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Abstract

The BET family of proteins consists of BRD2, BRD3, BRD4, and BRDt. Each protein contains two distinct bromodomains (BD1 and BD2). BET family bromodomain inhibitors under clinical development for oncology bind to each of the eight bromodomains with similar affinities. We hypothesized that it may be possible to achieve an improved therapeutic index by selectively targeting subsets of the BET bromodomains. Both BD1 and BD2 are highly conserved across family members (>70% identity), whereas BD1 and BD2 from the same protein exhibit a larger degree of divergence (~40% identity), suggesting selectivity between BD1 and BD2 of all family members would be more straightforward to achieve. Exploiting the Asp144/His437 and Ile146/Val439 sequence differences (BRD4 BD1/BD2 numbering) allowed the identification of compound **27** demonstrating greater than 100-fold selectivity for BRD4 BD2 over BRD4 BD1. Further optimization to improve BD2 selectivity and oral bioavailability resulted in the clinical development compound **46** (ABBV-744).

Introduction

The BET (Bromodomain and ExtraTerminal) family of proteins, consisting of BRD2, BRD3, BRD4 and BRDt, has attracted interest as an epigenetic target for drug discovery.[1,2] Family members each contain two structural elements known as bromodomains which comprise a bundle of 4 helices with connecting loops. The bromodomains bind to acetylated lysine sidechains on chromatin and other proteins, with this recognition element playing a part in the assembly of multi-component protein complexes involved in gene transcription.[3] The involvement of BET family proteins in super enhancers is emerging as a biologically significant role for these proteins.[4,5] Many of the interacting transcription factors and their target genes are associated with disease pathways, leading to considerable drug discovery efforts against these targets and the clinical development of multiple compounds for a variety of indications.[6] Results reported to date provide some encouraging signals of clinical activity, but with toxicities believed to be mechanism-based at similar doses. There is thus a need for improved agents and or treatment protocols to provide greater benefits to patients.[6]

The two bromodomains of each BET protein differ in sequence, and when clustered by sequence the set of four *N*-terminal or BD1 bromodomains display much higher similarity with each other than to the set of four BD2 bromodomains. Understanding the roles and binding partners for each bromodomain is an active area of research, limited in part by a lack of widely available molecular probes with selectivity between the BET bromodomains. Some biologically important interactions have been established to involve interactions of both BET bromodomains with the same partner protein, for example the interaction of BRD4 with the acetylated Lys310 of RelA in recruitment of NF-κB.[7] In other contexts, the roles can be demonstrated to be distinct. Selective inhibition of BD1 has been reported to promote differentiation of

oligodendrocyte progenitors, while selective inhibition of BD2 had no effect, and inhibition of both hindered differentiation.[8] BD1-selective inhibition is also reported to selectively block Th17 cell differentiation over Th1, Th2 and Treg cells.[9] Detailed biochemical and genetic studies of the interaction of BRD4 with diacetylated Twist indicated that the Twist interaction occurs through BD2, while BD1 interacts with acetylated histone H4.[10] A recent study with "clickable" probes confirmed the differential relative affinity of BRD4 BD1 and BD2 for chromatin.[11] The greater role for BD1 in chromatin binding was also indicated in studies using a 'bump and hole" approach,[12] which in addition found differing dependencies on BD2 for gene expression among the BET-family members. Another study has reported that only BD1 of BRD3 leads to association of BRD3 with acetylated transcription factor GATA1.[13] In light of the potential for differentiated biology and better tolerated agents, we were interested in discovering BET-BD2 selective compounds with appropriate properties for pharmaceutical development.

Most reported BET bromodomain inhibitors have similar affinity for all bromodomains of the family; in contrast, they exhibit limited binding to non-BET family bromodomains. These will be referred to as Dual-bromodomain BET inhibitors throughout the text. The first generation of BET bromodomain inhibitors that have entered clinical development for oncology indications are Dual-bromodomain BET inhibitors, including OTX-015 **1**,[14] Ten-010 **2**,[15] I-BET762 **3**,[16] CPI-610 **4**,[17] ABBV-075 **5**,[18] BMS-986158 **6**,[19] INCB054329 **7**,[20] INCB057643 **8**,[21] and PLX51107 **9**.[22](Figure 1) An exception to this trend is the clinical development compound RVX-208 **10** (Figure 2), being developed for cardiovascular indications and reported to be selective for the BD2 bromodomains. A small number of compounds reported to display selectivity within the BET bromodomains have been reported in the scientific literature. Among

these are compounds reported to be selective for the bromodomains of BRD4 over other BET family proteins,[23, 24] as well as compounds reported to be selective for the first bromodomain of each BET-family member.[8, 9,25-28] Compounds reported to be selective for the second bromodomain of each BET family member have begun to appear in the literature, (Figure 2, Table 1) such as **10**,[29] **11,**[30] **12**,[31] **13**,[32] **14**,[33] **15**[34] and **16**.[35] Additional BD1-selective compounds[36-41] and BD2-selective compounds[42-46] have been reported in the patent literature, although the basis for selectivity of these compounds is yet to be described. Interestingly, PROTAC AT-1 has been reported to achieve a degree of selectivity in degrading BRD4 in preference to other BET proteins,[47] potentially providing a different approach to bromodomain selectivity.

While the BD2-selective compounds reported in the literature demonstrate that some degree of selectivity is achievable (Table 1), we sought to identify compounds with both greater potency and selectivity, as well as ADME properties suitable for *in vivo* evaluation. In this paper we describe our successful efforts to identify a BD2-selective BET bromodomain inhibitor from the pyrrolopyridone chemotype used in our clinical Dual-bromodomain BET inhibitor ABBV-075.

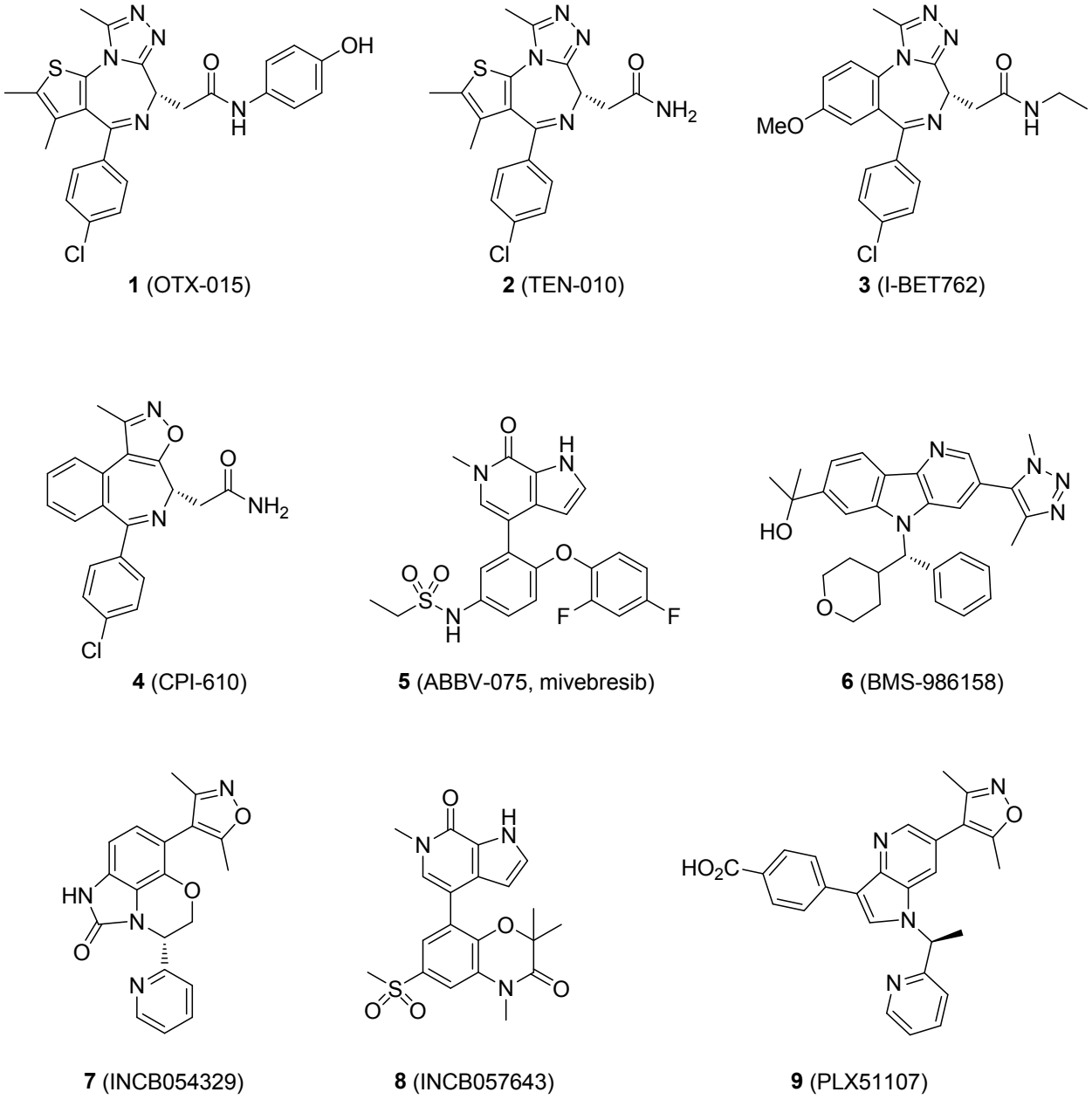

Figure 1. Dual-bromodomain BET inhibitors of known structure in clinical development.

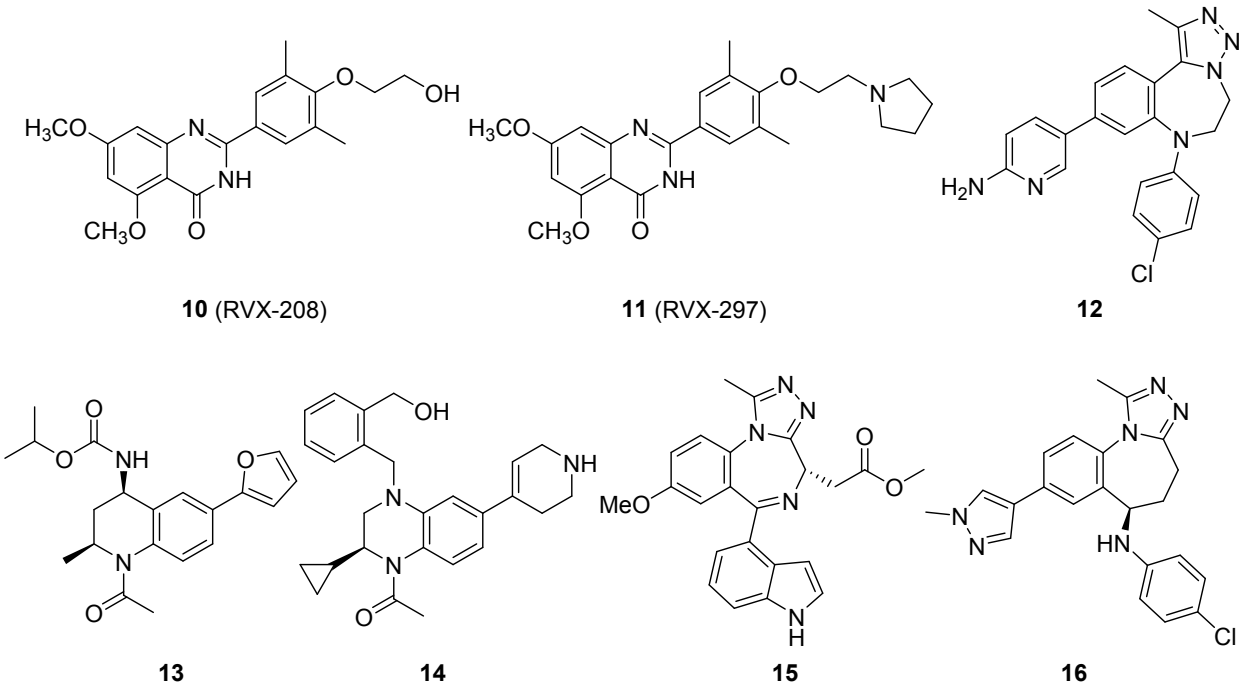

Figure 2. BD2-selective BET bromodomain inhibitors described in the literature.

Table 1. BD2-Selective BET Bromodomain Inhibitors

Compound	Published BRD4 bromodomain affinity		
	BD1 (nM)	BD2 (nM)	Selectivity (fold)
5[a]	2.8	1.3	2
10[b]	1,142	135	8.5
11[c]	1,160	20	58
12[d]	13	6	2
13[e]	2,020	610	3.3
14[f]	3,200	63	50
15[g]	520	50	10
16[h]	80	7.3	11

[a]K_i by TR-FRET, ref 18; [b]K_D by ITC, ref 29; [c]IC_{50} by AlphaScreen, ref 30; [d]IC_{50} by AlphaScreen, ref 31; [e]IC_{50} by TR-FRET, ref 32; [f]IC_{50} by TR-FRET, ref 33; [g]K_D by ITC, ref 34; [h]K_i by FP, ref 35.

Compound Evaluation

Final compounds were evaluated for binding to the isolated first and second bromodomains of BRD4 using a time-resolved fluorescence energy transfer (TR-FRET) assay to measure K_i values as described in the Experimental Section. Results for this assay reported in the tables are the geometric mean ± standard error of three independent measurements unless otherwise noted. Cellular activity was evaluated in 5-day cell growth assays using SKM-1 and H1299 cells. During the course of the project, the growth of AML-derived SKM-1 cells was found to be inhibited following 5-day treatment with BD2-selective inhibitors. In contrast, H1299 cells were observed to be minimally impacted by BD2 inhibition, and growth inhibition was measurable only in the presence of Dual-bromodomain inhibitors or when the concentration of the BD2-selective inhibitor reached a level wherein BD1 was also engaged.[48] The activity differential between cell lines was more pronounced at later time points, and 5 day assays were chosen as a practical balance between greater differentiation and experimental efficiency. The ratio of activity in these cell lines was used as a rough measure of cellular selectivity to inform iterative compound optimization. Results from the cellular assays are reported as the average of two independent determinations unless otherwise noted. Compounds were also evaluated for stability in the presence of human, rat and mouse liver microsomes, and evaluated in a PAMPA permeability assay to provide a high throughput survey of potential ADME properties and inform selection of compounds for pharmacokinetic analysis.

