25 mL of solvent remained. The mixture was purified by chromatography on silica gel with a gradient of 15% to 80% ethyl acetate in hexanes. Approximately 50% of the material precipitated on top of the column. The precipitated solid was removed, dissolved in 300 mL of warm dichloromethane and then purified on a plug of silica gel eluting with 50% then 60% ethyl acetate/hexane to give additional desired product. 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile **(10k)** (9.65 g combined, 83% yield over two steps) was obtained as an off-white solid. Enantiomeric excess (>99%) was determined by chiral HPLC as described in the general chemistry section. Retention time for (1*S*,2*R*)-diastereomer: 2.07 minutes; retention time for (1*R*,2*S*)-diastereomer: 2.36 minutes. LC-MS ESI (+) *m*/*z* 383 ($M+NH_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 1H), 7.21–7.20 (m, 1H), 7.12–7.11 (m, 1H), 7.03–6.98 (m, 2H), 5.71–5.65 (m, 1H), 5.46–5.33 (m, 1H), 3.66 (dd, 1H), 3.31 (s, 3H), 3.27–3.05 (m, 2H).

Preparation of 3-fluoro-5-(((1*S*,2*S*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile (**10l**): Crude product from the asymmetric transfer hydrogenation as described in the preparation of **10k** (Step B) contained a small amount of the *trans*-product **10l**. Impure 3-fluoro-5-(((1*S*,2*R*)-2-fluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)benzonitrile (1 g) was purified by chromatography on silica gel eluting with isocratic 10% MTBE/dichloromethane to afford 65 mg of slightly impure *trans* product. 20 mg of this material was further purified by preparative TLC (2 mm, 10% MTBE/dichloromethane) obtaining 15 mg of enriched product, which was purified again using the same conditions affording 3-fluoro-5-[(1*S*,2*S*)-2-fluoro-1-hydroxy-7-methylsulfonyl-indan-4-yl]oxy-benzonitrile **(10l)** (8.4 mg). Enantiomeric excess (98%) was determined by chiral HPLC as described in the general chemistry section. Retention time for (1*S*,2*S*)-enantiomer: 1.97 minutes;

retention time for (1*R*,2*R*)-enantiomer: 2.11 minutes. LC-MS ESI (+) *m/z* 383 ($M+NH_4$). ^{1}H NMR (400 MHz, CDC_3): δ 7.87 (d, 1H), 7.23-7.21 (m, 1H), 7.13-7.12 (m, 1H), 7.05-7.00 (m, 2H), 5.62-5.56 (m, 1H), 5.44-5.29 (m, 1H), 3.66 (dd, 1H), 3.49-3.35 (m, 1H), 3.20 (s, 3H), 3.17-3.06 (m, 1H).

3-((6,6-Difluoro-5-hydroxy-4-(methylsulfonyl)-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)-5-fluorobenzonitrile (10m). Step A: Preparation of 8-bromo-5-hydroxy-tetralin-1-one: Glassware was flame dried prior to the reaction. A solution of 8-bromo-5-methoxy-tetralin-1-one (0.510 g, 2.00 mmol) in 1,2-dichloroethane (10 mL) was treated with aluminum trichloride (1.17 g, 8.80 mmol) and the resulting suspension was stirred at 85 °C for 3.5 h. The reaction mixture was carefully poured into 34 mL 10% HCl and stirred for 2 h. The reaction mixture was diluted with 22 mL CH_2Cl_2 and vigorously stirred. The mixture was filtered through Celite to remove black-colored insoluble materials to give 8-bromo-5-hydroxy-tetralin-1-one (0.198 g, 40% crude yield), which was used without further purification. LCMS ESI (+) *m/z* 241.0, 243.0 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 7.36 (d, 1H), 6.90 (d, 1H), 2.79 (t, 2H), 2.57 (dd, 2H), 2.01-1.92 (m, 2H).

Step B: Preparation of 3-(8-bromo-1-oxo-tetralin-5-yl)oxy-5-fluoro-benzonitrile: A suspension of 3,5-difluorobenzonitrile (211 mg, 1.52 mmol), 8-bromo-5-hydroxy-tetralin-1-one (183 mg, 0.773 mmol), and cesium bicarbonate (162 mg, 0.835 mmol) in 1-methyl-2-pyrrolidone (3.0 mL) was stirred at 150 °C by microwave irradiation for 30 minutes. The reaction mixture was poured into 40 mL water and extracted with 3 x 20 mL Et_2O. The combined organics were rinsed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness to give 3-(8-bromo-1-oxo-tetralin-5-yl)oxy-5-fluoro-benzonitrile (72 mg crude product). The product was isolated as a mixture of bromo and des-bromo derivatives and used without further purification. LCMS ESI (+) *m/z* 359.9, 361.9 (M+H).

Step C: Preparation of 3-fluoro-5-((4-(methylsulfonyl)-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)benzonitrile **(34)**: A solution of 3-(8-bromo-1-oxo-tetralin-5-yl)oxy-5-fluoro-benzonitrile (51.5 mg, 0.14 mmol), sodium methanesulfinate (16.1 mg, 0.16 mmol) and copper(I) iodide (136 mg, 0.715

mmol) in dimethyl sulfoxide (1 mL) was heated to 100 °C for 30 minutes. The reaction mixture, while vigorously stirred, was diluted with 4 mL Et_2O and then diluted with 2 mL of water. The resulting suspension was filtered through Celite and the filter cake rinsed extensively with Et_2O. The filtrate was poured into 20 mL of water and extracted with 3 x 10 mL Et_2O. The combined organic layers were washed with 10 mL brine, dried with $MgSO_4$, filtered, and concentrated to dryness. Purification was achieved by chromatography on silica using a 10% to 50% EtOAc in hexane gradient to give 3-fluoro-5-((4-(methylsulfonyl)-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)benzonitrile (31.8 mg, 12% over 2 steps). LCMS ESI (+) *m/z* 360.0 (M+H).