Results and Discussion

Examination of the protein sequences of the small-molecule binding site of the BET family bromodomains (Figure 3) revealed that many of the positions have identical amino acids across the family, with very few residues unique to a single family member. This observation suggested that targeting a single bromodomain in the family would be challenging. There are, however, a number of positions where the BD1 bromodomains have a common composition while the BD2 bromodomains have a different common composition. We hoped these positions would represent an opportunity to achieve selectivity for the set of BD2 bromodomains relative to the BD1 bromodomains. As shown for the two bromodomains of BRD4 (Figure 3), many of these amino acid differences are distal to the binding site occupied by compound **5** and other BET inhibitors, or have the sidechains directed away from the binding site. Due to their proximity, the Asp144/His 437 and Ile146/Val439 differences (BRD4 BD1/BD2 numbering) were of particular interest.

```
BRD2 BD1 FAWPFRQPVDAVKLGLPDY CYIYNKPTDDIVLM
BRD2 BD2 YAWPFYKPVDASALGLHDY CYKYNPPDHDVVAM
BRD3 BD1 FAWPFYQPVDAIKLNLPDY CYIYNKPTDDIVLM
BRD3 BD2 YAWPFYKPVDAEALELHDY CYKYNPPDHEVVAM
BRD4 BD1 FAWPFQQPVDAVKLNLPDY CYIYNKPGDDIVLM
BRD4 BD2 YAWPFYKPVDVEALGLHDY CYKYNPPDHEVVAM
BRDT BD1 FSWPFQRPVDAVKLQLPDY CYLYNKPGDDIVLM
BRDT BD2 YAWPFYNPVDADALGLHNY CYKYNPPDHEVVAM
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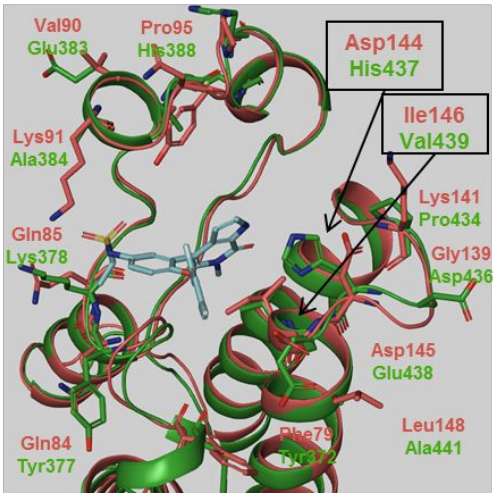
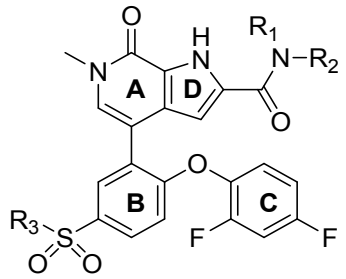


Figure 3. Left: BET bromodomain sequence comparison in the binding site region. Residues constant for a given position are underlined, residues unique for the position among the family are in bold italic, residues consistent among the 4 BD1 domains are in blue, residues consistent

among the BD2 domains are shown in red. The Asp144/His 437 and Ile146/Val439 differences (BRD4 BD1/BD2 numbering) are boxed for emphasis Right: Location of amino acid pair differences in the binding site region, with residues Asp144/His 437 and Ile146/Val439 again boxed for emphasis. Compound **5** bound to BRD4 BD1 (salmon, resolution 2.14 Å, PDB code 5UVW) superimposed with the BRD4 BD2 protein (green, resolution 1.53 Å, PDB code 5UVX). Sidechains of identical residues are omitted for clarity.

During the medicinal chemistry campaign which led to the identification of the Dual-bromodomain BET inhibitor ABBV-075 (mivebresib, **5)**, a number of substitutions at the C-2 position on the pyrrolopyridone ring were examined. When reviewing the selectivity of compounds prepared for the project, amide **17** stood out as one of the few analogs observed to display reproducible BD2-selective binding beyond the MSR of the assay (Table 2). After mono-alkylation of the primary amide of compound **17** with an ethyl group, the resulting compound **18** showed slightly better BD2 selectivity. However, di-alkylation of the amide of compound **17** to provide **19** completely changed the BD1/BD2-selectivity landscape. In fact, compound **19** exhibited slight BD1 selectivity. Compound **20**, bearing a slightly longer ethyl sulfone, showed similar selectivity to **17** and **18**. These initial amide-containing compounds have excellent cellular activity against the SKM-1 cell line, and compounds **17** and **18** demonstrated differential activity between the sensitive and insensitive cell lines. The compounds also exhibited suitable *in vitro* unbound clearance and permeability despite the addition of additional polar functionality to the pyrrolopyridone core.

Table 2. Initial Amide SAR Around 2-Position of Pyrrolopyridone Core



Compound	R_1	R_2	R_3	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/BD2 (fold)	SKM-1 IC_{50} (μM)[b]	H1299 IC_{50} (μM)[b]	$Cl_{int,u}$ in liver microsomes (L/(h·kg))[c]			PAMPA (10^{-6} cm/s)
				BD1	BD2				Human	Mouse	Rat	
17	H	H	-Me	8.6 ± 0.6	1.2 ± 0.1	7	0.010	0.60	4.6	<7.2	<4.1	2.4 (MDCK)
18	-Et	H	-Me	21.6 ± 14	1.3 ± 0.3	17	0.0066	0.37	3.6	<5.5	<3.1	10.8
19	-Et	-Me	-Me	13 ± 1.2	40 ± 1.9	0.3	0.056	0.39	3.8	17.3	16.9	16.0
20	-Et	H	-Et	6.6 ± 1.0	0.7 ±0.1	9	0.031	0.11	3.0	<6.2	11.3	3.18

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by the number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

The X-ray co-crystal structures of compound **18** in the binding site of BRD4 BD1 and BD2 were solved, providing hypotheses for the origin of the modest selectivity between the two bromodomains (Figure 4). Many of the interactions with the bromodomain proteins are shared, including hydrogen bonding interactions with the key Asn sidechain, positioning of the methyl group at the 6-position of the pyrrolopyridone in an amphipathic water network, occupation of

the WPF shelf region by the aryl ether ring and positioning of the sulfone in a cleft adjacent to the ZA-loop where it accepts a hydrogen bond from a backbone NH. As highlighted in the space filling views in Figure 4, bottom panel, the ethyl amide of compound **18** is making van der Waals contact with the hydrophobic sidechains of amino acids Tyr432 and His437 in BRD4 BD2, which form a cleft. In BRD4 BD1, the position corresponding to His437 is Asp144 whose sidechain points away from the ligand, leading to a less favorable interaction. Based on the structure of **18** bound to BRD4 BD2, a rationalization for the reduced BD2 affinity of the tertiary amide **19** is that while methylation of the amide would disrupt the hydrogen bond to the asparagine amide, forcing the amide to rotate significantly to avoid a clash in either bromodomain, this would position the alkyl groups in a more crowded region adjacent to His437 in BD2 vs a more open area adjacent to Asp144 in BD1.

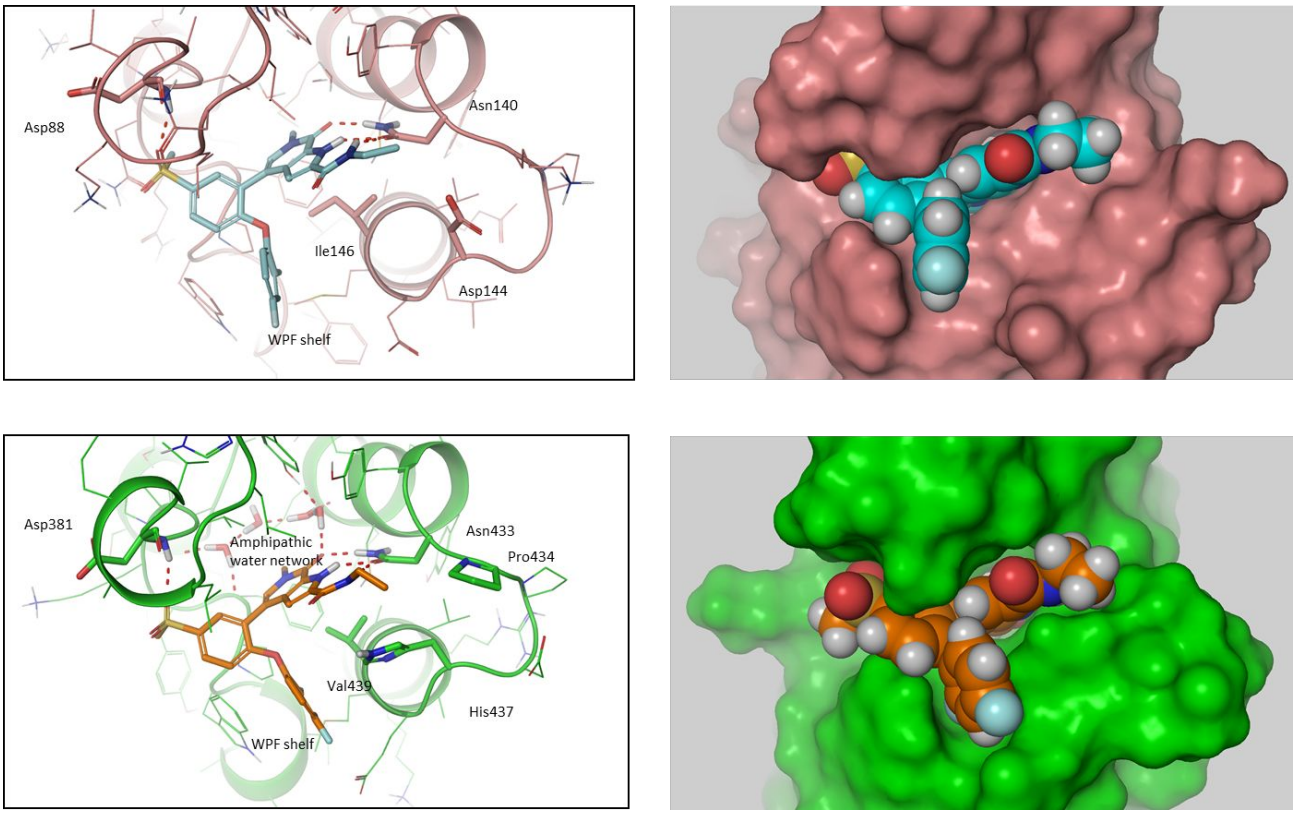
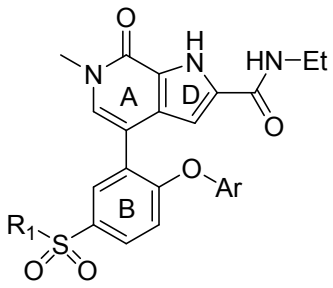


Figure 4. X-ray co-crystal structures of **18** with BRD4 BD1 (top, resolution 2.45 Å, PDB code 6VIW) and BRD4 BD2 (bottom, resolution 2.13 Å, PDB code 6VIX). The left panels show hydrogen bonds predicted by Schrödinger Maestro between ligand and protein as dotted lines. The hydrogen bonding network of the amphipathic water network is shown in the lower left panel. The right panels show a space filling representation.

An additional observation from these X-ray co-crystal structures concerned the position of the 2,4-difluorophenoxy portion of **18**, which differs slightly in the two co-crystal structures. In the BD1 structure, the aryl moiety is canted toward the tryptophan of the WPF shelf and away from Ile146, whereas in the BD2 structure the aryl group is located closer to His437 and Val439. As noted in Figure 3, the Ile/Val difference is consistent across the BET family, and this

particular position is a part of the rigid pocket and buried deeply in the binding site. We explored this subtle residue difference for the improvement of the BD2 selectivity by placing appropriate substituents in the aryl ether region of the lead structure. While the size differential is modest, a favorable precedent exists in the exploitation of the difference between valine and isoleucine in COX-2 inhibitors related to SC-58125.[50] The results of varying this portion of the molecule are summarized in Table 3.

Table 3. C-ring SAR



Compound	R_1	Ar	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/BD2 (fold)	SKM-1 IC_{50} (nM)[b]	H1299 IC_{50} (nM)[b]	$Cl_{int,u}$ in liver microsomes[c] (L/(h·kg))			PAMPA (10^{-6} cm/s)
			BD1	BD2				Human	Mouse	Rat	
21	-Et		8.4 ± 1.2	0.8 ± 0.2	11	3.3	95	8.5	66	NV	3.68
22	-Et		6.5 ± 0.4	0.5 ± 0.1	13	3.3	340	12	72	72	13.8
23	-Et		22 ± 0.7	2.1 ± 0.1	10	21	460	97	NV	86	5.6
24	-Et		13 ± 0.7	0.9 ± 0.1	15	2.5	260	9.0	NV	152	15.4
25	-Et		30 ± 0.9	0.9 ± 0.1	35	6.2	670	15.3	NV	127	2.73
26	-Et		45 ± 1.4	1.0 ± 0.1	45	9.8	730	16	113	81	10.5
27	-Et		120 ± 48 (10)	1.1 ±0.48 (8)	112	5.2	450	5.4	42	64	7.68
28	-Et		400 ± 36	15 ±0.6	27	290	3,200	NV	NV	NV	NV

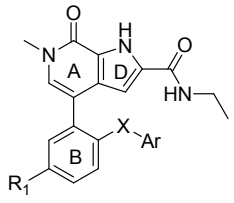
29	-Et		69 ± 2.9	3.2 ± 0.1	21	37	730	41	49	92	15.3
30	-Et		470 ± 20 (2)	5.8 ± 0.8	81	28	1,200	4.5	54	12	15.2
31	-Et		8.3 ± 0.5	0.7 ± 0.1	12	2.6	94	32	96	97	3.1
32	-Me		140 ± 9.5	1.2 ± 0.1	120	12	790	5.5	33	39	10.7
33			38 ± 0.5	0.6 ±0.1	67	20	730	18	103	107	8.33

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by the number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

When the 2-position of the phenyl C-ring is substituted with a small group, such as methyl (**21**) or chlorine (**22**), compounds maintained potent activity against BRD4 BD2 and modest BD2 selectivity. Incorporation of a larger *t*-butyl group (**23**) caused slight loss of both BD1 and BD2 activity. It was quickly appreciated, because of unrestricted rotation of the C-ring around the oxygen, that both the 2- and 6-positions of the phenoxyl C-ring needed to be occupied to ensure there would be always one substituent pointing into the floor of the pocket formed by the Ile (BD1) and Val (BD2) sidechains. Thus, several 2,6-disubstituted phenyl C-ring analogs were synthesized and tested. When a fluorine atom was attached to the 6-postion of the C-ring (**24**), no improvement for BRD4 BD2 selectivity was noted. When either a 2-chlorine (**25**) or 2-bromine (**26**) atom was introduced paired with a methyl at the 6-position, better BD2 selectivity was achieved. Gratifyingly, introduction of the 2,6-dimethyl phenyl C-ring (**27**) provided BD2 selectivity of more than 100-fold. More importantly, compound **27** maintained potent cellular

activity against the SKM-1 cell line and adequate microsomal stability. Using a larger t-butyl group (**28**) or a polar nitrile substituent (**29**) to replace one methyl group of **27** resulted in a significant erosion of BD2 activity, BD2 selectivity, and cellular activity. It was clear that the 2,6-disubstitution pattern of the substituents on the phenyl moiety is critical to achieve BD2 selectivity in this context, because when a 3,5-dimethyl phenyl C-ring was incorporated, compound **31** lost significant BD2 selectivity. When a methyl sulfone replaced the ethyl sulfone (**32**), BD2 selectivity was comparable to that of compound **27**, but its cellular activity against SKM-1 dropped slightly. However, when the slightly bigger cyclopropyl sulfone is used (**33**), decreases in both BD2 selectivity and cellular activity against SKM-1 were noted.

Table 4. Examination of Linker Between B- and C-rings



Compound	R_1	Ar	X	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/ BD2 (fold)	SKM-1 IC_{50} (nM)[b]	H1299 IC_{50} (nM)[b]	$Cl_{int,u}$ in liver microsomes (L/(h·kg))[c]			PAMPA (10^{-6} cm/s)
				BD1	BD2				Human	Mouse	Rat	
32	$-SO_2Me$		O	140 ± 9.5	1.2 ± 0.1	120	11	790	5.5	33	39	10.7
34	$-SO_2Me$		NH	250 ± 8.6	4.3 ± 0.1	58	68	3,600	7.0	29	26	3.59
35	H		CH_2	2,100 ± 100	25 ± 1.5	83	150	4,200	320	2,300	1,300	3.81
36	$-SO_2Et$		-	>12,000	22 ± 0.4	>580	1,300	>10,000	33	NV	37	9.0
37	$-SO_2Et$		-	180 ± 8.5	1.1 ± 0.1	160	9.5	2,600	6.7	45	21	10.3
38	$-SO_2Et$		-	170 ± 11	0.9 ± 0.1	178	34	3,900	8.4	31	14	3.5

39	-SO_2Et		-	140 ± 3.3	1.8 ± 0.1	78	50	1,300	27	130	38	15.9
40	-SO_2Et		-	380 ± 7.3	1.1 ± 0.1	344	23	1,900	42	110	93	14.7
41	-SO_2Et		-	9.0 ± 0.7	0.5 ± 0.1	18	4.2	340	NV	NV	NV	NV

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by the number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

Having identified 2,6-dimethyl phenyl as an optimal C-ring, the linker between the B- and C-rings was also examined, with the results listed in Table 4. When the oxygen of compound **32** was replaced with an NH group, the resulting compound **34** showed a modest drop in BD2 activity and selectivity. However, its cellular activity showed a 6-fold decrease. Using a methylene group (**35**) to replace the oxygen did not offer any benefit, as overall activity weakened substantially and microsomal stability was negatively impacted. Interestingly, when a biphenyl moiety was incorporated, completely removing the ether linkage, compound **36** exhibited excellent BD2 selectivity compared to compound **27**, albeit at the expense of its BD2 binding affinity and subsequent cellular activity. However, removal of one methyl group resulted in compound **37** with restored BD2 activity and cellular anti-proliferative activity in SKM-1. The BD2 selectivity of compound **37** was also on par with that of compound **27**, indicating that in contrast to the observations with diaryl ethers, 2,6-disubstitution was not required for differentiation with the more rigid biaryl. Several biaryl heterocycles were also investigated. Although compound **40** showed improved BD2 selectivity over compound **27**, its

cellular activity and microsomal stability were adversely impacted. Reducing the indole of compound **40** to indoline rendered compound **41** with much diminished BD2 selectivity. In general, bi-aryl compounds **37-41** also tended to demonstrate poorer solubility compared to the bi-aryl ether counterparts.

Table 5. Pharmacokinetics of Compound 27 in Mouse, Rat, Dog, and Monkey

Species	$Cl_{mic, u}$ (L/(h·kg))	IV					PO			
		Dose (mg/kg)	$t_{1/2}$ (h)	Vss (L/kg)	AUC (ng•h/mL)	CLp (L/(h·kg))	Dose (mg/kg)	$t_{1/2}$ (h)	AUC (ng•h/mL)	F (%)
Mouse	42	1	1.0	0.8	1,440	0.69	1	1	760	53
Rat	64	1	1.4	3.5	384	2.71	1	1	27	7
Dog	12	0.1	3.7	1.7	291	0.34	0.3	0.3	644	74
Monkey	32	0.1	1.5	2.3	89	1.2	0.3		0	0

Since compound **27** stood out as a BD2-selective analog with acceptable ADME properties, its pharmacokinetic properties were studied in multiple species (Table 5). While compound **27** showed adequate PK profiles in mouse and dog, its PK profiles in rat and monkey were rather disappointing. Specifically, **27** demonstrated high clearance, poor oral exposure, and single digit bioavailability in dog. Due to the fact that compound **27** was metabolized extensively by enzyme CYP3A4, it showed high clearance and no oral exposure in monkey.

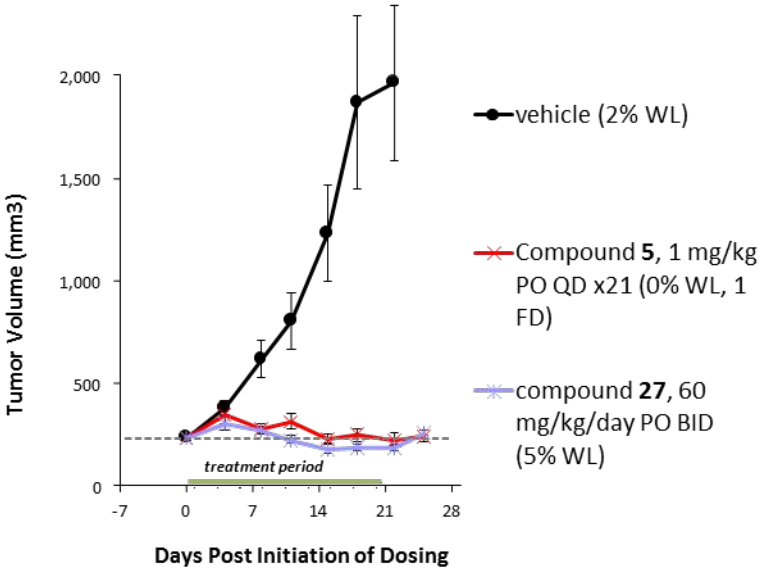


Figure 5. *In vivo* SKM-1 MDS model with compound **27**

In spite of its pharmacokinetic shortcomings, compound **27** was utilized as a tool compound to establish that BD2-selective BET inhibitors could maintain strong anti-tumor activity *in vivo*. Compound **27** dosed orally twice a day for three weeks in an SKM-1 flank xenograft model of AML resulted in efficacy comparable to that achieved with the Dual-bromodomain BET inhibitor **5** given at its maximum tolerated dose (Figure 5). Both compounds produced sustained tumor growth inhibition throughout the dosing period, thus confirming the potential antitumor activity of BD2-selective inhibitors.

To evaluate our design hypothesis, we sought co-crystal structures of **27** with both bromodomains. We were able to obtain structures of **27** co-crystalized with BRD4 BD1 and BRD2 BD2 (Figure 6). Superimposing the proteins (left panel) highlights the displacement of

the C-ring engendered by the additional methyl group of the Ile sidechain in BD1. The binding mode of **27** bound to BRD2 BD2 was in accordance with that observed for compound **18** with BRD4 BD2, with the ligand making an edge to face interaction with the His433 sidechain as well as filling a cleft formed by the His433 and Pro430 with the ethyl amide, both features being present in BD2 and not BD1.

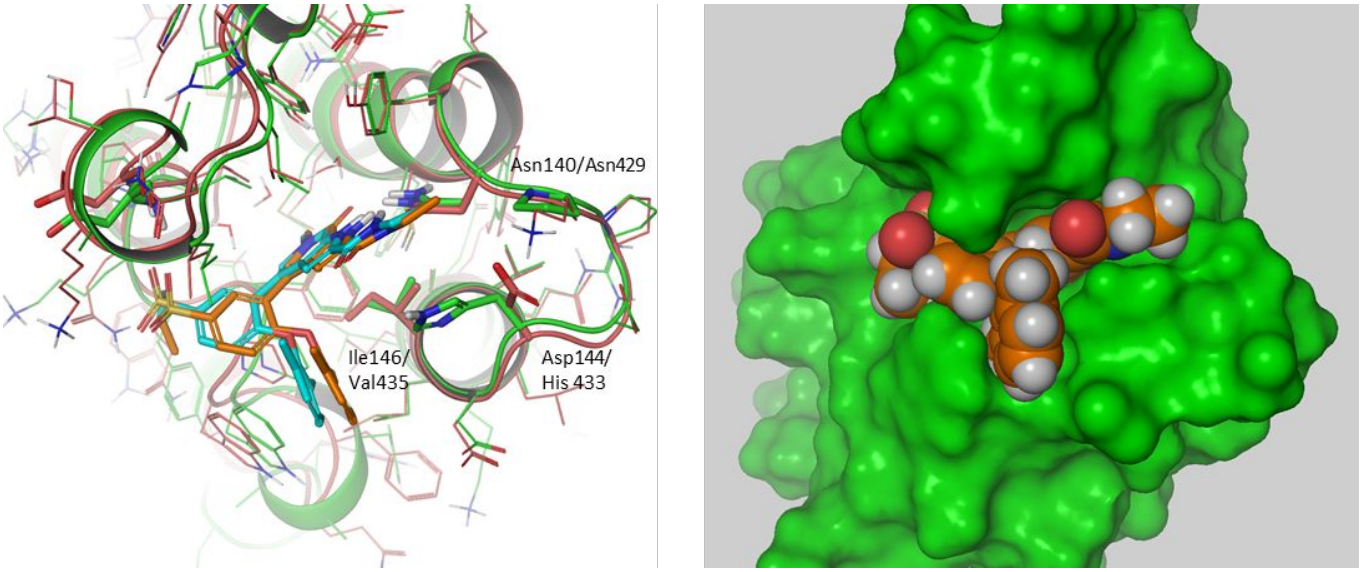
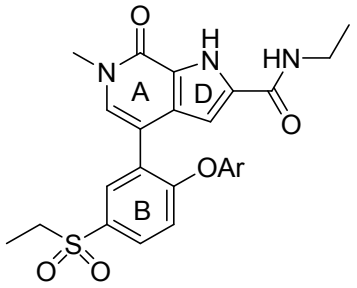


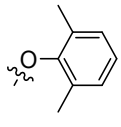
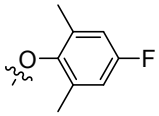
Figure 6. Left panel, X-ray co-crystal structures of **27** with BRD4 BD1 (salmon protein, cyan ligand, 2.37 Å, PDB code 6VIY) and BRD2 BD2 (green protein, orange ligand, 1.90 Å, PDB code 6VIX). Right panel, space filling representation of **27** with BRD2 BD2.

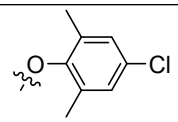
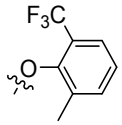
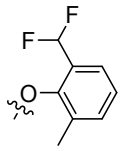
Further improvements on compound **27** were desired, both in terms of selectivity as well as physical/ADME properties. In some respects these needs worked against each other, as growing the molecule to add additional differentiating interactions with the bromodomains would add molecular weight to a compound already nearing the limits of what is typically considered to be the preferred property space for orally active drugs (MW 507, cLogP 3.88, eLogD 4.08, TPSA 108.57).

One successful approach to improving PK properties identified during the discovery of Dual-bromodomain BET inhibitor **5** was based on the observation that oxidative metabolism of aryl ether rings corresponding to the 2,6-dimethylphenyl ether of **27** presented a significant limitation, particularly in rats. Accordingly, we examined the addition of electron-withdrawing substituents to the aryl ether while retaining 2,6-disubstitution to maintain selectivity (Table 6). Introduction of a 4-F substituent was observed to improve microsomal stability vs rat liver microsomes, while the performance of **42** in the binding and cellular assays was slightly weaker but within assay variability. The corresponding 4-Cl analog **43** maintained selectivity, but was less permeable and more prone to microsomal metabolism. Introduction of fluorines on the benzylic carbons (**30**, Table 3, and **44**) led to reduced BD2 affinity and loss of potency in the SKM-1 assay.

Table 6. Additional Examination of the C-Ring and Linker



Compound	OAr	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/BD2 (fold)	SKM-1 IC_{50} (nM)[b]	H1299 IC_{50} (nM)[b]	$Cl_{int,u}$ in liver microsomes (L/(h·kg))[c]			PAMPA (10^{-6} cm/s)
		BD1	BD2				Human	Mouse	Rat	
27		120 ± 49	1.1 ± 0.5	110	5.2	450	12	42	64	7.68
42		79 ± 16	1.3 ± 0.1	64	14	810	10	55	28	6.12

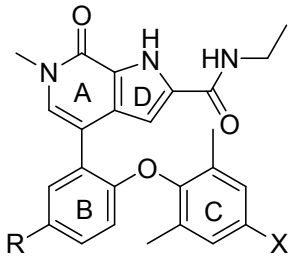
43		82 ± 5	0.8 ± 0.1	100	110	700	47	120	95	1.46
30		470 ± 20	5.8 ± 0.8	81	28	1,200	14	110	18	6.31
44		160 ± 3	2.1 ± 0.1	74	24	880	4.5	54	12	15.2

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by the number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

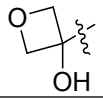
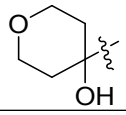
Another area of investigation was replacement of the sulfone substituent, in some cases in combination with the introduction of the 4-F substituent found in **42** (Table 7). As observed for compound 18, analysis of the crystal structures showed that the ethyl sulfone occupies a cleft adjacent to the ZA-loop and accepts a hydrogen bond from a backbone amide. We hoped that these features could be achieved by other substituents that would offer improvements in the ADME properties of the molecule. Use of a sulfonamide group as a hydrogen-bond acceptor provided compounds such as **47-48** that maintained potent BD2 binding, but were less selective due to improved binding to BD1. The reversed sulfonamide **49** showed similar selectivity to ethyl sulfone **42,** but displayed poor solubility to such an extent that it could not be tested in the *in vitro* ADME assays. Compounds **51-54** and **58** with a carbonyl hydrogen-bond acceptor such as an acid, amide or carbamate showed similar activity profiles to **27** and **42**, but offered no advantage over the sulfone and generally displayed reduced stability toward mouse liver

microsomes. In contrast, introduction of a dimethyl carbinol moiety provided compounds **45** and **46** with similar potency, a slight improvement in selectivity and in the case of **46** improved *in vitro* ADME properties. The related primary alcohol **50** was less active in the SKM-1 cellular assay. Cyclic tertiary alcohol analogs **55-57** were examined, but proved inferior in metabolic stability to the gem-dimethyl. Similarly, larger alkyl groups in place of one or both methyls provided compounds with greater BD2 selectivity, at the expense of microsomal stability (data not shown). Of these analogs, **46** provided the best combination of activity and *in vitro* ADME properties.

Table 7. Variations of the B-Ring Substituent



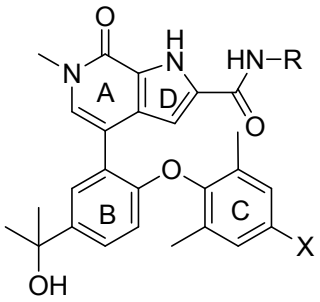
Compound	R	X	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/BD2 (fold)	SKM-1 IC_{50} (nM)[b]	H1299 IC_{50} (nM)[b]	$Cl_{int,u}$ in liver microsomes (L/(h·kg))[c]			PAMPA (10^{-6} cm/s)
			BD1	BD2				Human	Mouse	Rat	
27	$-SO_2CH_2CH_3$	H	120 ± 49	1.1 ± 0.5	110	5.2	450	12	42	64	7.68
42	$-SO_2CH_2CH_3$	F	79 ± 16	1.3 ± 0.1	64	14	810	10	55	28	6.12
45		H	160 ± 9	0.6 ± 0.1	280	11	1,200	37	170	65	6.3
46		F	520 ± 26	1.6 ± 0.2	330	6.7	1,600	8.6	45	12	2.0
47	$-NHSO_2CH_2CH_3$	H	17 ± 1	0.8 ± 0.1	22	1.7	300	11	79	880	0.22
48	$-NHSO_2CH_2CH_3$	F	49 ± 1	1.1 ± 0.1	44	42	970	19	120	NV	0.23
49	$-SO_2NH_2$	H	66 ± 3	1.1 ± 0.1	62	7.0	3,000	NV	NV	NV	NV

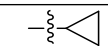
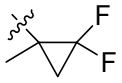
50	-CH_2OH	H	270 ± 51	1.7 ± 0.1	160	65	3,000	25	140	NV	1.69
51	-$CONHCH_2CH_3$	H	130 ± 16	1.8 ± 0.2	71	19	1,500	13	19	NV	2.63
52	-$NHC(O)OCH_3$	F	290 ± 19	2.9 ± 0.3	100	50	2,400	33	380	NV	0.92
53	-$NHC(O)CH_3$	H	76 ± 6	0.5 ± 0.1	160	3.5	730	5.0	120	40	1.96
54	-$NHC(O)CH_3$	F	90 ± 1	1.1 ± 0.1	82	14	1,600	11	140	15	1.06
55		F	220 ± 9	1.5 ± 0.1	140	26	2,200	350	940	380	1.56
56		F	170 ± 13	1.1 ± 0.1	150	24	2,700	21	32	16	1.66
57		F	300 ± 4	1.2 ± 0.1	250	6.7	2,100	520	100	49	1.47
58	-CO_2H	H	300 ± 24	2.8 ± 0.2	110	3,100	>10,000	NV	NV	NV	0.74

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by a number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

Metabolite studies on compound **27** had indicated that oxidative dealkylation of the secondary amide was a route of metabolism. Accordingly, several secondary amides were examined (Table 8). Although several examples with large alkyl groups showed good selectivity, the desired improvement in microsomal stability was not achieved. Compound **46** exhibited the best overall profile of potency, selectivity and *in vitro* ADME properties, and was selected for more thorough characterization.

Table 8. Amide Variations



#	R	X	TR-FRET (BRD4) K_i, (nM)[a]		Selectivity BD1/BD2 (fold)	SKM-1 IC_{50} (nM)[b]	H1299 IC_{50} (nM)[b]	$Cl_{int,u}$ in liver microsomes (L/(h·kg))[c]			PAMPA (10^{-6} cm/s)
			BD1	BD2				Human	Mouse	Rat	
45	$-CH_2CH_3$	H	160 ± 9	0.6 ± 0.1	280	11	1,200	37	170	65	6.3
46	$-CH_2CH_3$	F	520 ± 26	1.6 ± 0.2	330	6.7	1,600	8.6	45	12	2.0
59	$-C(CH_3)_3$	H	220 ± 16	1.1 ± 0.1	200	14	1,400	47	260	180	1.26
60	$-C(CH_3)_3$	F	310 ± 37	1.3 ± 0.1	240	25	1,500	130	520	87	NV
61		F	440 ± 68	1.3 ± 0.1	340	10	1,100	120	710	NV	0.97
62	$-CH_3$	F	140 ± 5	1.0 ± 0.1	140	13	1,200	24	33	10	0.55
63		F	230 ± 9	0.5 ± 0.1	490	6.2	1,900	48	200	20	1.13
64	$-C(CH_3)_2CF_3$	F	4,700 ± 2,100	6.9 ± 1.7	680	80	2,600	570	2,800	1,100	0.57
65		F	780 ± 49	2.0 ± 0.1	400	66	2,900	67	210	84	0.76

[a]TR-FRET K_i values are reported as the geometric mean derived from 3 independent measurements unless otherwise indicated by the number of replicates in parentheses. [b]IC_{50} values are reported as the mean derived from two independent measurements. [c]For reference, average in-house positive control values for dextromorphan and verapamil, respectively, are $Cl_{int,u}$ (human) = 7.4 L/(h·kg) (low) and $Cl_{int,u}$ (human) = 30 L/(h·kg) (high).

Compound **46** was tested for binding against the first and second bromodomains of BRD2, BRD3 and BRDt in the TR-FRET binding assay and displayed similarly potent and selective binding to that observed with BRD4 (Table 9). This result was unsurprising, given the sequence similarities in the binding site discussed previously. Binding selectivity between the two bromodomains of BRD4 was also examined in a cellular setting using a bioluminescence resonance energy transfer-based method,[49] which showed greater than 700-fold BD2 selectivity (Table 9). Selectivity was also demonstrated against a panel of non-BET family bromodomains using the DiscoveRx BROMOSCAN assay (see Table S1 in SI for data).

Table 9. Compound 46 Selectively Inhibits BD2 in Biochemical and Cellular Assays

TR-FRET								NanoBRET	
BRD2 K_i (nM)		BRD3 K_i (nM)		BRD4 K_i (nM)		BRDt K_i (nM)		Cellular IC_{50} (nM)	
BD1	BD2	BD1	BD2	BD1	BD2	BD1	BD2	BRD4 BD1	BRD4 BD2
1,162	4.6	3,140	4.9	521	1.6	917	1.0	20,700	27.5

BRD = bromodomain; BRET = bioluminescence resonance energy transfer; IC_{50} = half maximal inhibitory concentration; K_i = inhibitory constant; TR-FRET = time resolved fluorescence resonance energy transfer

To confirm the structural basis for bromodomain selectivity, X-ray co-crystal structures were obtained for **46** with both the first and second bromodomains of BRD2 (Figure 7). As observed for other compounds from the pyrrolopyridone series, the heterocyclic core exhibits

key hydrogen bonding interactions with the conserved asparagine. As intended, the tertiary alcohol of **46** was able to accept the same hydrogen bond from the amide backbone of the ZA-loop observed with the sulfones of **18** and **27**. Superposition of the BD1 and BD2 structures (Figure 7, lower left panel) shows the displacement of the 2,6-disubstituted aryl ether in the BD1 complex induced by the Ile162 sidechain. When **46** is positioned in the pose observed in the BD2 complex, one of the methyl groups would lie inside of the solvent accessible surface of the Ile in BD1. The additional buried surface area from interactions with His433 discussed earlier rationalizes the selectivity between BRD2 BD1 and BD2. These key residues are identical across the BET family, consistent with the observed uniformly good selectivity between the two bromodomains of each family member.

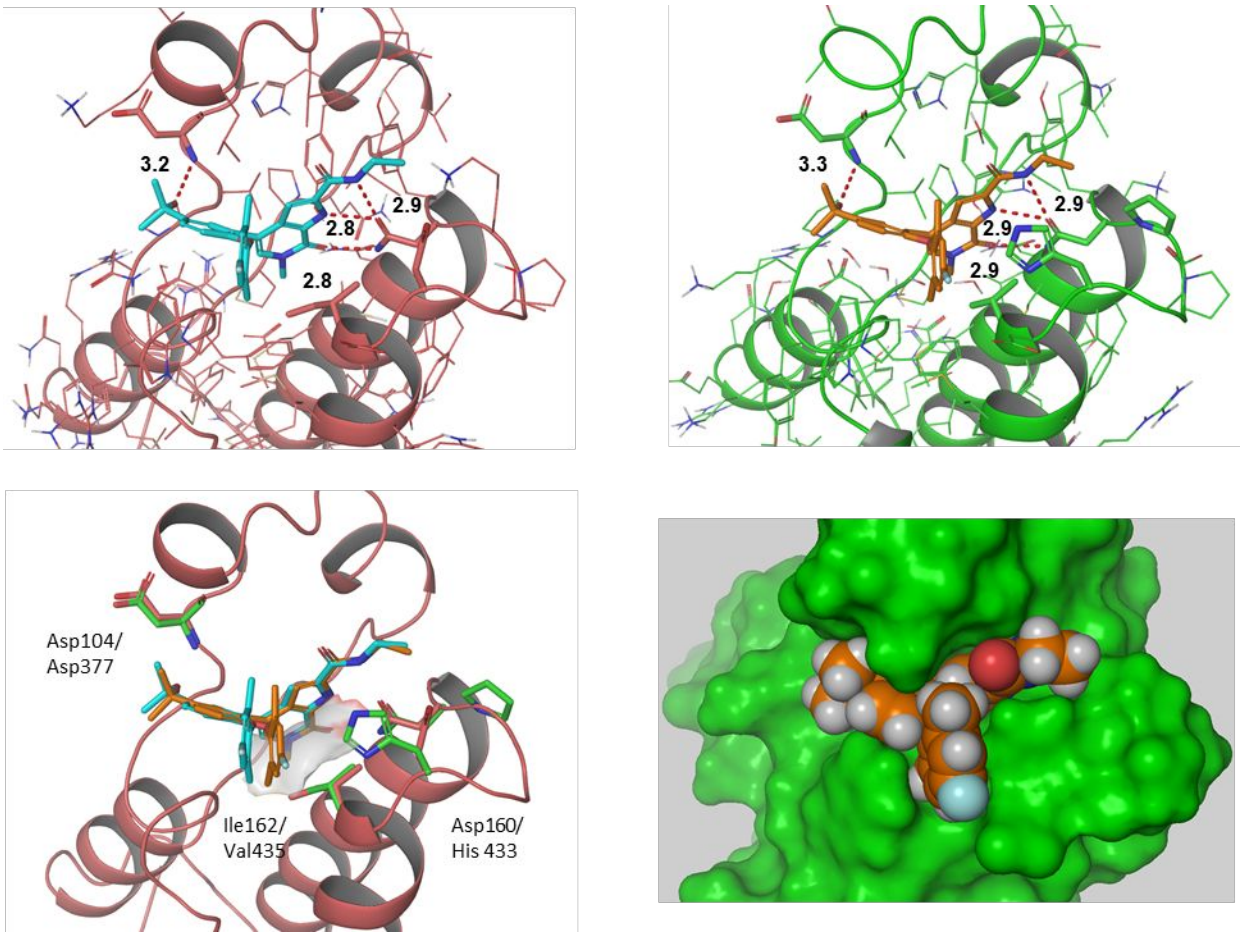


Figure 7. Upper left panel, co-crystal structure of **46** with BRD2 BD1(2.0 Å, PDB code 6ONY) showing the distances observed between selected heavy atoms in Angstroms. Upper right panel, co-crystal structure of **46** with BRD2 BD2 (2.3 Å, PDB code 6E6J) showing the distances observed between selected heavy atoms in Angstroms. Lower left panel, superimposed aligned X-ray co-crystal structures of **46** with BRD2 BD1 (salmon protein, cyan ligand) and BRD2 BD2 (green protein, orange ligand). The solvent accessible surface of Ile162 on BRD2 BD1 shown in gray excludes the space occupied by a methyl in the pose when bound to BRD2 BD2. Lower right panel, space filling representation of **46** with BRD2 BD2.

High throughput screening assays for microsomal stability and permeability predicted that **46** would display improved pharmacokinetic behavior over the initial lead **27**. Experimental data showed that the preclinical pharmacokinetic profiles of **46** are characterized by low clearance in mouse and dog, with moderate clearance in rat and monkey, which correlates well with the intrinsic metabolic clearance measured in hepatocytes (IVIVE ratio between 2-5-fold). Moderate to high volume of distribution is observed across species, with half-life ranging from 2.0 to 4.4 h (Table 10). Following oral administration, mono-exponential disposition profiles are observed in all of the preclinical species tested. The oral bioavailability of **46** in preclinical species ranges from 7% in monkey to 77% in dog, with fa*fg ranging from 19% to 87%. With the exception of reduced AUC on oral dosing in dogs, these values were superior to those observed for **27**, and allowed examination of **46** in preclinical models to compare efficacy and preclinical safety of a BD2-selective BET bromodomain inhibitor with Dual BET bromodomain inhibitors.

Table 10. DMPK Data

	IV Dose					PO Dose						
Species	**Dose**	**$t_{1/2}$**	**V_{ss}**	**AUC**	**CL_p**	**Dose**	**$t_{1/2}$**	**T_{max}**	**C_{max}**	**AUC**	**F**	**fa*fg**
Mouse	1	3.0	1.3	3.80	0.29	1	2.8	6.0	0.21	2.35	58	81
Rat	1	2.9	5.3	0.50	0.67	1	3.4	7.5	0.012	0.12	24	52
Dog	0.1	4.4	1.5	0.46	0.24	0.3	4.2	2.8	0.116	1.05	77	87
Monkey	0.3	2.0	3.4	0.20	1.54	0.3	2.5	1.5	0.005	0.014	7	19

Units: Dose (mg/kg); $t_{1/2}$ (h); V_{ss} (L/kg); AUC(μg•h/mL); CL_p (L/(h·kg)); C_{max} (μg/mL); F (%)
po formulation (Rat, Dog, Mouse): 10:30:60 Ethanol:PEG-400: Phosal 53 MCT
po formulation (Monkey): 10:90 (v/v) DMSO:PEG-400

As has been discussed elsewhere in more detail,[51] selective inhibition of the second bromodomain results in a more restricted range of antiproliferative activity relative to Dual-bromodomain BET inhibitors. Whereas potent Dual-bromodomain BET inhibitors such as **5** show potent anti-proliferative effects against a wide range of cancer cell lines,[48] **46** shows

substantially higher relative potency against cell lines derived from prostate cancer and AML, implying that BD1 inhibition is not required to inhibit proliferation in a subset of cancer indications.[51] The potent *in vitro* activity against the SKM-1 cell line and low clearance in mice were reflected in the activity of **46** in a xenograft tumor growth inhibition model, with a 18.8 mg/kg po q.d. dose providing 83% tumor growth inhibition with minimal (2%) weight loss over 21 days of dosing (Figure 8). In comparison, in the same study Dual-bromodomain BET inhibitor **5** dosed at the maximally tolerated dose of 1 mg/kg provided similar tumor growth inhibition; however, 7% weight loss was observed, and one animal had to be removed from the study. This trend toward improved tolerability, albeit modest in magnitude, supported the premise underlying our project that a more selective BET bromodomain inhibitor might achieve a better therapeutic index in settings sensitive to the mechanism of action. A more systematic evaluation supporting this hypothesis in AML models will be published separately in due course.[52]

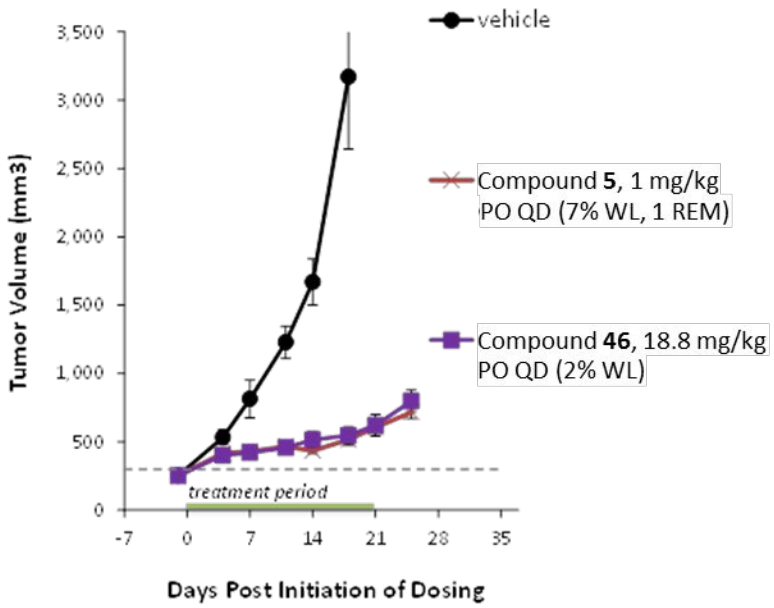


Figure 8. *In vivo* SKM-1 MDS model with compound **46**

Synthesis

In general, the compounds examined in this study were prepared using the synthetic approaches developed during the discovery of **5,**[18] with the incorporation of the pyrrole amide representing the most significant distinguishing factor from that effort. As we will show, the strategic disconnections shown in Figure 9 could be employed in a variety of different orders, depending on the availability of intermediates and upon whether a convergent or divergent synthesis was desired. This synthetic flexibility enabled the rapid generation of a wide range of inhibitors, and allowed for a thorough examination of structure activity relationships (SAR).

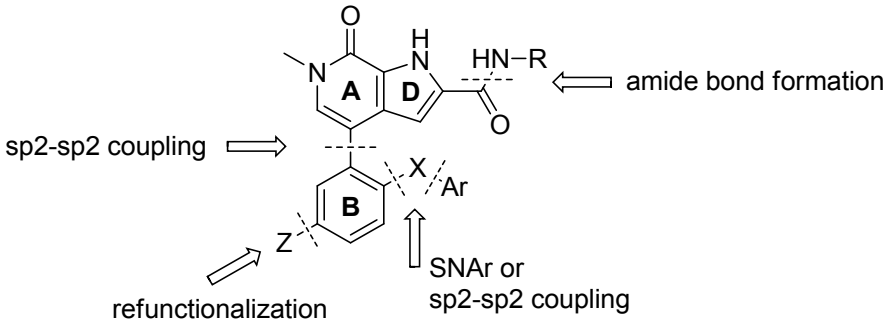
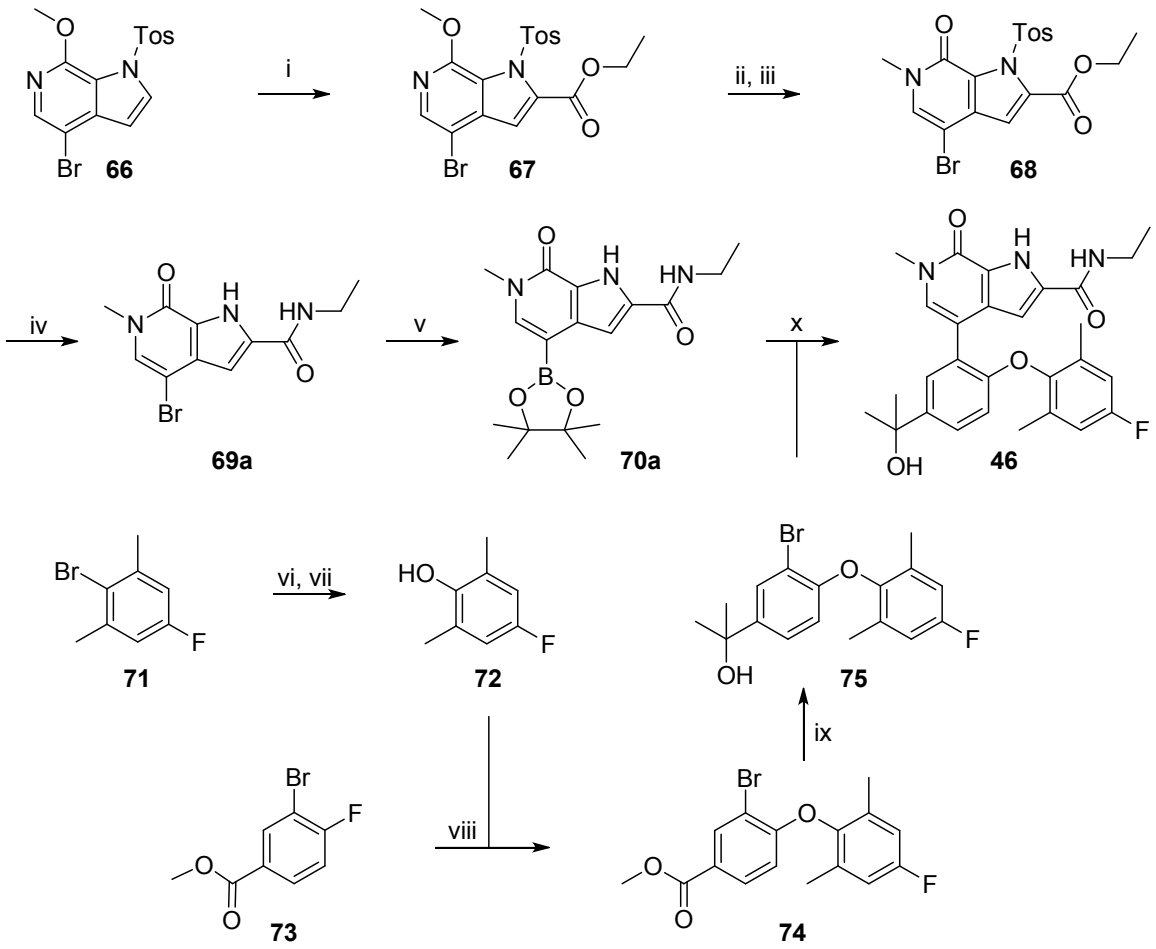


Figure 9. Strategic disconnections

One of the most efficient routes for the synthesis of any given target compound involves a convergent sequence incorporating formation of the biaryl bond at the 4-position of the pyrrolopyridone as the final step in the sequence as illustrated for key compound **46** in Scheme 1. In order to generate an intermediate suitable for incorporation of the crucial pyrrole amide, functionalization of the pyrrolopyridone 2-position was achieved by metallation of the known compound **66**,[18] followed by acylation with ethyl chloroformate. Transposition of the methoxypyridine **67** to the *N*-methylpyridone **68** and conversion to the ethyl amide with concomitant hydrolysis of the *N*-tosyl protecting group provided 4-bromo intermediate **69a**. Conversion to the valuable pinacol boronate **70a** prepared the pyrrolopyridone fragment for Suzuki-Miyaura coupling with the bottom portion. Coupling partner **75** was prepared by an S_NAr addition of phenol **72** to the fluoroaryl ester **73,** followed by addition of methyl Grignard reagent to generate the tertiary alcohol. Biaryl cross-coupling then provided **46** in good overall yield.

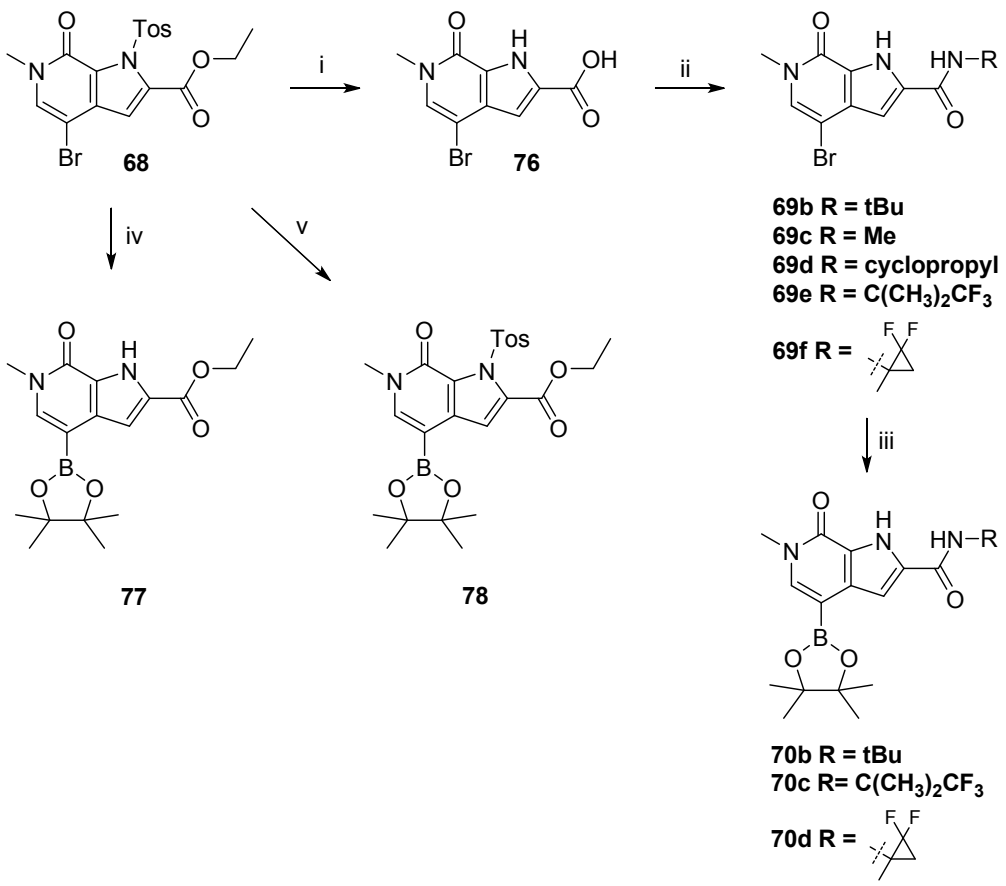
Scheme 1[a]



[a]Reagents and conditions: (i) LDA, ethyl chloroformate, THF, 91%; (ii) TMSCl, NaI, CH_3CN; (iii) CH_3I, Cs_2CO_3, DMF, 90%; (iv) $Mg(OCH_3)_2$, $CH_3CH_2NH_2$, THF/CH_3OH, 98%; (v) B_2Pin_2, KOAc, XPhos, XPhos Pd precatalyst G2, 2-MeTHF, 86%; (vi) nBuLi, $B(OCH_3)_3$, THF, -78 °C-RT; (vii) NaOH, 30% H_2O_2, THF, 67%; (viii) Cs_2CO_3, DMSO, 80 °C, 97%; (ix) CH_3MgBr, THF, 83%; (x) $Pd_2(dba)_3$, PAPh, K_3PO_4, dioxane/H_2O, 73%.

As demonstrated in Scheme 2, intermediate **68** could be converted to a variety of related aryl bromide and aryl pinacol boronate reagents with variations of the pyrrole 2-substituent. Variations of **69** and **70** set the amide substituent at the outset of the synthesis, while intermediates **77** and **78** bearing an ester at the 2-position allow for incorporation of various amides later in the sequence.

Scheme 2[a]

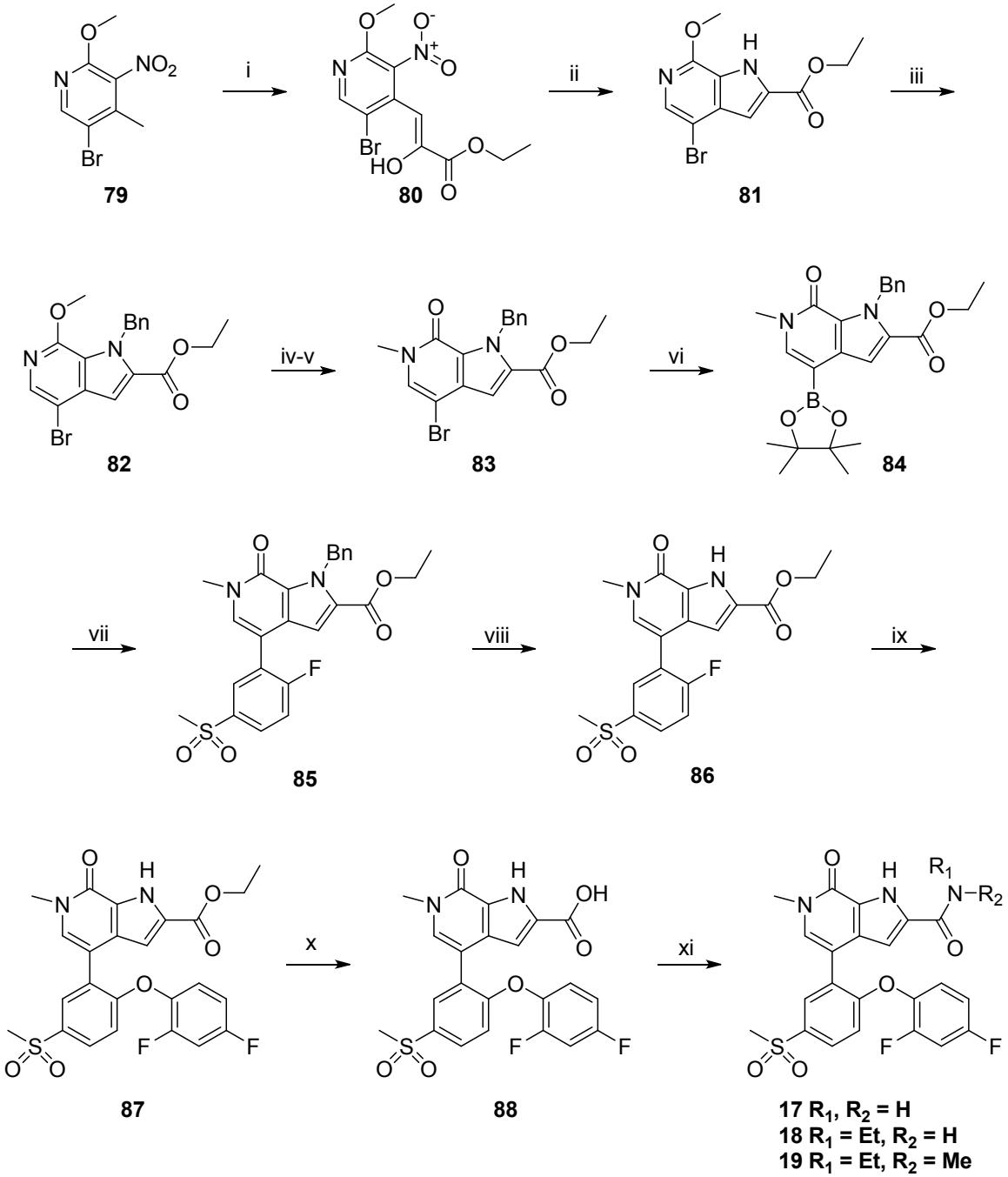


[a]Reagents and conditions: (i) NaOH, dioxane, 80 °C, 94%; (ii) oxalyl chloride, H_2NR, DCM/THF (93% for **69b**); (iii) B_2Pin_2, KOAc, XPhos, XPhos Pd precatalyst G2, 2-MeTHF (52% for **70b**); (iv) B_2Pin_2, KOAc, XPhos, $Pd_2(dba)_3$, dioxane, 80 °C, 91%; (v) B_2Pin_2, KOAc, XPhos, $Pd_2(dba)_3$, dioxane, 90 °C, 91%.

Compounds **17-19** (Table 2) were prepared using an alternative synthesis of the 2-substituted pyrrolopyridone ring system by condensation of **79** with diethyl oxalate followed by nitro group reduction and pyrrole ring closure. In this sequence a benzyl protecting group for the pyrrole nitrogen was used rather than tosyl. As previously demonstrated,[18] the bottom portion of the molecule could then be elaborated by nucleophilic aromatic substitution after introduction of a suitably activated aryl fluoride B-ring. Hydrolysis of the ester followed by amide bond formation allowed the synthesis of **17-19**. While this sequence was utilized early in the program,

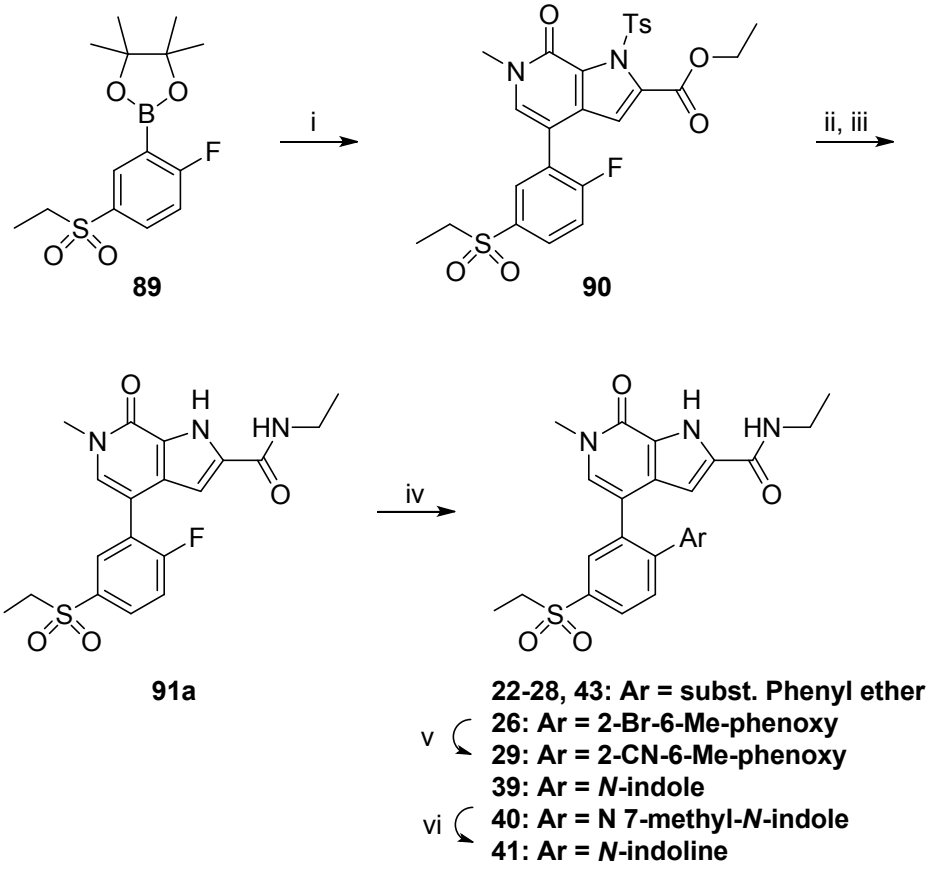
this route through intermediates **79**-**85** was found to be less practical than the route through compounds **68**, **69** and **70**. Thus, many compounds from Tables 3 and 4 were prepared by conducting a late stage S_NAr reaction on intermediate **91a** to add the C-ring with the D-ring ethyl amide in place, as shown in Scheme 4. In the case of compound **20**, the S_NAr reaction was performed prior to introduction of the ethyl amide, as shown in Scheme 5.

Scheme 3[a]



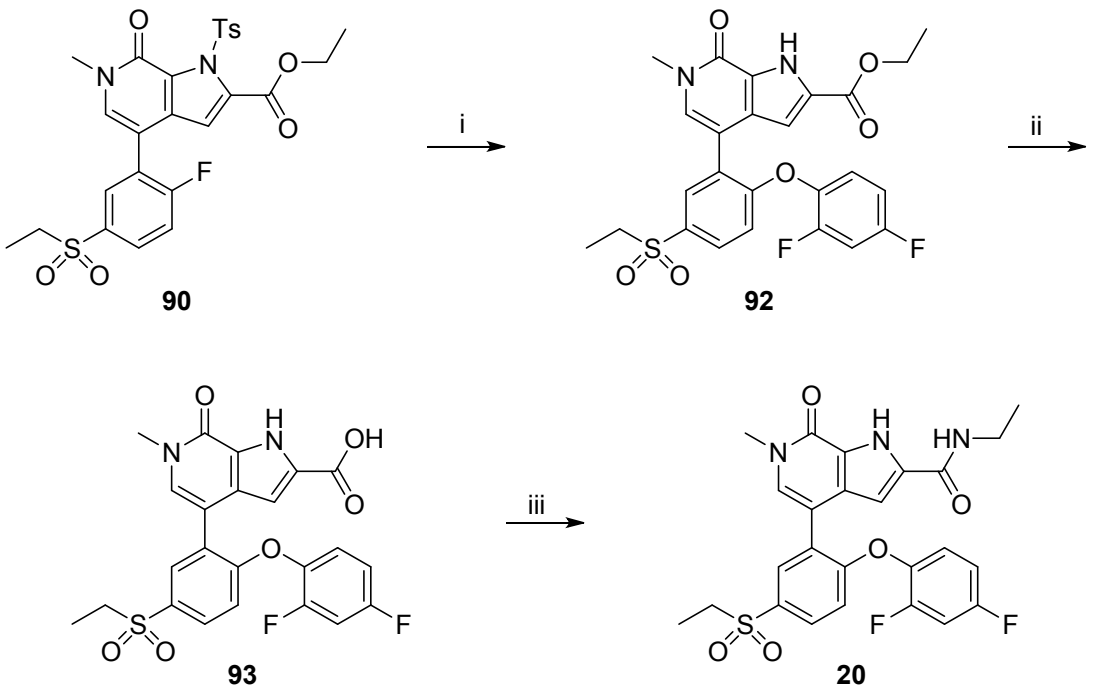
[a]Reagents and conditions: (i) KOEt, diethyl oxalate, Et_2O/EtOH, 45 °C, 15%; (ii) Fe, EtOH/HOAc, 100 °C, 55%; (iii) NaH, BnBr, DMF, 91%; (iv) HCl, dioxane, 45 °C, 16 h, 83%; (v) NaH, CH_3I, DMF, 2 h, 65%; (vi) B_2Pin_2, KOAc, XPhos, $Pd_2(dba)_3$, dioxane, 90 °C, 16 h, 40%; (vii) 2-Br-1-F-4-methylsulfonylbenzene, $Pd_2(dba)_3$, PAPh, K_3PO_4, dioxane/H_2O, 60 °C, 92%; (viii) H_2SO_4, anisole, TFA, 90 °C, 84%; (ix) 2,4-difluorophenol, Cs_2CO_3, DMSO, 110 °C, 85%; (x) NaOH, dioxane, 90 °C, 94%; (xi) oxalyl chloride, HNR_1R_2, DCM (47% for **17**).

Scheme 4[a]



[a]Reagents and conditions: (i) **78**, $Pd_2(dba)_3$, PAPh, K_3PO_4, dioxane/H_2O, 92%; (ii) NaOH, dioxane/water, 80 °C, 95%; (iii) oxalyl chloride, DMF, $H_2NCH_2CH_3$, DCM, 89%; (iv) various phenols and indoles, Cs_2CO_3, DMSO, 110 °C; (v) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C, 70%; (vi): $NaCNBH_3$, HOAc, 78%.

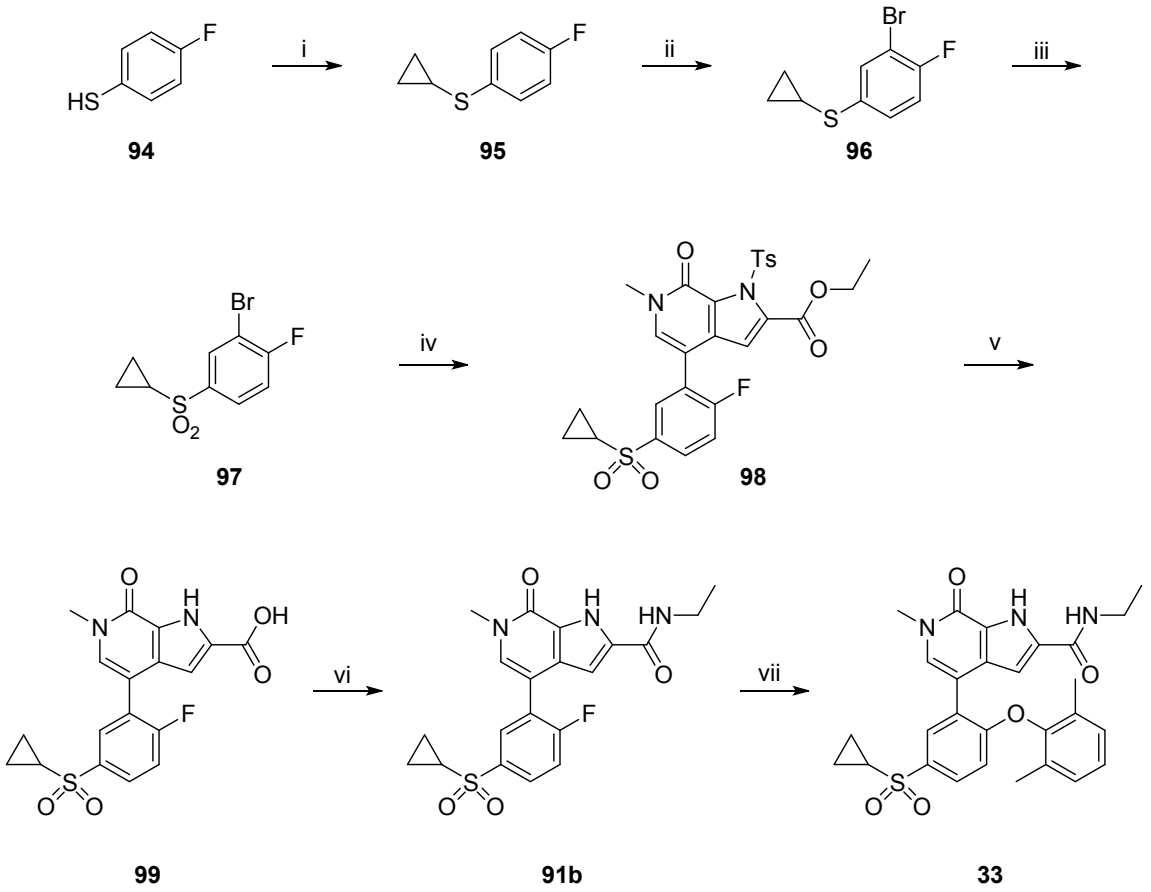
Scheme 5[a]



[a]Reagents and conditions: (i) 2,6-difuorophenol, Cs_2CO_3, DMSO, 110 °C, 79%; (ii) NaOH, dioxane/H_2O, 90 °C, 97%; (iii) oxalyl chloride, DMF, DCM, $H_2NCH_2CH_3$, THF, DMF, 72%.

A similar sequence was used to prepare cyclopropyl sulfone **33** (Scheme 6). In this case the requisite sulfone B-ring fragment **97** was prepared by alkylation of **94** followed by bromination and oxidation. Introduction of the B-ring by Suzuki-Miyaura cross-coupling was followed by ester hydrolysis with concomitant tosyl removal and introduction of the ethyl amide. Nucleophilic aromatic substitution then provided the test compound **33**.

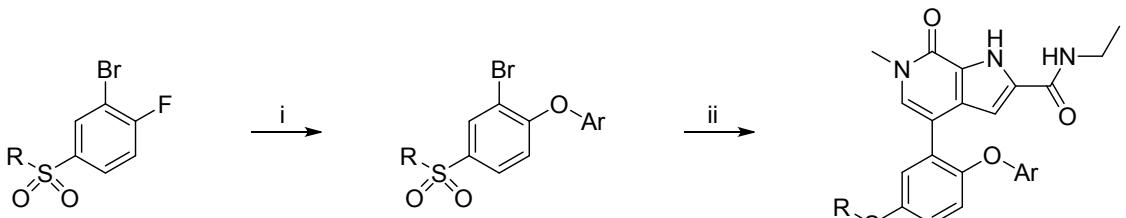
Scheme 6[a]



[a]Reagents and conditions: (i) bromocyclopropane, Cs_2CO_3, DMSO, 70 °C, 72%; (ii) *m*-CPBA, DCM, 84%; (iii) NBS, H_2SO_4, 100%; (iv) **78**, PAPh, $Pd_2(dba)_3$, K_3PO_4, dioxane/H_2O (4:1), 60 °C, 94%; (v) LiOH, dioxane/H_2O, 90 °C, 100%; (vi) oxalyl chloride, DMF, $H_2NCH_2CH_3$, DCM, 92%; (vii) 2,6-dimethylphenol, Cs_2CO_3, DMSO, 150 °C, 66%.

Ethyl sulfone analogs were also generated by conducting the S_NAr reaction prior to biaryl coupling with **70a** (Scheme 7), allowing for a more convergent synthesis.

Scheme 7[a]



100a R = Et
100b R = Me

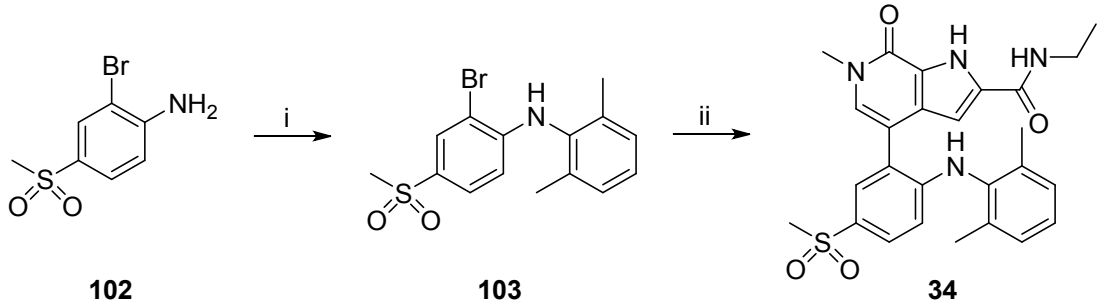
101a R = Et, Ar = 2-tolyl
101b R = Et, Ar = 2-Me-6-CF_3Ph
101c R = Et, Ar = 3,5-dimethylphenyl
101d R = Me, Ar = 2,6-dimethylphenyl

21, 30-32

[a]Reagents and conditions: (i) various phenols, Cs_2CO_3, DMSO, heat; (ii) **70a**, $Pd_2(dba)_3$, PAPh, Na_2CO_3, THF/H_2O.

Analogs linking the B- and C-rings with NH (Scheme 8) and CH_2 (Scheme 9) were prepared by linking the B- and C-rings with Pd-catalyzed coupling reactions, followed by biaryl formation with intermediate **70a**. Molecules **36-38** linking the B- and C-rings with a direct bond were prepared by the sequence shown in Scheme 10. Aryl fluoride **91a** was converted by a two-step procedure to aryl triflate **107**, which was then coupled with the appropriate boronic acid to provide compounds **36-38**.

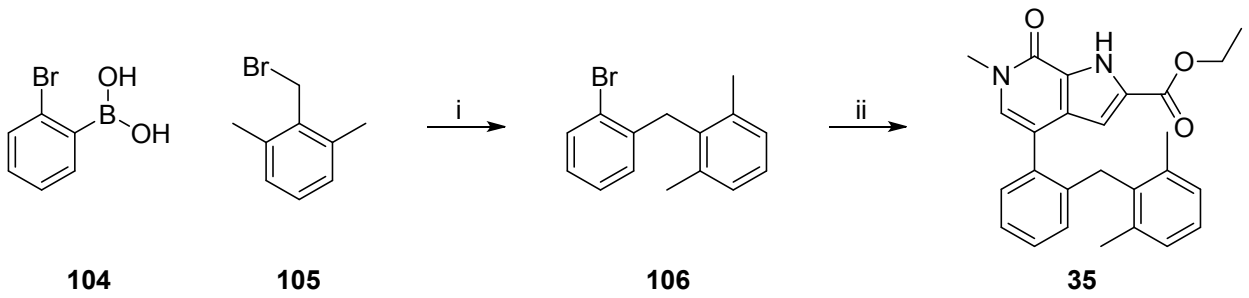
Scheme 8[a]



102 **103** **34**

[a]Reagents and conditions: (i) $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 2-iodo-1,3-dimethylbenzene, dioxane, 100 °C, 48 h, 35%; (ii) **70a**, PAPh, $Pd_2(dba)_3$, Na_2CO_3, THF/H_2O (4:1), 60 °C, 54%.

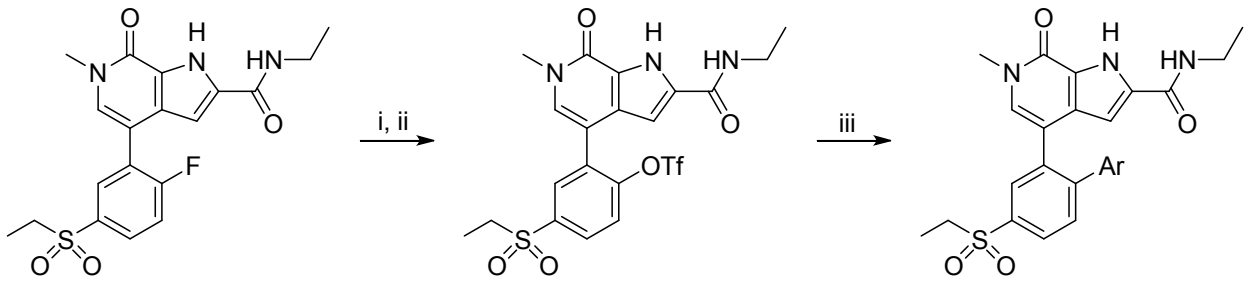
Scheme 9[a]



104 **105** **106** **35**

[a]Reagents and conditions: (i) $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, EtOH, 69%; (ii) **70a**, $Pd(PPh_3)_4$, CsF, DME/MeOH, 120 °C, 45%.

Scheme 10[a]



91 **107**

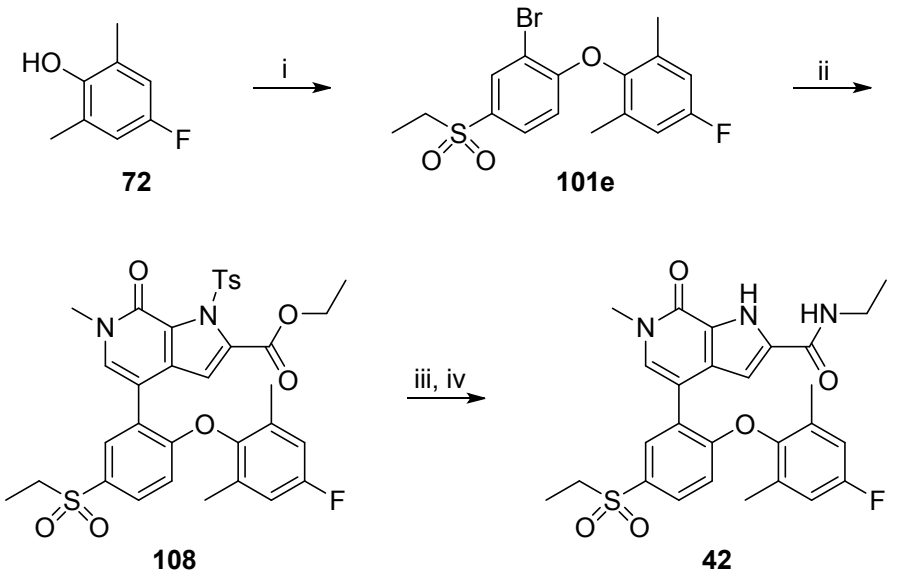
36: Ar = 2,6-di-Me-phenyl
37: Ar = 2-Me-phenyl
38: Ar = 7-indole

[a]Reagents and conditions: (i) 5 M KOH, DMSO, 90 °C, 59%; (ii) 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide, DIPEA, DMF, 90%; (iii) PAPh, $Pd_2(dba)_3$, Na_2CO_3, dioxane/H_2O (4:1), 60 °C, various phenyl boronic acids, 59-75%.