Step D: 3-((6,6-Difluoro-5-hydroxy-4-(methylsulfonyl)-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)-5-fluorobenzonitrile **(10m)**: The remaining steps of the synthesis were analogous to the procedures for compound **10f** using Steps D and E, and compound **10d** finishing with Step F. LCMS ESI (+) *m/z* 398.0 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 1H), 7.23 (ddd, 1H), 7.12-7.10 (m, 1H), 7.01 (dt, 1H), 6.97 (d, 1H), 5.55-5.48 (m, 1H), 5.53 (dd, 1H), 3.26 (s, 3H), 3.24-3.16 (m, 1H), 2.91 (ddd, 1H), 2.64-2.44 (m, 1H), 2.36-2.25 (m, 1H).

(*S*)-4-((5-Chloropyridin-3-yl)oxy)-7-(difluoromethylsulfonyl)-2,2-difluoro-2,3-dihydro-1*H*-inden-1-ol (10n). Prepared analogously to the procedure for compound **10f** substituting 5-chloropyridin-3-ol for 3-fluoro-5-hydroxy-benzonitrile in Step B. Enantiomeric excess (98%) was determined by chiral HPLC as described in the general chemistry section. Retention time for (*S*)-enantiomer: 2.09 minutes; retention time for (*R*)-enantiomer: 2.29 minutes. LCMS ESI (+) *m/z* 409.9, 411.9 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.54 (m, 1H), 8.40-8.39 (m, 1H), 7.91 (d, 1H), 7.52-7.49 (m, 1H), 6.93 (d, 1H), 6.44 (t, 1H), 5.53-5.49 (m, 1H), 3.64-3.48 (m, 2H), 3.35 (d, 1H).

3-((4-((Difluoromethyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[b]thiophen-5-yl)oxy)-5-fluorobenzonitrile (11). For the synthesis of **11**, see step G in the synthesis of **8b**.

3-(3-Cyano-5-fluorophenoxy)-2-(difluoromethyl)-6-((difluoromethyl)sulfonyl)benzoic acid (12). To a stirred solution of 3-[4-(difluoromethyl)-1,1,3-trioxo-benzothiophen-5-yl]oxy-5-fluoro-benzonitrile **(11)** (10 mg, 0.027 mmol) in acetonitrile (0.3 mL) was added 1 N NaOH (55 μL, 0.055 mmol). The reaction mixture was stirred at rt for 1 h and then diluted with water. The mixture was extracted with MTBE. To the aqueous layer was added dropwise 0.1 N HCl to adjust pH to 3. The mixture was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give 3-(3-cyano-5-fluorophenoxy)-2-(difluoromethyl)-6-((difluoromethyl)sulfonyl)benzoic acid (8.0 mg, 70%). LCMS ESI (+) *m/z* 439 ($M+NH_4$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, 1H), 7.80 (d, 1H), 7.68 (s, 1H), 7.62 (d, 1H), 7.43 (t, 1H), 7.21 (t, 1H), 7.16 (d, 1H).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX.

Additional details concerning the SPA assay, luciferase assay, VEGF assay, crystallography methods/collection statistics, in vitro microsomal stability assay, plasma protein binding assay, permeability assay, CYP inhibition assessment, thermodynamic solubility measurement, in vivo pharmacokinetic experiments, PK/PD study (of **9a**, **10f**, **10h**, **10i**, and **10n**), in vivo efficacy study (of **9a**, **10f**, **10h**, **10i**, and **10n**), hERG profiling, kinase profiling, and Panlabs profiling. Also select spectral images for **10i** and **9a**. (link)

A molecular formula strings file with in vitro activity data (link).

Accession Codes

Authors will release the atomic coordinates and experimental data upon article publication.

Atomic coordinates have been deposited in the Protein Data Bank (PDB code: 6D0B for **4a**, 6CZW for **6c**, 6D09 for **9a**, and 6D0C the empty complex of HIF2a-PasB* and ARNT-PasB*.

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ABBREVIATIONS USED

ARNT, aryl hydrocarbon receptor nuclear translocator; ccRCC, clear cell renal cell carcinoma; F-TEDA-BF_4, 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); HIF, hypoxia-inducible factor; HRE, hypoxia-responsive element; ITC, isothermal titration calorimetry; PHD, prolyl-hydroxylase; pVHL, von Hippel-Lindau protein; SBDD, structure based drug design; SPA, scintillation proximity assay; VEGFA, vascular endothelial growth factor A; VHL, von Hippel-Lindau.

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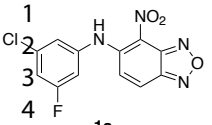
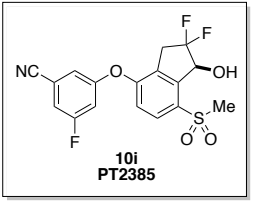


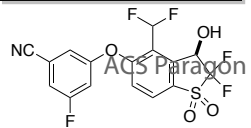
1a
Literature lead

Structure-based design

2 scaffolds
Important fluorination effect



10i
PT2385



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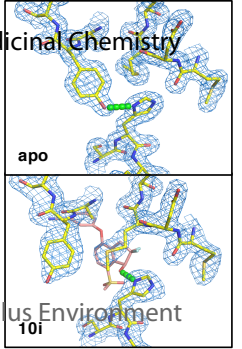

Allosteric inhibition from structural perturbation

Tumor regression