Compound **42** (Scheme 11) was prepared by carrying out the S_NAr reaction prior to coupling with intermediate **78** with subsequent deprotection and refunctionalization of the ester to the amide. This approach illustrates that the strategic disconnections can generally be done in any order, based on need and building block availability. In the case of compound **44** (Scheme

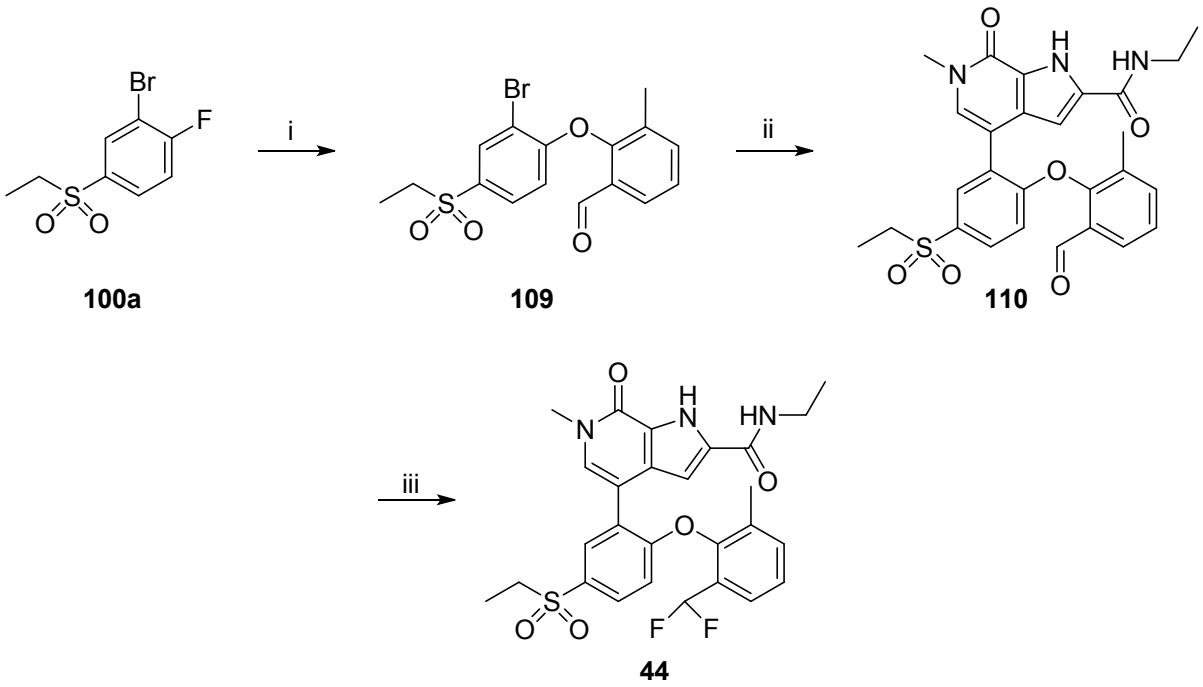
12), the difluoromethyl functionality was introduced as the final step in the sequence using DAST.

Scheme 11[a]



[a]Reagents and conditions: (i) **100a**, Cs_2CO_3, DMSO, 90 °C, 83%; (ii) **78**, $Pd_2(dba)_3$, PAPh, K_3PO_4, dioxane/H_2O, 60 °C 100%; (iii) NaOH, dioxane/H_2O 90 °C, 95%; (iv) oxalyl chloride, DMF, $H_2NCH_2CH_3$, DCM, 73%.

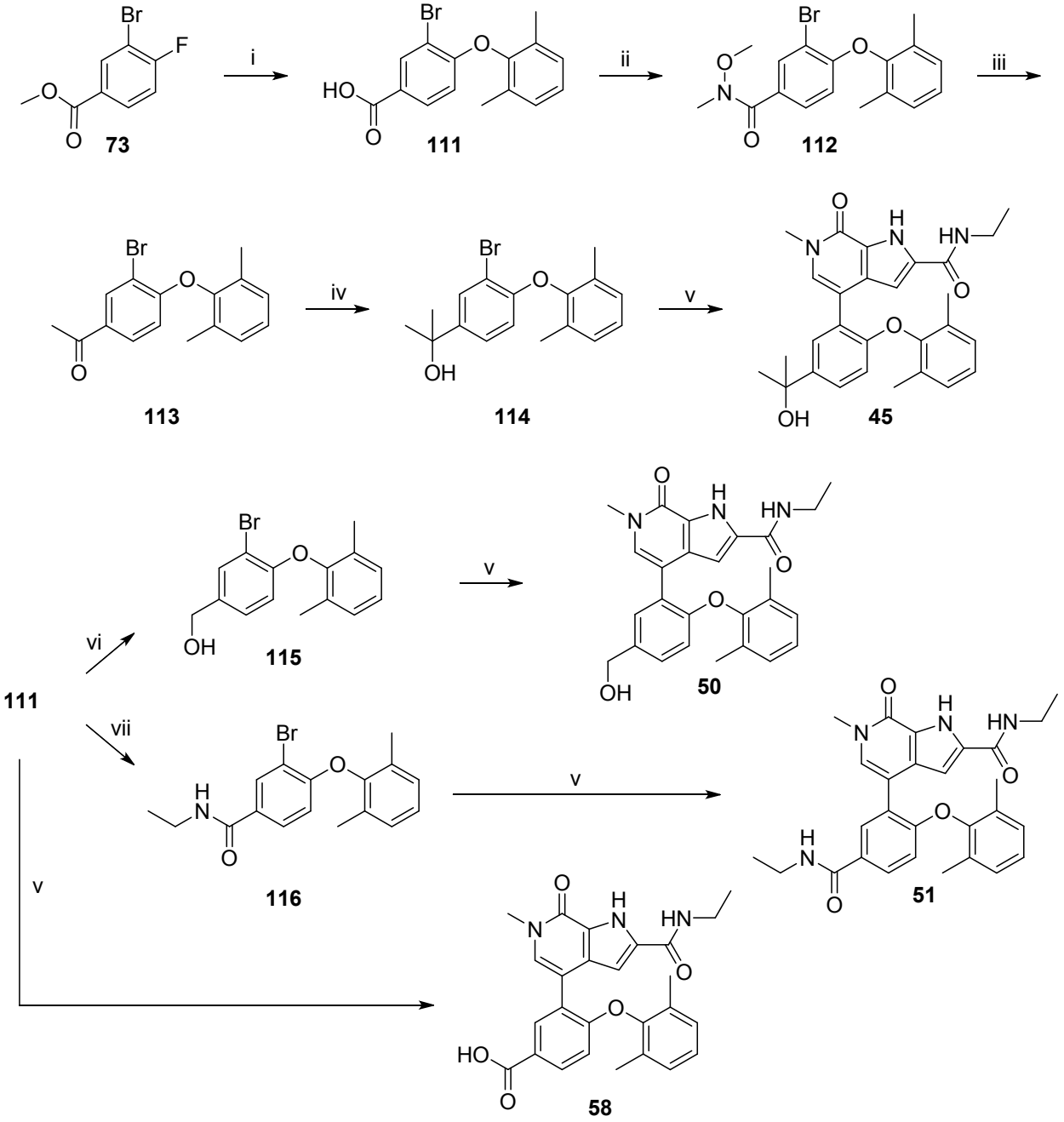
Scheme 12[a]



[a]Reagents and conditions: (i): 2-hydroxy-3-methylbenzaldehyde, Cs_2CO_3, DMSO, 110 °C, 94%; (ii) **70a**, PAPh, $Pd_2(dba)_3$, Na_2CO_3, THF/H_2O (4:1), 60 °C, 84%; (iii): DAST, DCM, 50%.

Many compounds found in Table 7 were made by routes similar to that shown in Scheme 1. As shown in Scheme 13, refunctionalization of the S_NAr product **111** followed by biaryl coupling with **70a** provided access to a variety of hydrogen bond accepting functional groups on the B-ring.

Scheme 13[a]

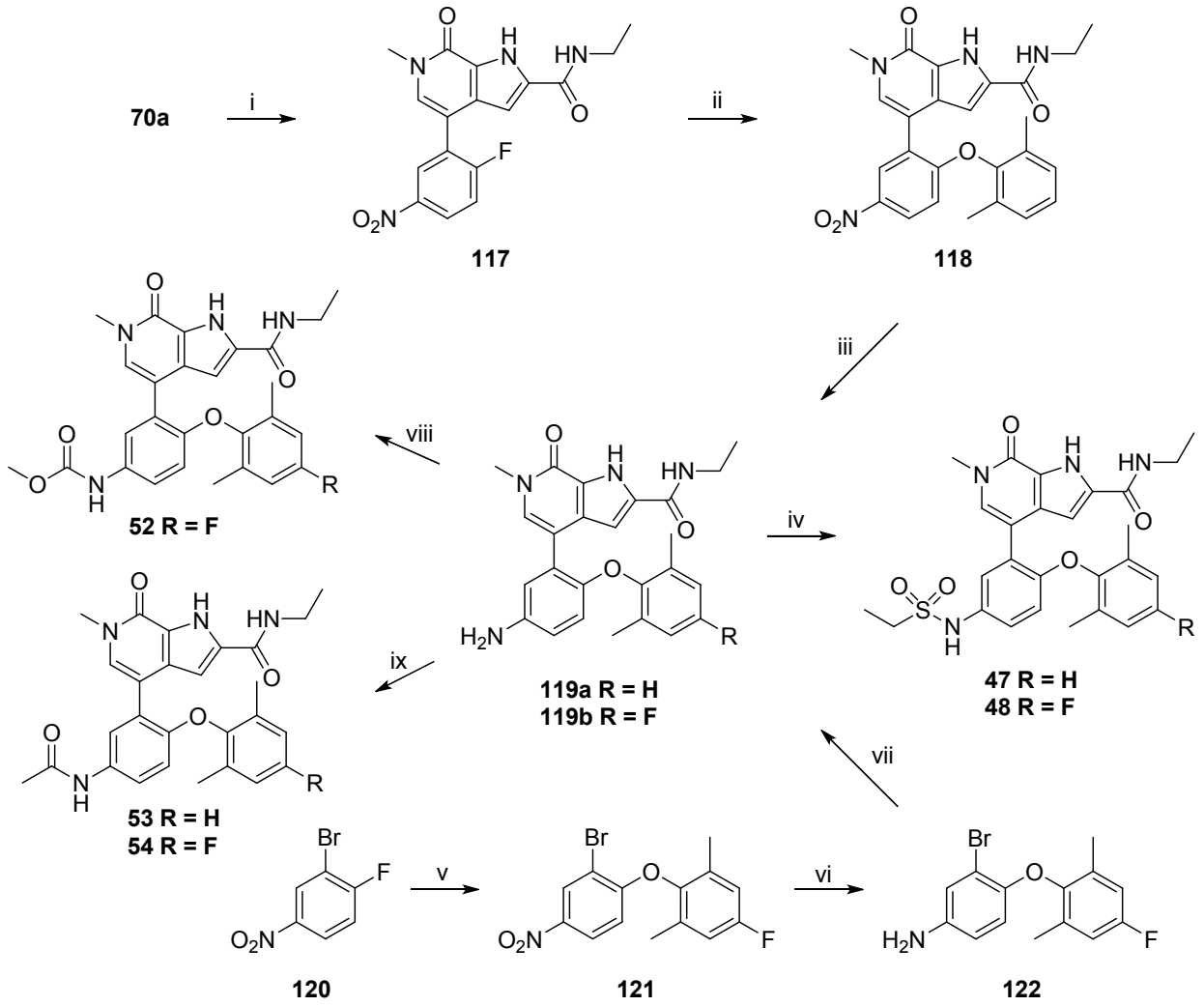


[a]Reagents and conditions: (i) 2,6-dimethylphenol, Cs_2CO_3, DMSO, 190 °C, 91%; (ii) $HN(CH_3)OCH_3$ HCl, EDCI, HOBT, NMM, DCM, 92%; (iii) CH_3MgCl, THF, 61%; (iv) CH_3MgCl, THF, 64%; (v) **70a**, $Pd_2(dba)_3$, PAPh, K_3PO_4, THF/H_2O, 60% for **45**; (vi) DIBALH, 0 °C, DCM, 73%; (vii) HATU, DIPEA, $H_2NCH_2CH_3$, DMF/DCM, 97%; (viii) **70a**, $Pd_2(dba)_3$, PAPh, Cs_2CO_3, THF/H_2O, 73%.

To introduce functional groups linked to the B-ring through nitrogen (compounds **52-54**), use of a nitro group facilitated the S_NAr aryl ether formation, with subsequent reduction to reveal

the amine for further functionalization. (Scheme 14) The S_NAr reaction could be carried out either before or after biaryl formation as desired.

Scheme 14[a]

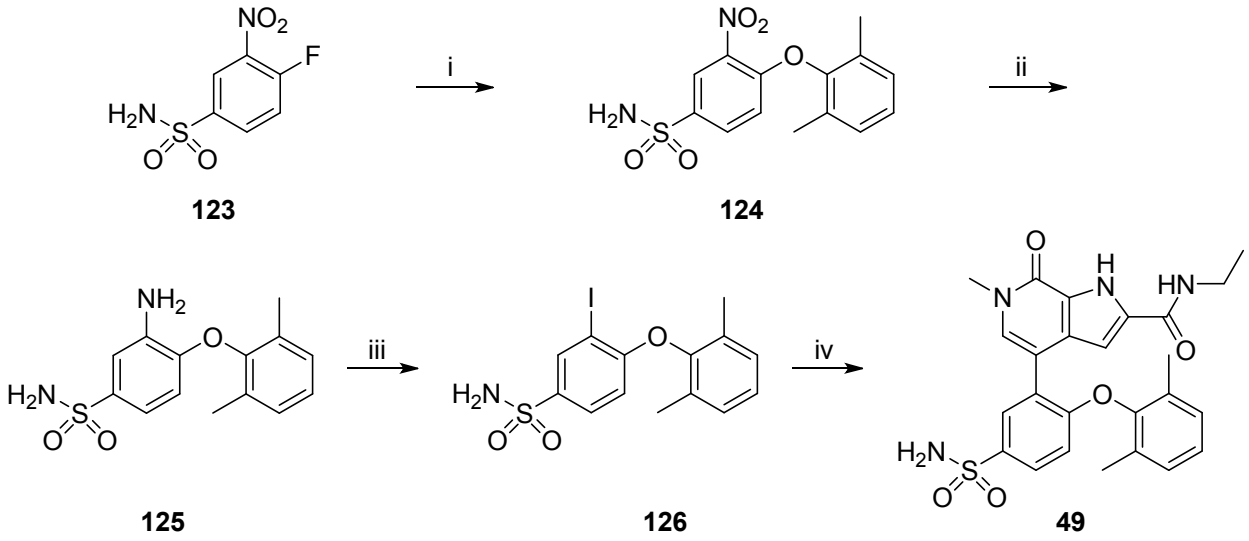


[a]Reagents and conditions: (i) 2-fluoro-5-nitrophenyl boronic acid, $Pd_2(dba)_3$, PAPh, Na_2CO_3, dioxane/H_2O, 73%; (ii) 2,6-dimethylphenol, Cs_2CO_3, DMSO, 50 °C, 98%; (iii) Zn, NH_4Cl, THF/EtOH/H_2O, 83%; (iv) $EtSO_2Cl$, DIPEA, DCM; 2 N NaOH, 48% for **47**; (v) **72**, Cs_2CO_3, DMSO, 90 °C, 85%; (vi) Fe, NH_4Cl, EtOH/H_2O, 94%; (vii) **70a**, $Pd_2(dba)_3$, PAPh, Na_2CO_3, THF/H_2O, 89%; (viii) methyl chloroformate, Et_3N, DCM, 69%; (ix) acetyl chloride, Et_3N, DCM, 66% for **53**.

A related sequence was used to prepare sulfonamide analog **49** (Scheme 15). In this case, nitro sulfonamide **123** was identified as a convenient starting material. Following introduction of

the aryl ether, the nitro group was converted to iodide to set up the union with the AD-ring fragment via biaryl coupling.

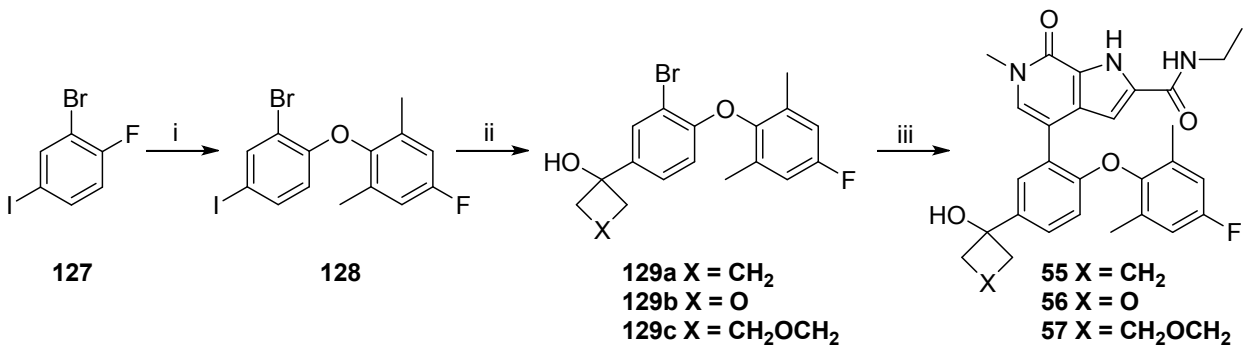
Scheme 15[a]



[a]Reagents and conditions: (i) 2,6-dimethylphenol, NaH, DMF, 91%; (ii) H_2, 10% Pd/C, MeOH/EtOAc, 88%; (iii) HCl, $NaNO_2$, KI, dioxane, 87%; (iv) **70a**, $Pd_2(dba)_3$, PAPh, Na_2CO_3, THF/H_2O, 44%.

Tertiary alcohols **55**-**57** were prepared from trihalobenzene **127** (Scheme 16) by taking advantage of differential reactivity to sequentially introduce the aryl ether by F displacement, followed by selective metal-halogen exchange of the iodide and addition to the requisite cyclic ketone, then biaryl coupling to the remaining bromide.

Scheme 16[a]

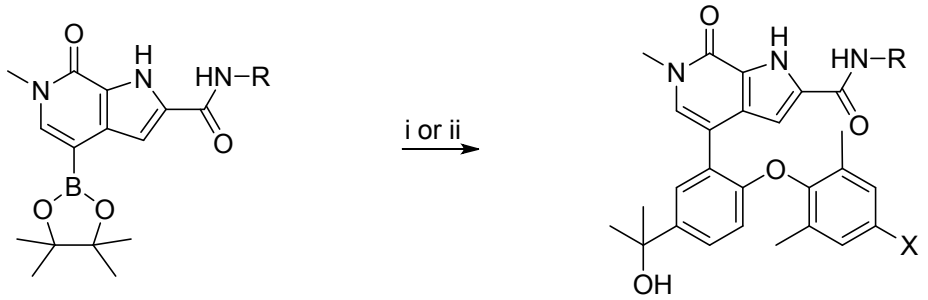


127 **128** **129a X = CH_2** **129b X = O** **129c X = CH_2OCH_2** **55 X = CH_2** **56 X = O** **57 X = CH_2OCH_2**

[a]Reagents and conditions: (i) **72**, Cs_2CO_3, DMSO, 110 °C, 76%; (ii) *t*-BuLi, cycloalkanone, hexanes/toluene, -78 °C-rt, 24% for **129a**; (iii) **70a**, $Pd(PPh_3)_4$, CsF, DME/MeOH, 120 °C, 72% for **55**.

Amide analogs found in Table 8 were prepared by the routes shown in Schemes 17 and 18. The syntheses of **62** and **63** demonstrated that the aryl halide and aryl boronate functionalities can be deployed on either the A- or B-ring as desired. The sequences originally used for the synthesis of each individual final compound are presented in the experimental section that follows; however, in most cases there is no particular reason why the synthesis could not or should not have been carried out with a different sequence of bond formations . The flexibility of these various approaches allowed for rapid generation of a wide variety of analogs to fully examine structure activity relationships as needed.

Scheme 17[a]

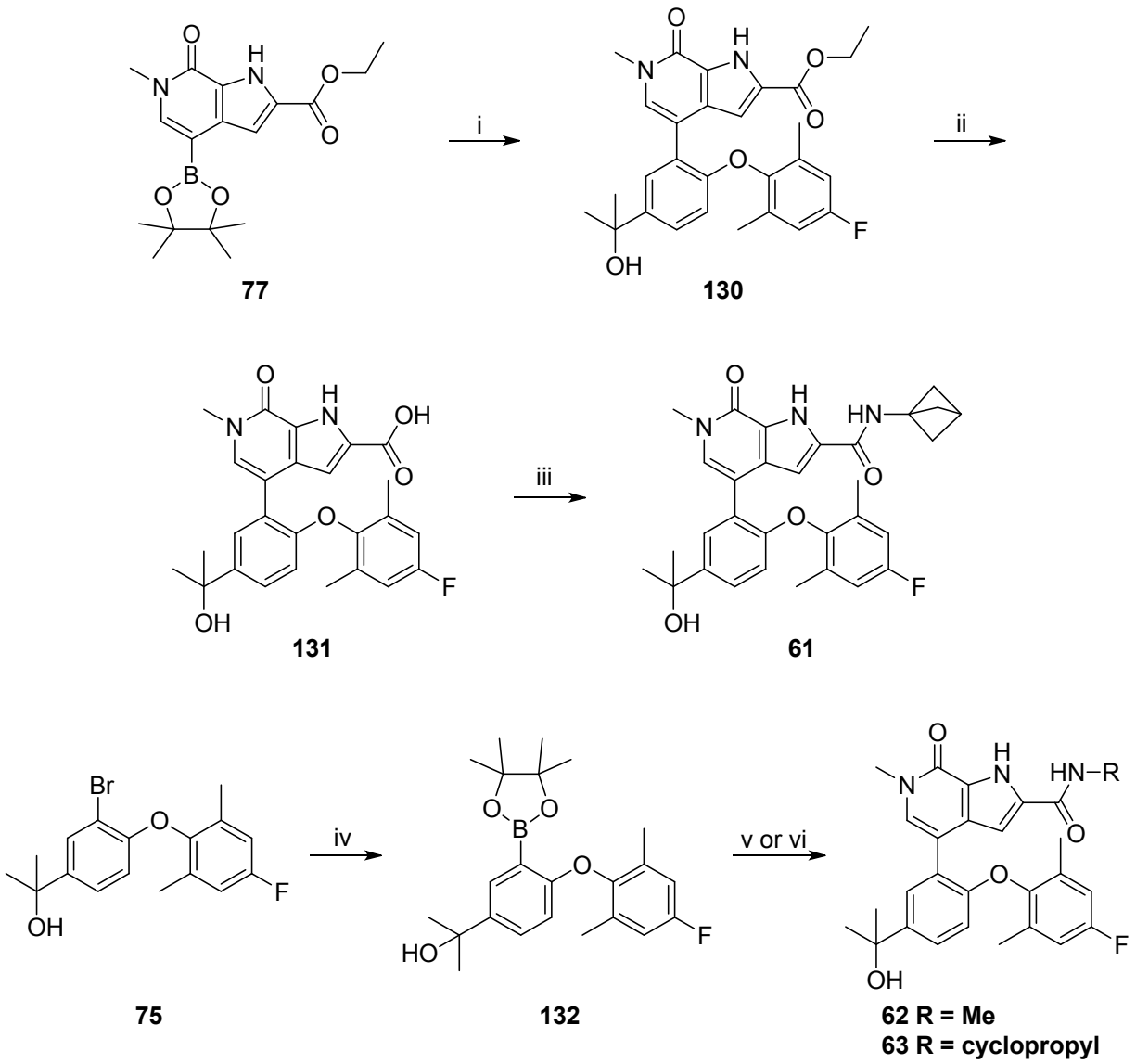


70b R = *t*-Bu
70c R= $C(CH_3)_2CF_3$
70d R = 

59 R = *t*-Bu, X = H
60 R = *t*-Bu, X = F
64 R= $C(CH_3)_2CF_3$, X = F
65 R =  **X = F**

[a]Reagents and conditions: (i) **75** or **114**, $Pd_2(dba)_3$, PAPh, K_3PO_4, dioxane/H_2O, 89% for **59**; (ii) **75**, Pd_2dba_3, PAPh, K_3PO_4, THF/H_2O, 56% for **64**.

Scheme 18[a]



[a]Reagents and conditions: (i) **75**, $Pd_2(dba)_3$, PAPh, Cs_2CO_3, THF/H_2O, 85%; (iv) LiOH, dioxane/H_2O 70 °C, 85%; (v) bicyclo[1.1.1]pentanamine, EDCI, HOBT, NMM, DCM, 66%; (iv) *n*-BuLi, THF, iPrOBpin, 53%; (v) **69c**, $Pd(PPh_3)_4$, CsF, DME/MeOH, 65%; (vi) **69d**, $Pd_2(dba)_3$, PAPh, Na_2CO_3, THF/H_2O, 75%.

Conclusions

Structure-based design targeting key active-site sequence differences between the first and second BET-family protein bromodomains was applied to achieve high selectivity for BD2. The combination of a secondary amide to bury hydrophobic surface on BD2-specific His and Pro residues and 2,6-disubstitution of an aryl ether to exploit the proximal Ile vs Val sequence difference provided the basis for selectivity. Introduction of a fluorine blocking group at a site of metabolism and replacement of an ethyl sulfone with a dimethylcarbinol to accept a hydrogen bond in the channel adjacent to the ZA-loop provided an improved ADME profile, allowing the identification of compound **46** (ABBV-744), a novel and potent BD2-selective inhibitor of BET-family proteins with DMPK properties suitable for clinical development. Compound **46** shows greater affinity and selectivity for BRD4 BD2 than compounds previously disclosed in the literature (Table 1), making it a valuable tool for examining the role of the respective bromodomains in biological systems. Furthermore, the ADME profile allows for use in animals to examine activity in disease models. A recent publication has exploited this compound to uncover the role of BRD4 BD2 in super enhancer-driven AR-dependent gene transcription in prostate cancer cell lines.[51] Additional studies using compound **46** to study epigenetic regulation in AML will be reported in due course.[52] In this paper we have demonstrated that compound **46** displays potent single agent oral activity in a mouse model of AML at tolerated doses. Compound **46** is currently under examination in Phase I clinical trials (ClinicalTrials.gov identifier NCT03360006).

EXPERIMENTAL SECTION

Protein expression and purification. Human BDR4 BD1 (residues 57-168), BRD4 BD2 (residues 352-457), BRD2 BD1 (residues 73-194) and BRD2 BD2 (residues 348-455) were cloned

into the pET28b vector to make *N*-terminal His6 with thrombin cleavage site constructs. All the proteins were expressed in *E. Coli* BL21(DE3) cells and purified from the soluble fraction using a Ni-NTA column. For X-ray studies, the His6-tag was cleaved with thrombin protease and the protein was further purified using size exclusion chromatography.

BRD protein crystallization method. Human BRD4 BD1, BRD2 BD1 and BRD2 BD2 proteins were concentrated to 10-15 mg/mL in 20 mM HEPES, pH 7.5, 300 mM NaCl, 1 mM TCEP buffer and BRD4 BD2 protein was concentrated to ~4 mg/mL in 10 mM Bis-Tris, pH 6.8, 100 mM NaCl, 5 mM DTT buffer for crystallization. Protein was incubated with compounds at a 3:1 mM ratio of compound to protein at 4 °C for 2 h. The protein-compound complexes were screened against SGC-1 and SGC Redwing custom screens (prepared by Rigaku) at 17 °C. Some protein-compound complexes were also screened against commercially available screens PEGRx and SaltRx (Hampton Research) at 17 °C. Vapor-diffusion sitting drops were prepared using a Mosquito liquid dispenser (TTP Labtech) in MRC 2 Well Crystallization plates (Hampton Research.) The drops contained 0.3 μL of protein and 0.3 μL of reservoir solution over wells of 40 μL of reservoir solution. BRD4 BD1 with compound **18** was crystallized with a reservoir solution of 2 M sodium formate, 0.1 M Tris, pH 8.5; BRD4 BD2 with compound **18** was crystallized with a reservoir solution of 25% PEG3350, 0.2 M ammonium sulfate, 0.1 M sodium cacodylate, pH 5.5; BRD2 BD2 with compound **27** was crystallized with a reservoir solution of 25% PEG 1500, 0.2 M ammonium sulfate, 0.1 M sodium cacodylate, pH 5.5; BRD4 BD1 with compound **27** was crystallized with a reservoir solution of 2.0 M sodium formate, 0.1 M Bis-Tris Propane, pH 7.0.

TR-FRET bromodomain binding assay. A time-resolved fluorescence resonance energy transfer (TR-FRET) assay was used to determine the affinities (K_i) of compounds for the BD1 and BD2 bromodomains of BRD4. Compound dilution series were prepared in DMSO via an approximately 3-fold serial dilution. Compound dilutions were added directly into white, low-volume assay plates (Perkin Elmer Proxiplate 384 Plus# 6008280) using a Labcyte Echo in conjunction with Labcyte Access and Thermo Multidrop CombinL robotics. Compounds were then suspended in 8 μL of assay buffer (20 mM sodium phosphate, pH 6.0, 50 mM NaCl, 1 mM ethylenediaminetetraacetic acid disodium salt dihydrate, 0.01% Triton X-100, 1 mM DL-dithiothreitol) containing His-tagged bromodomain, europium-conjugated anti-His antibody (Invitrogen PV5596) and Alexa-647-conjugated probe. The final concentration of 1X assay mixture contained 0.5% DMSO, 5 nM His tagged BRD4 BD1 or BRD4 BD2 and 30 nM probe, and 1 nM europium-conjugated anti-His-tag antibody, and compound concentrations in the range of: 49.75 μM-0.18 nM. After a 1 h equilibration at rt, TR-FRET ratios were determined using an Envision multilabel plate reader (Ex 340, Em 495/520). TR-FRET data were normalized to the means of 24 no-compound controls ("high") and 8 controls containing 1 μM un-labeled probe ("low"). Percent inhibition was plotted as a function of compound concentration and the data were fit with the 4-parameter logistic equation to obtain IC_{50}s. Inhibition constants (K_i) were calculated using the Cheng-Prussof equation from the IC_{50}s, probe K_d (0.021 μM for BRD4 BD2) and probe concentration. The probe K_d was determined directly in TR-FRET by serial dilution of probe at several different protein concentrations for each bromodomain. The TR-FRET binding assay had a running MSR = 1.2 and Test-retest MSR = 2.1 The synthesis of the Alexa647-conjugated probe is described in the Supporting Information of reference 18. The literature compound JQ1 was tested as a positive control for this assay; a comparison with published data is presented in the

Supporting Information Table (S2). A representative curve used for the determinations of TR-FRET K_i for compound **46** are shown in the Supporting Information (Figure S1).

Cellular proliferation assays. Cell lines were originally obtained from ATCC and subsequently maintained by a Core Cell Line Facility that performed routine testing for mycoplasma using the MycoAlert Detection Kit (Lonza, Walkersville, MD) and authentication by STR analysis using the Gene Print10 kit (Promega, Madison, WI). Cells were grown in 10% FBS (Gibco). Cells were plated onto 96-well or 384-well plates in culture medium and incubated at 37 °C in an atmosphere of 5% CO_2. After overnight incubation, a serial dilution of compounds was prepared and added to the plate. The cells were further incubated for 5 days, and the CellTiter-Glo assay (Promega, Madison, WI) was then performed according to manufacturer's instructions to determine cell proliferation. The luminescence signal from each well was acquired using an Enspire plate reader (PerkinElmer, Akron, OH), and the data was analyzed using the GraphPad Prism software (GraphPad Software Inc, La Jolla, CA).

NanoBRET assay. NanoBRET experiments were carried out according to manufacturer suggested protocols (Promega, Madison, WI). Briefly, Hela cells were transfected using NanoLuc-BRD4 BD1 or NanoLuc-BRD4 BD2 plasmids and incubated at 37 °C in an atmosphere of 5% CO_2 overnight. The transfected cells were then dispensed into 96-well plates using 90 μL cell suspension per well at $2X10^5$ cells/mL and 1X final concentration of tracer. 90 μL per well of cell suspension without tracer was also dispensed into at least 3 wells as "No tracer control samples." Serially diluted test compound (ABBV-744) was prepared at 10X concentration in Opti-MEM while maintaining a consistent concentration of compound solvent (e.g. DMSO) in each sample, and 10 μL per well of serially diluted inhibitor/test compound was added to the 96-well plates containing cells with 1X tracer. Plates were then incubated at 37 °C in an atmosphere of

5% CO_2 for 2 h before proceeding to BRET measurement. Briefly, immediately prior to BRET measurements, a 1:166 dilution (3X solution) of Nano-glo® Live Cell Solution in OptiMEM without serum or phenol red was prepared and 50 μL per well of 3X Nano-glo® Live Cell Solution was added. Following addition of Nano-glo® Live Cell Solution, donor emission (450 nm) and acceptor emission (610 nm) were measured using Envision (PerkinElmer) an Envision multilabel plate reader (Ex 340, Em 495/520). For data analysis, the raw BRET ratio was generated and converted to milliBRET units (mBU) with background correction using the formula: $[(Acceptor_{sample} / Donor_{sample}) – (Acceptor_{\ no\ tracer\ control}/Donor_{\ no\ tracer\ control})] \times 1000$. The mBU data was plotted as a function of compound concentration and IC_{50}s for the BRET assay were determined by nonlinear regression analysis of concentration response curves using the GraphPad Prism software.

Xenograft studies. All animal studies were conducted in a specific pathogen-free environment in accordance with the Internal Institutional Animal Care and Use Committee (IACUC, accredited by the American Association of Laboratory Animal Care under conditions that meet or exceed the standards set by the United States Department of Agriculture Animal Welfare Act, Public Health Service policy on humane care and use of animals, and the NIH guide on laboratory animal welfare. Overt signs of dehydration, lack of grooming, lethargy, >15% weight loss, and tumor volume >20% of body weight were used to determine tumor endpoint. For tumor models, a 1:1 mixture of $5X10^6$ cells/matrigel (BD Biosciences, CA) per site was inoculated subcutaneously into the right hind flank of female Fox Chase SCID® (Charles River Labs) mice (6-8 weeks of age) on study day 0. Administration of compound was initiated at the time of size match (8 mice/group). The tumors were measured by a pair of calipers twice a week starting at the time of size match and tumor volumes were calculated according to the formula $V = L \times W^2/2$

(V: volume, mm^3; L: length, mm; W: width, mm). Tumor growth inhibition, %TGI = 100 - mean tumor volume of treatment group / mean tumor volume of control group x 100.

Synthetic materials and methods. Unless otherwise specified, reactions were performed under an inert atmosphere of nitrogen and monitored by thin-layer chromatography (TLC) and/or LC-MS. All reagents were purchased from commercial suppliers and used as provided. 3-Mercaptopropyl-functionalized silica gel (Aldrich, catalog 538086) was routinely used to remove ionic palladium species during work up of Suzuki coupling reactions. 1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (Aldrich catalog 695459, CAS 97739-46-3) was a preferred ligand for Suzuki coupling reactions. Flash column chromatography was carried out on pre-packed silica gel cartridges. Reverse phase chromatography samples were purified by preparative HPLC on a Phenomenex Luna C8(2) 5 µm 100Å AXIA column (30 mm × 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/min (0-0.5 min 10% A, 0.5-7.0 min linear gradient 10-95% A, 7.0-10.0 min 95% A, 10.0-12.0 min linear gradient 95-10% A). Samples were injected in 1.5 mL DMSO:methanol (1:1). A custom purification system was used, consisting of the following modules: Waters LC4000 preparative pump; Waters 996 diode-array detector; Waters 717+ autosampler; Waters SAT/IN module, Alltech Varex III evaporative light-scattering detector; Gilson 506C interface box; and two Gilson FC204 fraction collectors. The system was controlled using Waters Millennium32 software, automated using an AbbVie-developed Visual Basic application for fraction collector control and fraction tracking. Fractions were collected based upon UV signal threshold and selected fractions subsequently analyzed by flow injection analysis mass spectrometry using positive APCI ionization on a Finnigan LCQ using 70:30 methanol:10 mM NH_4OH (aq) at a flow rate of 0.8 mL/min. Loop-injection mass spectra were acquired using a Finnigan LCQ running

LCQ Navigator 1.2 software and a Gilson 215 liquid handler for fraction injection controlled by an AbbVie-developed Visual Basic application. All NMR spectra were recorded on 300-500 MHz instruments as specified with chemical shifts given in ppm (δ) and are referenced to an internal standard of tetramethylsilane (δ 0.00). ^{1}H – ^{1}H couplings are assumed to be first-order and peak multiplicities are reported in the usual manner. HPLC purity determinations were performed on a Waters e2695 Separation Module / Waters 2489 UV/Visible Detector. Column types and elution methods are described in the Supporting Information section. The purity of all the biologically evaluated compounds was determined to be >95% using two separate HPLC methods. Solvents used for HPLC analysis and sample preparation were HPLC grade.

Compound Synthesis

4-[2-(2,4-Difluorophenoxy)-5-methylsulfonyl-phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (17). A solution of **88** (0.1 g, 0.211 mmol) in anhydrous DCM (5 mL) was treated sequentially with oxalyl chloride (0.037 mL, 0.422 mmol) and DMF (0.816 μL, 10.54 μmol), stirred at rt for 2 h and then concentrated to dryness. The residue was dissolved in DCM (5 mL), treated with ammonia (2 mL, 92 mmol) and stirred at rt overnight. The reaction mixture was then partitioned between water (15 mL) and ethyl acetate (25 mL). The aqueous layer was extracted with additional ethyl acetate (15 mL) twice. The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was slurried with ethyl acetate and the undissolved solid was collected by filtration, washed with DCM and dried under vacuum to give the title compound (48 mg, 4 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 7.98 (d, J = 2.3 Hz, 1H), 7.89 (dd, J = 8.7, 2.4 Hz, 1H), 7.82 (s, 1H), 7.59 – 7.35 (m, 4H), 7.24 – 7.11 (m, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.87 (s, 1H), 3.59 (s, 3H), 3.27 (s, 3H). MS (ESI+) m/z 474.5 $(M+H)^+$.

4-[2-(2,4-Difluorophenoxy)-5-methylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (18). A solution of **88** (0.1 g, 0.211 mmol) in anhydrous DCM (5 mL) was treated sequentially with oxalyl chloride (0.037 mL, 0.422 mmol) and DMF (0.816 μL, 10.54 μmol), stirred at rt for 2 h and then concentrated to dryness. The residue was dissolved in DCM (5 mL), treated with ethanamine (9.5 mg, 0.211 mmol) and stirred at rt overnight. The reaction mixture was partitioned between water (15 mL) and ethyl acetate (25 mL). The aqueous layer was extracted with additional ethyl acetate (15 mL) twice. The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by preparative HPLC on a C18 column using a gradient of 20-60% acetonitrile/10 mM aqueous ammonium bicarbonate to give the title compound (62 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (d, J = 2.3 Hz, 1H), 8.33 (t, J = 5.4 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.90 (dd, J = 8.8, 2.4 Hz, 1H), 7.58 – 7.29 (m, 3H), 7.17 (tdd, J = 9.0, 3.2, 1.6 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 3.48 – 3.19 (m, 5H), 1.12 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 502.1 $(M+H)^+$.

4-[2-(2,4-Difluorophenoxy)-5-methylsulfonyl-phenyl]-*N*-ethyl-N,6-dimethyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (19). A solution of **88** (0.05 g, 0.105 mmol) in anhydrous DCM (3 mL) was treated sequentially with oxalyl chloride (0.028 mL, 0.316 mmol) and DMF (8.16 μL, 0.105 mmol), stirred at rt for 2 h and then concentrated to dryness. The residue was dissolved in THF (2 mL) and DMF (1 mL), treated with *N*-methylethanamine (0.062 g, 1.054 mmol) and stirred at rt for 2 h. The solvent was removed, and the residue was purified by preparative HPLC to give the title compound (0.028 g, 52 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.7, 2.4 Hz, 1H), 7.51 (ddd, J = 11.5, 8.8, 3.0 Hz, 1H), 7.48 (s, 1H), 7.42 (td, J = 9.1, 5.4 Hz, 1H), 7.20 – 7.12 (m, 1H), 6.99 (d, J = 8.6 Hz, 1H),

6.49 (s, 1H), 3.58 (s, 3H), 3.48 – 3.19 (m, 5H), 2.99 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 516.1 $(M+H)^+$.

4-[2-(2,4-Difluorophenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (20). A solution of **93** (0.049 g, 0.1 mmol) in anhydrous DCM (3 mL) was treated sequentially with oxalyl chloride (0.026 mL, 0.300 mmol) and DMF (7.74 µL, 0.100 mmol), stirred at rt for 2 h and was then concentrated to dryness. The residue was dissolved in THF (1 mL) and DMF (0.5 mL), treated with a 1.0 N solution of ethanamine in THF (0.8 mL, 0.8 mmol) and stirred at rt for 2 h. The solvent was removed, and the residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.037 g, 72 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (d, J = 2.3 Hz, 1H), 8.29 (t, J = 5.3 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.45 (s, 1H), 7.38 (td, J = 9.2, 5.6 Hz, 1H), 7.14 (dddd, J = 9.3, 8.2, 3.0, 1.5 Hz, 1H), 6.99 (dd, J = 8.6, 1.0 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 3.56 (s, 3H), 3.34 – 3.18 (m, 4H), 1.07-1.13 (m, 6H). MS (ESI+) m/z 516.1 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(2-methylphenoxy)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (21)**. A 5 mL vial was charged with **101a** (0.0995 g, 0.280 mmol), **70a** (0.088 g, 0.255 mmol), sodium carbonate (0.094 g, 0.891 mmol), $Pd_2(dba)_3$ (0.012 g, 0.013 mmol), and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.013 g, 0.043 mmol). The solids were sparged with nitrogen for 30 min. Degassed THF (2.0 mL) and water (0.5 mL) were added. The reaction mixture was heated to about 60 °C for about 3 h. The reaction mixture was cooled to rt and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10-100% (3:1

EtOAc:EtOH):heptanes) to provide a white solid (94 mg, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.31 (t, J = 5.4 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.44 (s, 1H), 7.31 - 7.24 (m, 1H), 7.24 - 7.17 (m, 1H), 7.11 (td, J = 7.4, 1.3 Hz, 1H), 6.98 (dd, J = 8.1, 1.3 Hz, 1H), 6.88 - 6.81 (m, 2H), 3.55 (s, 3H), 3.34 - 3.17 (m, 4H), 2.03 (s, 3H), 1.10 (dt, J = 11.9, 7.3 Hz, 6H). MS (ESI+) m/z 494.1 $(M+H)^+$.

4-[2-(2-Chlorophenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (22). A mixture of **91a** (0.041 g, 0.1 mmol), 2-chlorophenol (0.019 g, 0.15 mmol), and cesium carbonate (0.049 g, 0.15 mmol) in DMSO (1 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.016 g, 31 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (d, J = 2.3 Hz, 1H), 8.30 (t, J = 5.4 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.83 (dd, J = 8.7, 2.4 Hz, 1H), 7.56 (dd, J = 8.3, 1.6 Hz, 1H), 7.46 (s, 1H), 7.36 (td, J = 7.5, 1.6 Hz, 1H), 7.24 (ddd, J = 8.3, 6.1, 1.7 Hz, 2H), 6.95 – 6.85 (m, 2H), 3.55 (s, 3H), 3.34 – 3.17 (m, 4H), 1.06-1.14 (m, 6H). MS (ESI+) m/z 514.1 $(M+H)^+$.

4-[2-(2-tert-Butylphenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (23). A mixture of **91a (**0.041 g, 0.1 mmol), 2-(tert-butyl)phenol (0.023 g, 0.15 mmol), and cesium carbonate (0.049 g, 0.15 mmol) in DMSO (1 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite®, and concentrated. The residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to provide the title compound (0.032 g, 60 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.37 – 12.23 (m, 1H), 8.31 (t, J = 5.4 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.7, 2.4 Hz, 1H), 7.45 (s, 1H), 7.39 (dd,

J = 8.0, 1.7 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.15 (td, *J* = 7.8, 1.3 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.81 (d, *J* = 2.2 Hz, 1H), 3.56 (s, 3H), 3.34 (q, *J* = 7.3 Hz, 2H), 3.28 – 3.22 (m, 2H), 1.15 (s, 9H), 1.16 (t, *J* = 7.3 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 536.2 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(2-fluoro-6-methyl-phenoxy)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (24)**. A mixture of **91a** (0.041 g, 0.1 mmol), 2-fluoro-6-methylphenol (0.025 g, 0.2 mmol), and cesium carbonate (0.065 g, 0.2 mmol) in DMSO (1 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.042 g, 82 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.31 (t, *J* = 5.4 Hz, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.47 (s, 1H), 7.27 – 7.14 (m, 3H), 6.87 – 6.76 (m, 2H), 3.59 (s, 3H), 3.34 – 3.19 (m, 4H), 2.12 (s, 3H), 1.08-1.14 (m, 6H). MS (ESI+) m/z 512.1 $(M+H)^+$.

4-[2-(2-Chloro-6-methyl-phenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (25). A mixture of **91a (**0.041 g, 0.1 mmol), 2-chloro-6-methylphenol (0.021 g, 0.15 mmol), and cesium carbonate (0.049 g, 0.15 mmol) in DMSO (1 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.0056 g, 11 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (d, *J* = 2.2 Hz, 1H), 8.30 (t, *J* = 5.4 Hz, 1H), 7.90 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.36 – 7.28 (m, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 8.6

Hz, 1H), 3.58 (s, 3H), 3.49 – 3.17 (m, 4H), 2.08 (s, 3H), 1.07-1.13 (m, 6H). MS (ESI+) m/z 528.1 $(M+H)^+$.

4-[2-(2-Bromo-6-methyl-phenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (26). A mixture of **91a (**0.243 g, 0.6 mmol), 2-bromo-6-methylphenol (0.224 g, 1.2 mmol), and cesium carbonate (0.391 g, 1.2 mmol) in DMSO (3 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite®, and concentrated. The residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.134 g, 39 %). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.32 (d, J = 2.3 Hz, 1H), 8.32 (t, J = 5.4 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.80 (dd, J = 8.7, 2.4 Hz, 1H), 7.58 (dd, J = 8.1, 1.5 Hz, 1H), 7.49 (s, 1H), 7.36 (dt, J = 7.5, 1.3 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H), 3.59 (s, 3H), 3.34 – 3.20 (m, 4H), 2.09 (s, 3H), 1.08-1.14 (m, 6H). MS (ESI-) m/z 570.1 $(M-H)^-$.

4-[2-(2,6-Dimethylphenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (27). A mixture of **91a (**0.041 g, 0.1 mmol), 2,6-dimethylphenol (0.018 g, 0.15 mmol), and cesium carbonate (0.049 g, 0.15 mmol) in DMSO (1 mL) was heated at 110 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC on a C18 column eluting with 20-80% acetonitrile in 0.1% TFA water solution to give the title compound (0.026 g, 51 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (d, J = 2.3 Hz, 1H), 8.31 (t, J = 5.4 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.77 (dd, J = 8.7, 2.4 Hz, 1H), 7.45 (s, 1H), 7.14 (d, J = 6.5 Hz, 2H), 7.08 (dd, J = 8.7, 6.0 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 3.58 (s, 3H), 3.20-3.30 (m, 4H), 2.00 (s, 6H), 1.07-1.12 (m, 6H). MS (ESI+) m/z 508.1 $(M+H)^+$.

4-[2-(2-tert-Butyl-6-methyl-phenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (28). A mixture of **91a** (40.5 mg, 0.1 mmol), 2-(tert-butyl)-6-methylphenol (32.8 mg, 0.2 mmol) and cesium carbonate (114 mg, 0.35 mmol) in DMSO (1 mL) was heated at 120 °C for 24 h, cooled to rt, and partitioned with ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by reverse phase HPLC (50-100% acetonitrile in 0.1% TFA/water) to give the title compound (22 mg, 40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.36 (t, J = 5.3 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.42 (s, 1H), 7.28 (dd, J = 7.7, 1.7 Hz, 1H), 7.21 – 7.11 (m, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.59 (s, 3H), 3.35 – 3.22 (m, 4H), 1.94 (s, 3H), 1.18 – 1.08 (m, 15H). MS (ESI+) m/z 550 $(M+H)^+$.

4-[2-(2-Cyano-6-methyl-phenoxy)-5-ethylsulfonyl-phenyl]-N-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (29). A mixture of compound **26** (0.03 g, 0.052 mmol), dicyanozinc (0.012 g, 0.105 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.03 g, 0.026 mmol) in DMF (0.5 mL) was heated at 120 °C for 24 h. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 3% methanol in ethyl acetate to give the title compound (0.019 g, 70 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (d, J = 2.3 Hz, 1H), 8.24 (t, J = 5.4 Hz, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.85 – 7.73 (m, 2H), 7.73 – 7.66 (m, 1H), 7.45 (s, 1H), 7.39 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 3.57 (s, 3H), 3.33 – 3.18 (m, 4H), 2.10 (s, 3H), 1.07-1.13 (m, 6H). MS (ESI+) m/z 519.1 $(M+H)^+$.

N-ethyl-4-[5-ethylsulfonyl-2-[2-methyl-6-(trifluoromethyl)phenoxy]phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (30). A mixture of **70a** (40 mg, 0.116 mmol), **101b** (44.6 mg, 0.105 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (3.6 mg, 0.012 mmol), $Pd_2(dba)_3$ (2.89 mg, 3.16 μmol), and sodium carbonate (44.7 mg, 0.421 mmol) in THF (1.6 mL) and water (0.4 mL) was degassed and back-filled with nitrogen several times. The reaction mixture was heated to about 60 °C for about 4 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was triturated with 1:1 ethyl acetate/hexanes to provide the title compound (0.049 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (d, J = 2.3 Hz, 1H), 8.31 (t, J = 5.4 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.78 (dd, J = 8.7, 2.4 Hz, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.45 – 7.36 (m, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 3.56 (s, 3H), 3.33 – 3.18 (m, 4H), 1.97 (s, 3H), 1.09 (td, J = 7.2, 4.8 Hz, 6H). MS (ESI+) m/z 562.1 $(M+H)^+$.

4-[2-(3,5-Dimethylphenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (31). A flask with stirbar containing **101c** (0.075 g, 0.2 mmol), **70a (**0.077 g, 0.22 mmol), $Pd_2(dba)_3$ (5.58 mg, 6.09 μmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (5.94 mg, 0.02 mmol) and sodium carbonate (0.086 g, 0.812 mmol) was sparged with argon for 15 min. Meanwhile, a solution of 4:1 THF/water (1 mL) was sparged with nitrogen for 15 min and transferred by syringe into the reaction vessel under argon. The mixture was stirred for 4 h under argon at 60 °C, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, treated with 3-mercaptopropyl functionalized silica gel, filtered and

concentrated. Purification by chromatography (reverse phase 10-90% acetonitrile in 0.1% trifluoroacetic acid/water) afforded the title compound (0.05 g, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (d, J = 2.1 Hz, 1H), 8.32 (t, J = 5.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.41 (s, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.72 – 6.67 (m, 2H), 3.54 (s, 2H), 2.20 (s, 4H), 1.10 (dt, J = 14.3, 7.3 Hz, 5H). MS (ESI+) m/z 508.3 $(M+H)^+$.

4-[2-(2,6-Dimethylphenoxy)-5-methylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (32). A flask was charged with **70a (**0.05 g, 0.145 mmol), **101d** (0.051 g, 0.145 mmol), $Pd_2(dba)_3$ (3.98 mg, 4.35 μmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (4.23 mg, 0.014 mmol) and sodium carbonate (0.061 g, 0.579 mmol) and sparged with argon for 15 min. Meanwhile, a solution of 4:1 THF/water (1.1 mL) was sparged with nitrogen for 15 min and transferred by syringe into the reaction vessel under argon. The mixture was stirred for 4 h under argon at 60 °C, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, treated with 3-mercaptopropyl functionalized silica gel, filtered and concentrated. Purification by chromatography (reverse phase 10-90% acetonitrile in 0.1% trifluoroacetic acid/water) afforded the title compound (0.048 g, 67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.35 (t, J=5.34 Hz, 1H), 7.98 (d, J=2.44 Hz, 1H), 7.84 (dd, J=8.54, 2.44 Hz, 1H), 7.49 (s, 1H), 7.07 - 7.21 (m, 3H), 6.86 (d, J=2.14 Hz, 1H), 6.60 (d, J=8.85 Hz, 1H), 3.62 (s, 3H), 3.25 - 3.30 (m, 2H), 3.24 (s, 3H), 2.03 (s, 6H), 1.12 (t, J=7.32 Hz, 3H). MS (ESI+) m/z 494.1 $(M+H)^+$.

4-[5-Cyclopropylsulfonyl-2-(2,6-dimethylphenoxy)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (33). A solution of **91b** (50.1 mg, 0.12 mmol), 2,6-dimethylphenol (29.3 mg, 0.24 mmol) and cesium carbonate (137 mg, 0.42 mmol) in DMSO (1

mL) was heated to 150 °C in a microwave reactor for 1 h, cooled to rt, and partitioned with ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 20-40% 3:1 ethyl acetate/ethanol in heptanes) to give the title compound (41 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.35 (t, J = 5.3 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.50 (s, 1H), 7.20 – 7.09 (m, 3H), 6.85 (s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 3.61 (s, 3H), 3.31 – 3.24 (m, 2H), 2.93 – 2.86 (m, 1H), 2.03 (s, 6H), 1.15 – 1.09 (m, 5H), 1.08 – 1.02 (m, 2H). MS (ESI+) m/z 520 $(M+H)^+$.

4-[2-(2,6-Dimethylanilino)-5-methylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (34). A flask was charged with **70a** (0.195 g, 0.565 mmol), **103** (0.2 g, 0.565 mmol), $Pd_2(dba)_3$ (0.016 g, 0.017 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.017 g, 0.056 mmol) and sodium carbonate (0.239 g, 2.258 mmol) and sparged with argon for 15 min. Meanwhile, a solution of 4:1 THF/water (4 mL) was sparged with nitrogen for 15 min and transferred by syringe into the reaction vessel under argon. The mixture was stirred for 3 h under argon at 60 °C, cooled, and diluted with 30 mL of water. The resulting solid was collected by filtration, washed with additional water and dried. Purification by chromatography (reverse phase 10-90% acetonitrile in 0.1% trifluoroacetic acid/water) afforded the title compound (0.15 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (d, J = 2.5 Hz, 1H), 8.35 (t, J = 5.4 Hz, 1H), 7.63 - 7.57 (m, 2H), 7.36 (s, 1H), 7.29 (s, 1H), 7.16 - 7.10 (m, 3H), 6.74 (d, J = 2.2 Hz, 1H), 6.10 (d, J = 8.7 Hz, 1H), 3.57 (s, 3H), 3.26 (qd, J = 7.1, 5.1 Hz, 2H), 3.12 (s, 3H), 2.09 (s, 6H), 1.11 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 493.1 $(M+H)^+$.

4-[2-[(2,6-Dimethylphenyl)methyl]phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (35). A mixture of **70a** (0.067 g, 0.195 mmol), **106** (0.041 g, 0.15

mmol), $Pd(PPh_3)_4$ (8.67 mg, 7.5 μmol), and cesium fluoride (0.068 g, 0.45 mmol) in DME (1 mL) and MeOH (0.5 mL) was heated at 120 °C for 40 min under microwave heating conditions. The reaction mixture was loaded onto a 15 g silica gel cartridge, and dried. It was then mounted onto a 12 g silica gel column, eluted with 5:95 MeOH: ethyl acetate to give crude product, which was then purified by reverse phase preparative HPLC to give the title compound (0.028 g, 45 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (d, J = 2.3 Hz, 1H), 8.34 (t, J = 5.4 Hz, 1H), 7.34 – 7.15 (m, 4H), 7.06 – 6.95 (m, 3H), 6.64 (d, J = 2.2 Hz, 1H), 6.59 (dd, J = 7.6, 1.4 Hz, 1H), 3.85 (s, 2H), 3.58 (s, 3H), 3.24 (qd, J = 7.2, 5.3 Hz, 2H), 2.04 (s, 6H), 1.09 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 414.1 $(M+H)^+$.

4-[2-(2,6-Dimethylphenyl)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (36). A flask containing **107** (0.05 g, 0.093 mmol), (2,6-dimethylphenyl)boronic acid (0.029 g, 0.193 mmol), $Pd_2(dba)_3$ (0.0088 g, 9.61 μmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (0.0083 g, 0.028 mmol) and sodium carbonate (0.043 g, 0.401 mmol) was sparged with nitrogen for 30 min. To this mixture were added nitrogen-sparged 1,4-dioxane (0.6 mL) and water (0.1 mL) via syringe. The reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, treated with 3-mercaptopropyl-functionalized silica gel for 20 min, dried over anhydrous magnesium sulfate, filtered through a plug of Celite® and concentrated. The residue was triturated with DMSO/water. The solid was collected by filtration and rinsed with additional water. The material was further purified by reverse phase HPLC (C18, acetonitrile/water (0.1% TFA), 10-80%) to provide the title compound (0.0272 g, 59%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.38 (t, J = 5.4 Hz, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.15 – 7.10 (m, 1H),

7.04 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 2.2 Hz, 1H), 6.42 (s, 1H), 3.43 (q, *J* = 7.3 Hz, 2H), 3.27 (qd, *J* = 7.2, 5.5 Hz, 2H), 3.20 (s, 3H), 1.89 (s, 6H), 1.19 (t, *J* = 7.3 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 492.4 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(o-tolyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (37)**. A flask was charged with **107** (0.03 g, 0.056 mmol), *o*-tolylboronic acid (0.015 g, 0.112 mmol), $Pd_2(dba)_3$ (2.56 mg, 2.8 μmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (2.5 mg, 8.4 μmol) and sodium carbonate (0.026 g, 0.241 mmol) and sparged with nitrogen for 30 minutes. Nitrogen-sparged 1,4-dioxane (0.4 mL) and water (0.1 mL) were added and the reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, treated with 3-mercaptopropyl-functionalized silica gel for 20 min, dried over anhydrous magnesium sulfate, filtered through a plug of Celite® and concentrated. The residue was purified by flash chromatography (silica gel 10 g Biotage KP-Sil Snap column, 0 to 50% of a 3:1 mixture of ethyl acetate/ethanol in heptanes) to provide 0.0236 g (88%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.31 (t, *J* = 5.3 Hz, 1H), 7.96 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.15 (m, 4H), 6.82 (s, 1H), 6.63 (s, 1H), 3.42 (q, *J* = 7.3 Hz, 2H), 3.30 (s, 3H), 3.25 (m, 2H), 1.93 (s, 3H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 478.1 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(1*H*-indol-7-yl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (38)**. A flask was charged with **107** (0.05 g, 0.093 mmol), 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (0.045 g, 0.187 mmol), $Pd_2(dba)_3$ (4.27 mg, 4.67 μmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (4.09 mg, 0.014 mmol) and sodium carbonate (0.043 g, 0.401 mmol) and sparged with nitrogen for 30 min. Nitrogen-sparged 1,4-dioxane (0.5 mL) and water (0.125 mL) were added and the reaction mixture was

stirred at 60 °C for 4 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, treated with 3-mercaptopropyl-functionalized silica gel for 20 min, dried over anhydrous magnesium sulfate, filtered through a plug of Celite® and concentrated. The residue was purified by flash chromatography (silica gel 25 g Biotage KP-Sil Snap column, 15 to 80% of a 3:1 mixture of ethyl acetate/ethanol in heptanes). The material was further purified by reverse phase HPLC (C18, acetonitrile/water (0.1% TFA), 10-100%) to provide 0.035 g (75%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 10.75 (s, 1H), 8.02 (td, J = 9.2, 8.1, 3.6 Hz, 2H), 7.95 (d, J = 1.9 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 7.0, 1.7 Hz, 1H), 7.22 (t, J = 2.8 Hz, 1H), 7.09 (s, 1H), 6.86 (m, 2H), 6.45 (d, J = 1.7 Hz, 1H), 6.38 (dd, J = 2.9, 1.8 Hz, 1H), 3.42 (q, J = 7.3 Hz, 2H), 3.33 (s, 3H), 3.20 (m, 2H), 1.23 (t, J = 7.3 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 503.1 $(M+H)^+$.

***N*-ethyl-4-(5-ethylsulfonyl-2-indol-1-yl-phenyl)-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (39)**. A mixture of **91a (**0.041 g, 0.1 mmol), 1*H*-indole (0.023 g, 0.2 mmol), and cesium carbonate (0.065 g, 0.2 mmol) in DMSO (1 mL) was heated to about 110 °C for about 16 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by preparative HPLC to provide the title compound (0.035 g, 70% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.16 (s, 1H), 8.09 (d, J = 7.4 Hz, 2H), 8.00 (t, J = 5.4 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.52 – 7.46 (m, 1H), 7.33 (d, J = 3.4 Hz, 1H), 7.27 (dd, J = 8.1, 1.1 Hz, 1H), 7.16 (s, 1H), 7.04 (dtd, J = 22.9, 7.1, 1.2 Hz, 2H), 6.50 (dd, J = 3.3, 0.9 Hz, 1H), 6.40 (s, 1H), 3.47 (q, J = 7.3 Hz, 2H), 3.38 (s, 3H), 3.18 (qd, J = 7.2, 5.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H).

***N*-ethyl-4-[5-ethylsulfonyl-2-(7-methylindol-1-yl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (40)**. A suspension of **91a** (200 mg, 0.493 mmol), 7-

methyl-1*H*-indole (129 mg, 0.987 mmol), and cesium carbonate (321 mg, 0.987 mmol) in DMSO (2 mL) was heated at 110 °C for 20 h. Additional 7-methyl-1*H*-indole (129 mg, 0.987 mmol) and cesium carbonate (321 mg, 0.987 mmol) were added to the reaction mixture. The reaction mixture was heated at 130 °C for another 24 h, cooled to rt, filtered, and purified by reverse phase HPLC (10-100% acetonitrile in 0.1% TFA/water), followed by re-purification by flash chromatography (silica gel, 2-5% methanol in dichloromethane) to give the title compound (130 mg, 51%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.30 (t, J = 5.4 Hz, 1H), 8.08 (d, J = 2.2 Hz, 1H), 8.05 (dd, J = 8.2, 2.2 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 3.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.74 (s, 1H), 6.60 (d, J = 3.3 Hz, 1H), 6.55 (s, 1H), 3.47 (q, J = 7.3 Hz, 2H), 3.29 – 3.23 (m, 2H), 3.14 (s, 3H), 1.90 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 517.5 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(7-methylindolin-1-yl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (41)**. A solution of **40** (90.0 mg, 0.174 mmol) and sodium cyanoborohydride (109 mg, 1.74 mmol) in acetic acid (3 mL) was stirred at rt for 24 h. Additional sodium cyanoborohydride (109 mg, 1.74 mmol) was added to the reaction mixture. The reaction mixture was stirred at rt for another 64 h, and concentrated. The residue was purified by reverse phase HPLC (10-100% acetonitrile in 0.1% TFA/water) to give the title compound (87 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (d, J = 1.6 Hz, 1H), 8.33 (t, J = 5.4 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.40 (s, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 2.2 Hz, 1H), 3.59 (s, 3H), 3.35 – 3.20 (m, 6H), 3.09 – 3.02 (m, 1H), 2.72 – 2.66 (m, 1H), 2.06 (s, 3H), 1.16 (t, J = 7.4 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 519.5 $(M+H)^+$.

***N*-ethyl-4-[5-ethylsulfonyl-2-(4-fluoro-2,6-dimethyl-phenoxy)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (42)**. A mixture of **108** (0.36 g, 0.529 mmol) in 1,4-dioxane (4 mL) was treated with a 2 M aqueous solution of sodium hydroxide (1.32 mL, 2.64 mmol), and heated at 90 °C for 2 h. Aqueous workup afforded 4-(5-(ethylsulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (0.25 g, 95%). A mixture of 4-(5-(ethylsulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 0.12 mmol) in DCM (5 mL) was treated sequentially with oxalyl chloride (0.032 mL, 0.36 mmol) and DMF (9.3 µL, 0.12 mmol), stirred at rt for 2 h and concentrated. The residue was dissolved in THF (5 mL), treated with a 1 M solution of ethylamine in THF (1.81 mL, 1.81 mmol) stirred at rt for 16 h and concentrated. The residue was purified by reverse phase HPLC (20-80% acetonitrile in 0.1% TFA/water) to give the title compound (46 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.30 (t, J = 5.4 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 8.7, 2.4 Hz, 1H), 7.44 (s, 1H), 7.01 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.57 (s, 3H), 3.29 – 3.20 (m, 4H), 1.99 (s, 6H), 1.12 – 1.06 (m, 6H). MS (ESI+) m/z 526.1 $(M+H)^+$.

4-[2-(4-Chloro-2,6-dimethyl-phenoxy)-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (43). A mixture of **91a** (0.043 g, 0.106 mmol), 4-chloro-2,6-dimethylphenol (0.05 g, 0.318 mmol), and cesium carbonate (0.104 g, 0.318 mmol) in DMSO (1 mL) was heated at 110 °C overnight. After cooling, the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite®, and concentrated. The residue was purified by reverse phase HPLC to give the title compound (0.038 g, 66 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.33 (t, J = 5.3 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.7, 2.4 Hz, 1H), 7.48 (s, 1H), 7.27 (s, 2H), 6.82 (d, J = 2.2 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 3.61 (s, 3H),

3.34 – 3.22 (m, 4H), 2.02 (s, 6H), 1.14 (t, *J* = 7.4 Hz, 3H), 1.12 (t, *J* = 7.3 Hz, 3H). MS (ESI+) m/z 542.0 $(M+H)^+$.

4-[2-[2-(Difluoromethyl)-6-methyl-phenoxy]-5-ethylsulfonyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (44). A mixture of **110** (0.057 g, 0.109 mmol) and DAST (0.043 mL, 0.328 mmol) in DCM (3 mL) was stirred at rt for 3 h. The solvent was removed, and the reaction mixture was quenched with MeOH. It was then diluted with DMSO. The reaction mixture was then purified by preparative HPLC to give the title compound (29.5 mg, 50 % yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.33 (d, *J* = 2.3 Hz, 1H), 8.32 (t, *J* = 5.3 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 (t, *J* = 10.6 Hz, 2H), 7.51 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 6.97 (m, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 3.58 (s, 3H), 3.34 – 3.21 (m, 4H), 1.93 (s, 3H), 1.11 (td, *J* = 7.3, 5.3 Hz, 6H). MS (ESI+) m/z 544.0 $(M+H)^+$.

4-[2-(2,6-Dimethylphenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (45). A 5 mL microwave tube was charged with **70a** (122 mg, 0.353 mmol), **114** (100 mg, 0.298 mmol), potassium phosphate (204 mg, 0.961 mmol), $Pd_2(dba)_3$ (10.2 mg, 0.011 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (11.6 mg, 0.04 mmol) and sealed. The vessel was purged with nitrogen for 10 min, followed by addition of a degassed mixture of THF (3.2 mL) / water (0.8 mL). The mixture was heated at 60 °C for 3.5 h. The mixture was diluted with 20 mL of ethyl acetate, washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, filtered and evaporated. The residue was purified by preparative RP-HPLC on a Phenomenex Luna C8(2) 5 µm 100Å AXIA column (30 mm × 75 mm) using a gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B), at a flow rate of 50 mL/min (0-1.0 min 5% A, 1.0-8.5 min linear gradient 5-100% A,

8.5-11.5 min 100% A, 11.5-12.0 min linear gradient 95-5% A) to provide the title compound (84.4 mg, 60%) as off-white needles. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (bds, 1H), 8.34 (t, J = 5.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.34 (s, 1H), 7.31 (dd, J = 8.6, 2.4 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.04 (m, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.28 (d, J = 8.6 Hz, 1H), 3.60 (s, 3H), 3.28 (m 2H), 2.02 (s, 6H), 1.44 (s, 6H), 1.12 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 474.2 $(M+H)^+$.

***N*-ethyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (46)**. A mixture of **75** (1.189 g, 3.36 mmol), **70a** (1.51 g, 4.37 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.098 g, 0.336 mmol), $Pd_2(dba)_3$ (0.092 g, 0.101 mmol), and potassium phosphate (1.786 g, 8.41 mmol) in 1,4-dioxane (30 mL) and water (7.5 mL) was degassed and back-filled with nitrogen six times. The reaction mixture was heated at 75 °C for 1 h. The reaction mixture was partitioned between water (200 mL) and MTBE (3 X 200 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 5 % methanol in ethyl acetate to give the title compound (1.21 g, 73 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 8.32 (t, J = 5.3 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.46 – 7.21 (m, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 8.6 Hz, 1H), 3.58 (s, 3H), 3.24 (dt, J = 12.6, 6.2 Hz, 2H), 2.00 (s, 6H), 1.42 (s, 6H), 1.10 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 159.9, 159.1 (d, J = 240.6 Hz), 154.8, 153.2, 147.4 (d, J = 2.4 Hz), 144.3, 134.0, 133.3 (d, J = 8.9 Hz), 130.3, 129.9, 128.40, 125.6, 124.7, 124.3, 115.6 (d, J = 22.7 Hz), 112.4, 112.0, 106.2, 70.8, 36.3, 34.2, 32.4, 16.6, 16.6, 14.9. HRMS (m/z): $(M+H)^+$ calcd for C28H30FN3O4, 492.2293; found, 492.2296.

4-[2-(2,6-Dimethylphenoxy)-5-(ethylsulfonylamino)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (47). A solution of **119a** (0.0624 g, 0.145 mmol) in THF (1.5 mL) was treated sequentially with ethanesulfonyl chloride (0.035 mL, 0.369 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.1 mL, 0.573 mmol) and stirred overnight at rt. Sodium hydroxide solution (4 M aq) (0.08 mL, 0.32 mmol) was added and the mixture was heated at 50 °C for 2 h. The reaction mixture was acidified with hydrochloric acid solution (2 M aq) and then partitioned between ethyl acetate and water. The organic layer was washed with brine. The aqueous layers were combined and extracted with ethyl acetate (1 x 100 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by reverse phase HPLC (C18, acetonitrile/water (0.1% TFA), 20-100%) to provide 0.036 g (48%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 9.62 (s, 1H), 8.34 (t, J = 5.4 Hz, 1H), 7.40 (s, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.09 (m, 4H), 6.87 (d, J = 2.1 Hz, 1H), 6.34 (d, J = 8.9 Hz, 1H), 3.60 (s, 3H), 3.26 (m, 2H), 3.06 (q, J = 7.3 Hz, 2H), 2.01 (s, 6H), 1.22 (t, J = 7.3 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 523.1 $(M+H)^+$.

***N*-ethyl-4-[5-(ethylsulfonylamino)-2-(4-fluoro-2,6-dimethyl-phenoxy)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (48)**. A 50 mL round-bottomed flask was charged with **119b** (0.0768 g, 0.171 mmol) in DCM (0.685 mL). Triethylamine (0.095 mL, 0.685 mmol) and ethanesulfonyl chloride (0.049 mL, 0.514 mmol) were added. The reaction mixture was stirred at rt for about 4 h. Additional triethylamine (0.095 mL, 0.685 mmol) and ethanesulfonyl chloride (0.049 mL, 0.514 mmol) were added. The reaction mixture was stirred at rt for about 1 h. The solvent was removed *in vacuo*, and 1,4-dioxane (2 mL) was added. Sodium hydroxide (2 N, 2.0 mL, 4.0 mmol) was added. The reaction mixture was stirred at rt for about 16 h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was

extracted 2x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (40-100% (3:1 EtOAc:EtOH):heptanes) to provide a tan solid (20.9 mg, 22% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 9.60 (s, 1H), 8.30 (t, J = 5.4 Hz, 1H), 7.35 (s, 1H), 7.27 (d, J = 2.8 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.33 (d, *J* = 8.9 Hz, 1H), 3.56 (s, 3H), 3.27 - 3.17 (m, 2H), 3.02 (q, *J* = 7.3 Hz, 2H), 1.97 (s, 6H), 1.23 - 1.14 (m, 3H), 1.08 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 541.1 $(M+H)^+$.

4-[2-(2,6-Dimethylphenoxy)-5-sulfamoyl-phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (49). In a 50 mL round-bottomed flask was placed **126** (90 mg, 0.252 mmol), $Pd_2(dba)_3$ (23.07 mg, 0.025 mmol), sodium carbonate (80 mg, 0.756 mmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (7.36 mg, 0.025 mmol) and **70a** (104 mg, 0.302 mmol) in THF (6 mL) and water (1.5 mL). The mixture was heated at 60 °C for 3 h under nitrogen. The mixture was allowed to cool to rt and water was added followed by ethyl acetate. The aqueous phase was extracted two more times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by preparative HPLC. Column:XBridge RP C18, 19*150 mm, 5 μm; Mobile Phase A: Water/0.05 % TFA, Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 6 % B to 60 % B in 7.0 min, 254 nm (55 mg, 44 % yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.35 (m, 1H), 7.90 (s, 1H), 7.73 (m, 1H), 7.32 (m, 3H), 7.17, (m, 3H), 6.83 (s, 1H), 6.51 (m, 1H), 4.02 (s, 3H), 3.26 (m, 2H), 1.98 (s, 6H), 1.14 (m, 3H). MS (ESI+) m/z 495.2 $[M+H]^+$.

4-[2-(2,6-Dimethylphenoxy)-5-(hydroxymethyl)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (50). A mixture of $Pd_2(dba)_3$ (10.61 mg, 0.012 mmol),

115 (74.7 mg, 0.243 mmol), **70a (**80 mg, 0.232 mmol), K_3PO_4 (148 mg, 0.695 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (6.77 mg, 0.023 mmol) in a mixture of THF (2.5 mL) and water (0.5 mL) was stirred in a microwave vial for 2 h at 65 °C. The reaction mixture was filtered through Celite® and the filtrate was evaporated *in vacuo*. The residue was purified by preparative HPLC (mobile phase: MeCN/water) to afford the title compound (40 mg, 39 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 - 12.22 (m, 1H), 8.33 (t, J = 5.4 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.34 (s, 1H), 7.16 (dd, J = 8.4, 2.2 Hz, 1H), 7.11 (d, J = 7.4 Hz, 2H), 7.04 (dd, J = 8.5, 6.3 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 5.14 (t, J = 5.7 Hz, 2H), 4.47 (d, J = 5.7 Hz, 2H), 3.58 (s, 3H), 3.25 (qd, J = 7.2, 5.2 Hz, 2H), 2.00 (s, 6H), 1.10 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 446.2 $(M+H)^+$.

4-[2-(2,6-Dimethylphenoxy)-5-(ethylcarbamoyl)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (51). A mixture of **116** (92 mg, 0.263 mmol)), **70a (**100 mg, 0.29 mmol)), $Pd_2(dba)_3$ (9.94 mg, 10.53 μmol)), potassium phosphate (168 mg, 0.79 mmol)) and 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (11.11 mg, 0.037 mmol) in THF (2.5 mL) and water (0.6 mL). The sealed vial was irradiated in the microwave at 80 °C for 2 h. After cooling, the reaction mixture was partitioned between ethyl acetate and H_2O. The aqueous phase was extracted twice with ethyl acetate . The combined organics were washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by preparative HPLC to give the title compound (62 mg, 48 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (s, 1H), 8.35 (dt, J = 19.3, 5.5 Hz, 2H), 7.95 (d, J = 2.3 Hz, 1H), 7.75 (dd, J = 8.6, 2.3 Hz, 1H), 7.40 (s, 1H), 7.13 (d, J = 7.3 Hz, 2H), 7.07 (dd, J = 8.6, 6.1 Hz, 1H), 6.83 (s, 1H), 6.40 (d, J = 8.6 Hz, 1H), 3.60 (s, 3H), 3.25 (ddt, J = 10.6, 7.3, 3.7 Hz, 4H), 2.00 (s, 6H), 1.09 (td, J = 7.2, 4.7 Hz, 6H). MS (ESI+) m/z 487.2 $(M+H)^+$.

Methyl *N*-[3-[2-(ethylcarbamoyl)-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridin-4-yl]-4-(4-fluoro-2,6-dimethyl-phenoxy)phenyl]carbamate (52). A 50 mL round-bottomed flask was charged with **119b** (0.08 g, 0.178 mmol) in DCM (0.714 mL) to give a yellow solution. Triethylamine (0.099 mL, 0.714 mmol) and methyl chloroformate (0.041 mL, 0.535 mmol) were added. The reaction mixture was stirred at rt for about 5 h. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (30-90% (3:1 EtOAc:EtOH):heptanes) to provide a white solid (62.7 mg, 69% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 9.54 (s, 1H), 8.30 (t, J = 5.4 Hz, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.32 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 9.2 Hz, 2H), 6.82 (d, J = 1.7 Hz, 1H), 6.29 (d, J = 8.9 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 3.28 - 3.17 (m, 2H), 1.97 (s, 6H), 1.08 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 507.1 $(M+H)^+$.

4-[5-Acetamido-2-(2,6-dimethylphenoxy)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (53). To a solution of **119a** (0.04 g, 0.093 mmol) and triethylamine (0.039 mL, 0.279 mmol) in DCM (0.9 mL) was added acetyl chloride (7.27 µL, 0.102 mmol). The mixture was stirred at rt under nitrogen for 2 h, diluted with water, and stirred for 10 minutes. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Purification by chromatography (silica, 1-5% methanol in DCM) afforded the title compound (0.03 g, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 9.90 (s, 1H), 8.33 (t, J = 5.3 Hz, 1H), 7.66 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 8.9, 2.6 Hz, 1H), 7.35 (s, 1H), 7.16 - 6.96 (m, 3H), 6.87 (s, 1H), 6.28 (d, J = 8.9 Hz, 1H), 3.57 (s, 3H), 3.27 - 3.21 (m, 2H), 1.99 (s, 6H), 1.10 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 473.1 $(M+H)^+$.

4-[5-Acetamido-2-(4-fluoro-2,6-dimethyl-phenoxy)phenyl]-*N*-ethyl-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (54). To a solution of **119b** (0.06 g, 0.13 mmol) and triethylamine (0.056 mL, 0.4 mmol) in DCM (1.34 mL) was added dropwise acetyl chloride (0.011 mL, 0.16 mmol). The mixture was stirred at ambient temperature under nitrogen for 2 h, diluted with water, and stirred for 10 minutes. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. Purification by chromatography (silica, 1-5% methanol in DCM) afforded the title compound (0.02 g, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 9.89 (s, 1H), 8.31 (t, J = 5.4 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.41 (dd, J = 8.9, 2.6 Hz, 1H), 7.33 (s, 1H), 6.94 (d, J = 9.1 Hz, 2H), 6.84 (s, 1H), 6.30 (d, J = 8.9 Hz, 1H), 3.56 (s, 3H), 3.24 (qd, J = 7.2, 5.3 Hz, 2H), 1.98 (d, J = 1.2 Hz, 9H), 1.09 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 491.1 $(M+H)^+$.

***N*-ethyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxycyclobutyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (55)**. A mixture of **70a (**0.09 g, 0.26 mmol), **129a** (0.073 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.012 g, 10 μmol), and cesium fluoride (0.091 g, 0.6 mmol) in DME (1 mL) and MeOH (0.5 mL) was heated at 120 °C for 40 min under microwave heating conditions. The reaction mixture was loaded onto a 15 g silica gel cartridge, and dried. It was then mounted onto a 12 g silica gel column and eluted with 3:97 MeOH: ethyl acetate to give crude product, which was then purified by reverse phase preparative HPLC to give the title compound (0.072 g, 72 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 8.32 (t, J = 5.4 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.37 – 7.30 (m, 2H), 6.97 (d, J = 9.1 Hz, 2H), 6.83 (s, 1H), 6.33 (d, J = 8.6 Hz, 1H), 5.44 (s, 1H), 3.58 (s, 3H), 3.31 – 3.19 (m, 2H), 2.49 – 2.38 (m, 2H), 2.24 (ddd, J = 11.6, 9.2, 7.2 Hz, 2H), 2.00 (s, 6H), 1.98 – 1.81 (m, 1H), 1.68 – 1.55 (m, 1H), 1.16 – 1.05 (m, 3H). MS (ESI+) m/z 504.1 $(M+H)^+$.

***N*-ethyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(3-hydroxyoxetan-3-yl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (56)**. A mixture of **70a** (0.056 g, 0.163 mmol), **129b** (0.046 g, 0.125 mmol), $Pd(PPh_3)_4$ (7.24 mg, 6.26 μmol), and cesium fluoride (0.057 g, 0.376 mmol) in DME (1 mL) and MeOH (0.5 mL) was heated at 120 °C for 40 min under microwave heating conditions. The reaction mixture was loaded onto a 15 g silica gel cartridge, and dried. It was then mounted onto a 12 g silica gel column and eluted with 3:97 MeOH: ethyl acetate to give crude product, which was then purified by reverse phase preparative HPLC to give the title compound (0.031 g, 49 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.31 (t, J = 5.3 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.46 (dd, J = 8.6, 2.4 Hz, 1H), 7.36 (s, 1H), 6.98 (d, J = 9.1 Hz, 2H), 6.84 (s, 1H), 6.40 (d, J = 8.6 Hz, 1H), 6.33 (s, 1H), 4.78 – 4.67 (m, 4H), 3.58 (s, 3H), 3.25 (qd, J = 7.2, 5.3 Hz, 2H), 2.01 (s, 6H), 1.10 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 506.1 $(M+H)^+$.

***N*-ethyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(4-hydroxytetrahydropyran-4-yl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (57)**. A mixture of **70a** (0.067 g, 0.195 mmol), **129c** (0.059 g, 0.15 mmol), $Pd(PPh_3)_4$ (8.67 mg, 7.50 μmol), and cesium fluoride (0.068 g, 0.450 mmol) in DME (1 mL) and MeOH (0.5 mL) was heated at 120 °C for 40 min under microwave heating conditions. The reaction mixture was loaded onto a 15 g silica gel cartridge, and dried. It was then mounted onto a 12 g silica gel column and eluted with 3:97 MeOH: ethyl acetate to give crude product, which was then purified by reverse phase preparative HPLC to give the title compound (0.047 g, 59 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 - 12.22 (m, 1H), 8.32 (t, J = 5.3 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.37 - 7.29 (m, 2H), 6.97 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 8.6 Hz, 1H), 3.81 - 3.64 (m, 4H), 3.59 (s, 3H), 3.24

(td, *J* = 7.3, 5.2 Hz, 2H), 2.00 (s, 6H), 1.94 (dt, *J* = 12.5, 6.7 Hz, 2H), 1.55 (d, *J* = 13.0 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 534.1 $(M+H)^+$.

4-(2,6-Dimethylphenoxy)-3-[2-(ethylcarbamoyl)-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridin-4-yl]benzoic acid (58). A 20-mL microwave vial with stirbar was charged with **70a** (1.371 g, 3.57 mmol), cesium carbonate (3.30 g, 10.13 mmol), $Pd_2(dba)_3$ (88.5 mg, 0.097 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (110.1 mg, 0.377 mmol) and sealed. The vessel was purged with nitrogen for 15 minutes, followed by addition of a degassed solution of **111** (1.01 g, 3.14 mmol) in a mixture of THF (16 mL) / water (4 mL). The mixture was heated at 60 °C for 17 h, then cooled and partitioned between 150 mL ethyl acetate and a mixture of 30 mL brine and 30 mL 1 M HCl. The organics were dried over magnesium sulfate. After filtration and solvent removal, the crude yellow foam was chromatographed on a 40 g silica cartridge eluting with 0-10% 3:1 methanol/DCM. The major peak provided 1.78 g of a brown foam. This material was chromatographed again on a 40 g silica cartridge eluting with 10-100% 3:1 EtOAc:EtOH/heptanes to provide the title compound (1.058 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 12.25 (d, *J* = 2.3 Hz, 1H), 8.31 (t, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.40 (s, 1H), 7.17 - 7.01 (m, 3H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 8.6 Hz, 1H), 3.57 (s, 3H), 3.23 (qd, *J* = 7.3, 5.3 Hz, 2H), 1.99 (s, 6H), 1.11 (dt, *J* = 21.2, 7.2 Hz, 4H). MS (ESI+) m/z 460.2 $(M+H)^+$.

***N*-tert-butyl-4-[2-(2,6-dimethylphenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (59)**. A stream of nitrogen gas was blown over a mixture of **70b** (15 g, 40.2 mmol), **114** (16.2 g, 48.2 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (1.175 g, 4.02 mmol), potassium phosphate (21.33 g, 100 mmol), and tris(dibenzylideneacetone)dipalladium (1.104 g, 1.206 mmol) for one h. In the

meantime, in a 1 L. flask a mixture of anhydrous 1,4-dioxane (300 mL) and water (75 mL) was degassed for one h by bubbling nitrogen through it. The solvents were then transferred via cannula into the mixture of degassed solids. As the solvents were added an exotherm was observed and the temperature rose from 20.5 °C to 32.0 °C. When the reaction mixture was sufficiently mixed, it was heated at 80 °C for 2.5 h. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate and water. The mixture was stirred for one h with 600 mg. (3.0 equivalents. based on moles of palladium) of ammonium pyrrolidine dithiocarbamate. The resulting mixture was filtered through diatomaceous earth. The diatomaceous earth pad was washed with ethyl acetate. The resulting filtrate was poured into a separatory funnel and the mixture diluted further with ethyl acetate and brine. The organic layer was washed with water (2X) and brine. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Grace Reveleris X2 MPLC using a Teledyne Isco RediSep Rf Gold 330 g. silica gel column eluting with 70 % to 80 % to 90 % ethyl acetate/heptanes to 100 % ethyl acetate. The resulting pure material was dissolved with heating in ethanol, concentrated under reduced pressure, and dried to produce the title compound (18.0 g, 89% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.34 (s, 1H), 7.85 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.33 (s, 1H), 7.28 (dd, J = 8.6, 2.4 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 7.03 (dd, J = 8.3, 6.6 Hz, 1H), 6.85 (s, 1H), 6.26 (d, J = 8.6 Hz, 1H), 4.97 (s, 1H), 3.59 (s, 3H), 2.00 (s, 6H), 1.42 (s, 6H), 1.35 (s, 9H). MS (ESI+) m/z 502.1 $(M+H)^+$.

***N*-tert-butyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (60)**. A flask was charged with **70b** (0.088 g, 0.25 mmol), **75** (0.121 g, 0.325 mmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (8.55 mg, 0.029 mmol), $Pd_2(dba)_3$ (6.87 mg, 7.5 μmol), and

potassium phosphate (0.133 g, 0.625 mmol), and sparged with nitrogen. Degassed dioxane (2 mL) and water (0.5 mL) were added and the mixture was heated at 60 °C for 6 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel, followed by reverse phase preparative HPLC to give the title compound (0.069 g, 53.1 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (d, J = 2.3 Hz, 1H), 7.86 (s, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.41 – 7.25 (m, 2H), 6.99 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 2.3 Hz, 1H), 6.31 (d, J = 8.6 Hz, 1H), 3.61 (s, 3H), 2.02 (s, 6H), 1.44 (s, 6H), 1.37 (s, 9H). MS (ESI+) m/z 520.1 $(M+H)^+$.

***N*-(3-bicyclo[1.1.1]pentanyl)-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (61)**.A mixture of **131** (59.4 mg, 0.128 mmol), N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (36 mg, 0.188 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol hydrate (33 mg, 0.215 mmol), bicyclo[1.1.1]pentan-1-amine, hydrochloride (24.7 mg, 0.207 mmol) and 4-methylmorpholine (65 µl, 0.591 mmol) in DCM (4 mL) was stirred for 16 h at ambient temperature. The mixture was partitioned between aqueous sodium bicarbonate and DCM. The organics were dried over anhydrous sodium sulfate, filtered, and concentrated. The residues were chromatographed (silica gel, 0-10 % ammonia-saturated methanol/DCM) to provide the title compound (0.045 g, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.85 (s, 1H), 7.49 (d, J = 2.4 Hz, 2H), 7.31-7.28 (m, 3H), 6.96 (d, J = 9.1 Hz, 1H), 6.83 (s, 1H), 6.29 (d, J = 8.6 Hz, 1H), 4.96 (s, 1H), 3.57 (s, 3H), 2.42 (s 1H), 2.02 (s, 6H), 1.93 (s, 6H), 1.42 (s, 6H). MS (ESI+) m/z 530.1 $(M+H)^+$. **4-[2-(4-Fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-**

ethyl)phenyl]-N,6-dimethyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (62). A mixture of **69c** (0.057 g, 0.2 mmol), **132** (0.096 g, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.012 g, 10 μmol), and cesium fluoride (0.091 g, 0.6 mmol) in DME (1 mL) and methanol (0.5 mL) was heated at 120 °C for 40 min under microwave heating conditions. The reaction mixture was adsorbed on silica and chromatographed on a 12 g silica gel column and eluted with 15:85 methanol: ethyl acetate, followed by reverse phase preparative HPLC (C18 column, acetonitrile/water (0.1 % trifluoroacetic acid)) to give the title compound (0.062 g, 65% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 – 12.09 (m, 1H), 8.31 (q, J = 4.5 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.34 – 7.26 (m, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 8.6 Hz, 1H), 3.58 (s, 3H), 2.74 (d, J = 4.5 Hz, 3H), 1.99 (s, 6H), 1.42 (s, 6H). MS (ESI+) m/z 478.1 $(M+H)^+$.

***N*-cyclopropyl-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (63)**. A microwave vial was charged with **69d** (0.12 g, 0.387 mmol), **132** (0.155 g, 0.387 mmol), $Pd_2(dba)_3$ (0.018 g, 0.019 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.017 g, 0.058 mmol) and sodium carbonate (0.176 g, 1.664 mmol) and sparged with nitrogen for 30 minutes. To this mixture were added nitrogen-sparged THF (2 mL) and water (0.5 mL) via syringe. The reaction mixture was stirred at 60 °C for 4.5 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, treated with 3-mercaptopropyl-functionalized silica gel overnight, dried over anhydrous magnesium sulfate, filtered through a plug of diatomaceous earth, and concentrated. The residue was purified by flash chromatography (silica gel 24 g Grace Reveleris column, eluting with a gradient of 0 to 60 % of a 3:1 mixture of ethyl acetate/ethanol in heptanes) to provide the title

compound as a mixture. The material was purified by a second flash chromatography (silica gel 24 g Grace Reveleris column, 15 to 35 % of a 3:1 mixture of ethyl acetate/ethanol in heptanes) to provide the title compound (0.147 g, 75%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.35 (d, J = 4.2 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.33 (s, 1H), 7.32 (dd, J = 9.0, 2.5 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 6.83 (s, 1H), 6.31 (d, J = 8.6 Hz, 1H), 4.98 (s, 1H), 3.59 (s, 3H), 2.82 (tq, J = 7.7, 4.0 Hz, 1H), 2.01 (s, 6H), 1.44 (s, 6H), 0.70 (td, J = 7.0, 4.9 Hz, 2H), 0.52 (m, 2H). MS (ESI+) m/z 504.1 $(M+H)^+$.

4-[2-(4-Fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-*N*-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (64). A mixture of **75** (80 mg, 0.226 mmol), **70c** (106 mg, 0.249 mmol), $Pd_2(dba)_3$ (7.67 mg, 8.38 μmol), K_3PO_4 (144 mg, 0.679 mmol) and 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (8.87 mg, 0.03 mmol) in THF (2.5 mL) and water (0.6 mL) under nitrogen was irradiated in the microwave at 70°C for 2 h. After cooling, the reaction mixture was partitioned between ethyl acetate and H_2O. The aqueous phase was extracted twice with ethyl acetate and the combined organics were washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by preparative HPLC to give the title compound (73 mg, 56.2 % yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.61 (d, J = 2.4 Hz, 1H), 7.45 7.25 (m, 2H), 7.06 (s, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.39 (d, J = 8.6 Hz, 1H), 3.72 (s, 3H), 2.05 (s, 6H), 1.67 (s, 6H), 1.55 (s, 6H). MS (ESI+) m/z 574.2 $(M+H)^+$.

***N*-(2,2-difluoro-1-methyl-cyclopropyl)-4-[2-(4-fluoro-2,6-dimethyl-phenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (65)**. A mixture of **75** (80 mg, 0.226 mmol), **70d** (101 mg, 0.249 mmol), $Pd_2(dba)_3$ (7.67 mg, 8.38 μmol), K_3PO_4 (144 mg, 0.679 mmol) and 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-

phosphaadamantane (8.87 mg, 0.030 mmol) in THF (2.5 mL) and water (0.6 mL) under nitrogen in a sealed vial was irradiated in the microwave at 70 °C for 2 h. After cooling, the reaction mixture was partitioned between ethyl acetate and H_2O, and the aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by preparative HPLC to give the title compound (49 mg, 39 % yield) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 (s, 1H), 7.2 – 7.3 (m, 2H), 6.87 (s, 1H), 6.73 (d, J = 8.9 Hz, 2H), 6.30 (d, J = 8.6 Hz, 1H), 3.62 (s, 3H), 1.95 (s, 6H), 1.35 – 1.55 (m, 11H). MS (ESI+) m/z 554.2 $(M+H)^+$.

Ethyl 4-bromo-7-methoxy-1-tosyl-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (67). To a solution of 4-bromo-7-methoxy-1-tosyl-1*H*-pyrrolo[2,3-c]pyridine[18] **66** (12 g, 31.5 mmol) in THF (150 mL) was added dropwise LDA (24.3 mL, 47.2 mmol) at -70 °C and the mixture stirred at -70 °C – 50 °C for 45 min, followed by dropwise addition of ethyl chloroformate (5.12 g, 47.2 mmol). After 1.5 h, the reaction mixture was quenched with NH_4Cl solution. THF was removed and the residue was extracted with ethyl acetate (3 X 300 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the crude product, which was triturated with DCM:MeOH (1:10) to give the title compound (13 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 – 8.08 (m, 3H), 7.25 (m, 2H), 7.25 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 160.7, 151.4, 146.5, 141.3, 137.3, 137.1, 135.4, 130.3, 128.7, 122.5, 113.7, 105.0, 62.9, 54.0, 21.7, 14.3. HRMS (m/z): $(M+H)^+$ calcd for C18H17BrN2O5S, 453.0114; found, 453.0119.

Ethyl 4-bromo-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (68). Chlorotrimethylsilane (10.43 g, 96 mmol) was added dropwise to a mixture of **67** (29 g, 64 mmol) and sodium iodide (14.38 g, 96 mmol) in acetonitrile (400 mL) and the

resulting mixture was stirred at rt for 1 h. Water (0.576 g, 32 mmol) was then added dropwise and the resulting mixture was stirred at 65 °C for 3 h. The reaction mixture was cooled to rt and filtered. The collected solid was dissolved in DCM, filtered, and concentrated to give a brown solid which was washed with petroleum ether and DCM to afford ethyl 4-bromo-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (32 g). To a portion of this material (18.72 g, 42.6 mmol) and Cs_2CO_3 (16.66 g, 51.1 mmol) in anhydrous DMF (200 mL), iodomethane (3.2 mL, 51.1 mmol) was added dropwise. After stirring over the weekend at ambient temperature, water was added (500 mL) to the reaction mixture inducing formation of a precipitate. The precipitate was collected by filtration, washed with water, and dried overnight in a vacuum oven at 55 °C to provide the title compound (17.9 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 8.1 Hz, 2H), 7.91 (s, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.02 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.43 (s, 3H), 2.41 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 160.7, 153.3, 145.4, 136.8, 135.6, 135.2, 133.7, 129.8, 129.3, 126.7, 112.9, 92.4, 62.5, 37.5, 21.8, 14.1. HRMS (m/z): $(M+H)^+$ calcd for C18H17BrN2O5S, 453.0114; found, 453.0116.

4-Bromo-*N*-ethyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69a). To a solution of **68 (**10 g, 22.06 mmol) and 2 M ethanamine in THF (90 mL, 180 mmol) at 20 °C was added 8% by weight of magnesium methanolate (88 mL, 66.7 mmol) in methanol. The reaction mixture was heated at 55 °C for 15 h in a sealed vessel. The mixture was diluted with 0.5 N HCl (800 mL), stirred for 5 min and filtered. The solid was washed with ice water and dried to afford the title compound (6.8 g, 98 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.43 (t, J = 5.4 Hz, 1H), 7.57 (s, 1H), 6.84 (d, J = 2.3 Hz, 1H), 3.48 (s, 3H), 3.26 (td, J = 7.2, 5.3 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ 159.6, 154.4,

134.4, 130.7, 130.1, 124.6, 105.1, 93.2, 36.2, 34.3, 15.0. HRMS (m/z): $(M+H)^+$ calcd for C11H12BrN3O2, 298.0186; found, 298.0188.

4-Bromo-*N*-(tert-butyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69b). To a slurry of **76** (2.98 g, 11 mmol) in DCM (30 mL) was added 4 drops of DMF, followed by the addition of oxalyl chloride (1.93 mL, 22 mmol). The mixture was stirred at ambient temperature for 3 h and concentrated. To the residue were added THF (30 mL) and 2-methylpropan-2-amine (3.47 mL, 33 mmol) and the resulting mixture was stirred at ambient temperature for 1 h. The mixture was partitioned with ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was triturated with ethyl acetate/heptanes (1:1) to provide the title compound (3.35 g, 10.27 mmol, 93 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 7.86 (s, 1H), 7.54 (s, 1H), 6.80 (s, 1H), 3.47 (s, 3H), 1.35 (s, 9H). MS (ESI+) m/z 325.9, 327.9 $(M+H)^+$.

4-Bromo-N,6-dimethyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69c). A solution of **76** (1.084 g, 4 mmol) in DCM (25 mL) was treated with oxalyl dichloride (0.7 mL, 8.0 mmol) and *N,N*-dimethylformamide (0.062 mL, 0.800 mmol). The reaction mixture was stirred at rt for 2 h. The solvent was removed, and the residue was treated with THF (20 mL) and DMF (10 mL). To this reaction mixture was added methanamine (2 M in THF, 20 mL, 40 mmol). The white suspension was stirred at rt for 2 h. Most of the THF was removed under reduced pressure, and the remaining organics were poured into water (300 mL). The precipitated solid was collected by filtration and dried in a vacuum oven overnight to give the title compound (0.95 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.41 (q, J = 4.5 Hz, 1H), 7.55 (s,

1H), 6.81 (d, *J* = 2.1 Hz, 1H), 3.46 (s, 3H), 2.75 (d, *J* = 4.5 Hz, 3H). MS (ESI+) m/z 284.0, 286.0 $(M+H)^+$.

4-Bromo-*N*-cyclopropyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69d). A solution of **76** (1 g, 3.69 mmol) in DMSO (18.5 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (HATU, 1.543 g, 4.06 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (2 mL, 11.45 mmol). The resulting mixture was stirred at ambient temperature for 5 min and was then treated with cyclopropanamine (0.3 mL, 4.33 mmol). The resulting mixture was stirred at ambient temperature overnight. Water (80 mL) was added to the reaction mixture, inducing precipitation of a light yellow solid. The solid was collected by filtration, rinsed with 300 mL of water and 50 mL of heptanes, and dried in a vacuum oven at 65 °C to provide the title compound (0.966 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.45 (d, *J* = 3.9 Hz, 1H), 7.59 (s, 1H), 6.85 (s, 1H), 3.50 (s, 3H), 2.84 (tq, *J* = 7.8, 3.9 Hz, 1H), 0.72 (td, *J* = 6.9, 4.9 Hz, 2H), 0.56 (m, 2H). MS (ESI+) m/z 309.9 $(M+H)^+$.

4-Bromo-6-methyl-7-oxo-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69e). To a solution of **76** (3 g, 11.07 mmol) in DCM (56 mL) was added oxalyl chloride (4.21 g, 33.2 mmol) under nitrogen, followed by dropwise addition of DMF (0.162 g, 2.213 mmol). The mixture was stirred at rt for 1 h and concentrated. The residue was azeotroped three more times with DCM, then the residue was dissolved in DCM (56 mL). 1,1,1-Trifluoro-2-methylpropan-2-amine (2.81 g, 22.13 mmol) was added followed by addition of triethylamine (3.36 g, 33.2 mmol). The reaction was stirred for 2 h, then quenched with water. The reaction mixture was partitioned between DCM and water. The aq layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried

over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel and eluted with (hexane/THF=3/1) to give the title compound (630 mg, 15%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (s, 1H), 7.10 (s, 1H), 3.61 (s, 3H), 1.69 (s, 6H). MS (ESI+) m/z 382.0, 382.0 $(M+H)^+$.

4-Bromo-*N*-(2,2-difluoro-1-methylcyclopropyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (69f). To a solution of **75** (200 mg, 0.738 mmol) in DCM (7.4 mL) was added oxalyl chloride (281 mg, 2.213 mmol) under nitrogen, followed by dropwise addition of DMF (10.79 mg, 0.148 mmol). The mixture was stirred at rt for 3 h and concentrated. The residue was azeotroped three more times with DCM, then the residue was dissolved in THF (7.40 mL). (+/-)-2,2-Difluoro-1-methylcyclopropylamine hydrochloride (159 mg, 1.107 mmol) was added, followed by addition of *N,N*-diisopropylethylamine (954 mg, 7.38 mmol). The reaction was stirred for 24 h, then quenched with water. The reaction mixture was partitioned between DCM and water. The aq layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with hexane/THF=1/9 to give the title compound (160 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.69 (s, 1H), 8.89 (d, J = 2.5 Hz, 1H), 7.60 (s, 1H), 6.92 (d, J = 1.6 Hz, 1H), 3.49 (s, 3H), 1.68 (ddt, J = 23.1, 12.5, 8.6 Hz, 2H), 1.45 (d, J = 2.2 Hz, 3H). MS (ESI+) m/z 359.9, 361.9 $(M+H)^+$.

***N*-ethyl-6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (70a).** A 1-L three-necked round bottom flask was charged with dried potassium acetate (17.18 g, 175 mmol), **69a** (17.4 g, 58.4 mmol), bis(pinacolato)diboron (29.6 g, 117 mmol), XPhos Pd precatalyst (G2) (1.837 g, 2.335 mmol), and XPhos (1.113 g, 2.335 mmol) and placed under nitrogen. Degassed anhydrous 2-Me THF (500

mL) was added and the mixture was heated at 75 °C overnight. The mixture was cooled to ambient temperature, diluted with water and ethyl acetate and the biphasic mixture was stirred for about one h with 1.2 g (3.0 equiv. based on moles of palladium) of ammonium pyrrolidine dithiocarbamate. The mixture filtered through a plug of Celite® with ethyl acetate and 10% MeOH/EtOAc washes. The filtrate was diluted further with ethyl acetate and brine, the layers were separated and the organic layer was washed with water and brine, dried with sodium sulfate, filtered, concentrated and triturated with 300 mL of 20% EtOAc/heptane. The dried solids provided the title compound (17.4 g, 86%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.39 (t, J = 5.3 Hz, 1H), 7.56 (s, 1H), 7.06 (d, J = 1.8 Hz, 1H), 3.55 (s, 3H), 3.28 (td, J = 7.3, 5.3 Hz, 2H), 1.31 (s, 12H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 155.6, 134.0, 134.1, 131.9, 124.4, 107.4, 83.7, 36.2, 34.2, 25.1, 15.0. HRMS (m/z): $(M+H)^+$ calcd for C17H24BN3O4, 346.1933; found, 346.1935.

***N*-(tert-butyl)-6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (70b).** A mixture of anhydrous potassium acetate (26.6 g, 271 mmol), **69b** (29.5 g, 90 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (45.9 g, 181 mmol), chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (2.85 g, 3.62 mmol), and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (1.725 g, 3.62 mmol) was degassed under a stream of nitrogen. To this mixture was added degassed anhydrous 2-methyltetrahydrofuran (1 L). The resulting yellow slurry was heated at 80 °C overnight. The reaction mixture was cooled to ambient temperature and then diluted with water (500 mL) and ethyl acetate (500 mL) and stirred for 90 min with 1.8 g. (3.0 equivalents based on moles of palladium) of ammonium pyrrolidine dithiocarbamate. The resulting mixture was filtered through diatomaceous earth and

the diatomaceous earth pad was rinsed with ethyl acetate. The filtrate was washed with brine. The organic layer was mixed with about 20 g SiliaMetS Thiol® (a thiol attached on silica via an alkyl chain, a palladium scavenger from Silicycle), and this mixture was stirred for one h. The mixture was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Grace Reveleris X2 MPLC using a Teledyne-Isco RediSep Rf Gold 750 g silica gel column, eluting with 50% to 60% to 70% to 80% ethyl acetate/heptane to provide the title compound. This material was sonicated in 250 mL of 20 % ethyl acetate/heptane. The solid was collected by filtration, washed with 20% ethyl acetate/heptane, and dried to provide the title compound (17.6 g, 52% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.24 (s, 1H), 7.85 (s, 1H), 7.53 (s, 1H), 7.01 (d, J = 1.2 Hz, 1H), 3.54 (s, 3H), 1.36 (s, 9H), 1.28 (s, 12H). MS (ESI+) m/z 374.1 $(M+H)^+$.

6-Methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (70c). To a solution of **69e** (630 mg, 1.657 mmol) and bis(pinacolato)diboron (1262 mg, 4.97 mmol) in dioxane (16 mL) was added KOAc (488 mg, 4.97 mmol), $Pd_2(dba)_3$ (76 mg, 0.083 mmol) and X-Phos (39.5 mg, 0.083 mmol). The mixture was heated at 80 °C for 18 h under nitrogen, then cooled to ambient temperature. The reaction mixture was partitioned between EtOAc and water, the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel and eluted with (hexane/THF =3/1) to give the title compound (350 mg, 49%) as a yellow solid. MS (ESI+) m/z 428.2 $(M+H)^+$.

***N*-(2,2-difluoro-1-methylcyclopropyl)-6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (70d).** A flask was charged with dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.095 g, 0.200 mmol), potassium acetate (0.654 g, 6.66 mmol), $Pd_2(dba)_3$ (0.046 g, 0.050 mmol), **69f** (0.6 g, 1.666 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.269 g, 5.00 mmol) in dioxane (8.33 mL) and sparged with argon for 15 min. The mixture was then heated under nitrogen for 18 h at 80 °C, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), treated with 3-mercaptopropyl functionalized silica gel, filtered and concentrated. Purification by chromatography (silica gel, 25-60% of 3:1 ethyl acetate/ethanol in heptanes) afforded the title compound (0.37 g, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.82 (d, J = 2.2 Hz, 1H), 7.54 (s, 1H), 7.08 (s, 1H), 3.53 (s, 3H), 1.74 – 1.58 (m, 2H), 1.44 (d, J = 2.4 Hz, 3H), 1.30 (s, 12H). MS (ESI+) m/z 408.1 $(M+H)^+$.

4-Fluoro-2,6-dimethylphenol (72). An oven-dried 1-L 3-neck flask with addition funnel and an internal temp probe was charged with 2-bromo-5-fluoro-1,3-dimethylbenzene (**71**) (25 g, 123 mmol) and THF (300 mL). The flask was cooled to -78 °C and the addition funnel was charged with *n*-BuLi (59.1 mL, 148 mmol) via canula. The *n*-BuLi solution was then added dropwise to the aryl bromide at such a rate to keep the internal temp at or below -75 °C. After stirring for 2 h, trimethyl borate (16.51 mL, 148 mmol) was added and the mixture stirred for 3 h. The cooling bath was removed, and the mixture allowed to warm to rt After 4 h, the flask was placed in a -10 °C bath and a premixed (for 20 min at -10 °C) solution of NaOH (7.39 g, 185 mmol), and 30% aqueous hydrogen peroxide (201 mL, 1970 mmol) was added slowly via addition funnel. Once the addition was complete the mixture was stirred at rt overnight. The pH was adjusted to pH 0-1

with 2 M HCl. The mixture was diluted with 400 mL of Et_2O and 200 mL of water and shaken in a separatory funnel. The aqueous layer was extracted 3x with Et_2O and the combined organics were washed with saturated $NaHCO_3$ and saturated NaS_2O_3. The organic phase should be checked for peroxides, and if peroxides are present, the Et_2O layer should be stirred with a saturated aqueous NaS_2O_5 solution (200 mL) for 15 min. The organic layer should be checked for peroxides again and the process repeated until no more peroxides can be detected in the organic layer. The layers were then separated, and the organic layer was dried with $MgSO_4$, filtered and concentrated to provide an orange oil, 21.5g. The oil was taken up in 1/1 Et_2O/pentane and flushed through a silica plug. White crystals began to crash out of the filtrate. After concentration, the precipitate was collected and dried to provide the title compound (11.47 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 6.72 (d, J = 9.2 Hz, 2H), 2.13 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d6) δ 155.7 (d, J = 233.8 Hz), 126.6 (d, J = 8.2 Hz), 114.3 (d, J = 22.1 Hz), 17.0 (d, J = 1.3 Hz). HRMS (m/z): $(M-H)^-$ calcd for C8H9FO, 139.0565; found, 139.0565.

Methyl 3-bromo-4-(4-fluoro-2,6-dimethylphenoxy)benzoate (74). To a solution of **72** **(**1.86 g, 13.27 mmol) and methyl 3-bromo-4-fluorobenzoate **73** (2.1 mL, 14.2 mmol) in DMSO (14 mL) was added cesium carbonate (6.49 g, 19.91 mmol). The mixture was heated at 80 °C for 2 h, cooled, and diluted with water (100 mL), then extracted with methyl tert-butyl ether (200 mL). The aqueous phase was extracted with additional portions (2 x 100 mL) of methyl tert-butyl ether. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by chromatography (silica gel, eluting with 0-25% ethyl acetate/heptanes) to provide the title compound (4.56 g, 97%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 8.19 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 8.7, 2.1 Hz, 1H), 7.08 (dt, J = 9.1, 0.7 Hz, 2H), 6.49 (d, J = 8.7 Hz, 1H), 3.81 (s, 3H), 2.02 (t, J = 0.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.1, 159.7

(d, J = 241.7 Hz), 157.4, 146.6 (d, J = 2.6 Hz), 134.9, 133.0 (d, J = 9.2 Hz), 131.3, 125.2, 116.1 (d, J = 23.1 Hz), 114.2, 110.8, 52.8, 16.1 (d, J = 1.2 Hz). HRMS (m/z): $(M+H)^+$ calcd for C16H14BrFO3, 353.0183; found, 353.0188.

2-(3-Bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)propan-2-ol (75). A flask containing a solution of **74** (2.49 g, 7.05 mmol) in THF (28 mL) was placed in a water bath, and then treated with 3 M methylmagnesium bromide in THF (7 mL, 21 mmol). After 30 minutes, the mixture was quenched by addition of 100 mL of aqueous ammonium chloride and partitioned with 100 mL of diethyl ether. The organics were washed with water and dried over anhydrous sodium sulfate. After filtration and solvent removal, the crude material was chromatographed (silica cartridge, 0-100 % ethyl acetate/heptanes) to provide the title compound (2.056 g, 83 %). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.73 (d, *J* = 2.2 Hz, 1H), 7.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.27 (d, *J* = 8.6 Hz, 1H), 5.06 (s, 1H), 2.03 (s, 6H), 1.37 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d6) δ 159.4 (d, J = 241.1 Hz), 151.8, 147.3 (d, J = 2.5 Hz), 146.3, 133.2 (d, J = 9.1 Hz), 130.3, 125.8, 115.8 (d, J = 22.9 Hz), 113.4, 110.0, 70.6, 32.2, 16.3. HRMS (m/z): $(M-H)^-$ calcd for C17H18BrFO2, 351.0401; found, 351.0401.

4-Bromo-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (76). A 500 mL round bottom flask was charged with **68** (7.9 g, 17.43 mmol) and dioxane (100 mL). To this solution was added 2 M NaOH (34.9 mL, 69.7 mmol), and the reaction mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was diluted with HCl (0.1 N) to pH 2. 1 N HCl was then added dropwise to lower the pH to about 1. The resulting mixture was stirred vigorously for about one h. The mixture was filtered and the resulting solid was washed with water and dried to provide the title compound (4.44 g, 94 % yield). ^{1}H NMR (400 MHz, DMSO-

d_6) δ 12.95 (bds, 1H), 7.58 (s, 1H), 6.76 (d, J = 2.2 Hz, 1H), 3.48 (s, 3H). MS (DCI/NH_3) m/z 287.8, 289.8 $(M+NH_4)^+$.

Ethyl 6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (77). A flask containing **68 (**8 g, 26.7 mmol), bis(pinacolato)diboron (20.37 g, 80 mmol), X-Phos (0.535 g, 1.123 mmol), $Pd_2(dba)_3$ (0.245 g, 0.267 mmol), and potassium acetate (7.87 g, 80 mmol) in dioxane (100 mL) under nitrogen was heated at 80 °C overnight. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate several times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was triturated with 3:7 ethyl acetate/heptanes to give 7.4 g of the title compound. The filtrate was then concentrated and purified by flash column chromatography on silica gel eluting with 70% ethyl acetate/heptanes to give another 1.0 g of material. (combined yield 8.4 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.55 (s, 1H), 7.06 (d, J = 2.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.52 (s, 3H), 1.30 (d, J = 7.1 Hz, 3H), 1.27 (s, 12H). MS (ESI+) m/z 347.1 $(M+H)^+$.

***N*-ethyl-6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (78).** A mixture of **68** (1.5 g, 3.31 mmol), bis(pinacolato)diboron (1.681 g, 6.62 mmol), potassium acetate (0.812 g, 8.27 mmol), $Pd_2(dba)_3$ (0.152 g, 0.165 mmol) and 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.158 g, 0.331 mmol) in degassed dioxane (15 mL) was stirred at 90 °C for 16 h under an argon atmosphere. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was

purified on a Grace Reveleris X2 MPLC using a Resolutions Systems Apogee-HE 330 g silica gel column eluting with 30% to 40% to 50% EtOAc/heptanes, providing the title compound (1.5 g, 3 mmol, 91 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 – 8.23 (m, 2H), 7.84 (s, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.14 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.30 (s, 3H), 2.40 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.28 (s, 12H). MS (ESI+) m/z 501.1 $(M+H)^+$.

(Z)-Ethyl 3-(5-bromo-2-methoxy-3-nitropyridin-4-yl)-2-hydroxyacrylate (80). A solution of 5-bromo-2-methoxy-4-methyl-3-nitropyridine **79**[18] (8.0 g, 13.83 mmol), diethyl oxalate (18.49 mL, 135 mmol) and potassium ethoxide (9.12 g, 108 mmol) in diethyl ether (250 mL) and ethanol (25 mL) was heated at 45 °C for 24 h. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with petroleum ether/EtOAc = 10/1 to give the title compound (8.0 g, 15%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 4.46 – 4.33 (m, 4H), 4.05 (s, 3H), 1.41 (t, J =7.1 Hz, 3H). MS (ESI+) m/z 347.0, 349.0 $(M+H)^+$.

Ethyl 4-bromo-7-methoxy-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (81). A mixture of **80** (10 g, 28.8 mmol) and iron (8.04 g, 144 mmol) in ethanol (70 mL) and acetic acid (70 mL) was heated at 100 °C for 1 h. The solids were filtered off, and then washed with additional ethyl acetate. The filtrates were concentrated under reduced pressure and the residue was washed with ethyl acetate several times to give the title compound (4.8 g, 55%) as a pale solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 7.86 (s, 1 H), 7.17 (d, J = 2 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.09 (s, 3 H), 1.43 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 299.0, 301.0 $(M+H)^+$.

Ethyl 1-benzyl-4-bromo-7-methoxy-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (82). A solution of **81** (5 g, 16.72 mmol) in DMF (60 mL) was treated with NaH (0.802 g, 20.06 mmol). The solution was stirred at rt for 10 min. To this solution was added benzyl bromide (2.088 mL, 17.55 mmol). The reaction mixture was stirred for another 2 h. It was partitioned between brine (1 L) and ethyl acetate (1 L). The aqueous layer was extracted with additional ethyl acetate once (200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the title compound (6.88 g, 91%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.29 – 7.19 (m, 2H), 7.23 – 7.13 (m, 2H), 6.92 (m, 2H), 6.04 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.29 – 1.12 (m, 3H). MS (ESI+) m/z 389.1, 391.0 $(M+H)^+$.

Ethyl 1-benzyl-4-bromo-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (83). To a solution of **82** (6.3 g, 16.19 mmol) in dioxane (60 mL) was added HCl (4 M in dioxane). The reaction mixture was stirred at 45 ℃ for 16 h. The reaction mixture was cooled to ambient temperature and concentrated. The residue was triturated with diethyl ether, filtered, and rinsed with additional diethyl ether and dried to provide ethyl 1-benzyl-4-bromo-7-hydroxy-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (5.61 g, 83%) as a pale solid. MS (ESI+) m/z 375.1, 377.1 $(M+H)^+$. A solution of ethyl 1-benzyl-4-bromo-7-hydroxy-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (5.16 g, 13.75 mmol) in DMF (100 mL) at rt was treated with NaH (0.660 g, 16.50 mmol) and the mixture was stirred at rt for 30 min. Iodomethane (1.032 mL, 16.50 mmol) was added into the reaction, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel

eluting with 20-40% ethyl acetate in hexanes to give the title compound (4.23 g, 65 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.27 – 7.19 (m, 2H), 7.19 – 7.12 (m, 1H), 6.98 – 6.90 (m, 3H), 6.23 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.45 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 389.0, 391.0 $(M+H)^+$.

Ethyl 1-benzyl-6-methyl-7-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (84). A mixture of **83** (2 g, 5.14 mmol), bis(pinacolato)diboron (2.61 g, 10.28 mmol), potassium acetate (1.109 g, 11.30 mmol), $Pd_2(dba)_3$ (0.235 g, 0.257 mmol) and X-phos (0.245 g, 0.514 mmol) in dioxane (50 mL) was stirred at 90 °C for 16 h under argon atmosphere. The mixture was filtered through Celite®, washed with ethyl acetate several times and concentrated. The residue was purified by silica gel chromatography (eluted with 1/1 PE/EtOAc to 1/3 to afford the title compound (1.15 g, 40%) as a pale solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.30 – 7.14 (m, 4H), 6.93 (dd, J = 7.1, 1.8 Hz, 2H), 6.27 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.52 (s, 3H), 1.32 (s, 12H), 1.24 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 3.3 Hz, 2H). MS (ESI+) m/z 437.2 $(M+H)^+$.

Ethyl 1-benzyl-4-(2-fluoro-5-(methylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (85). A mixture of 2-bromo-1-fluoro-4-(methylsulfonyl)benzene (0.7 g, 2.77 mmol), **84** (1.327 g, 3.04 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.095 g, 0.324 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.076 g, 0.083 mmol), and potassium phosphate (1.468 g, 6.91 mmol) in dioxane (8 mL) and water (2 mL) was degassed and back-filled with nitrogen several times. The reaction was heated at 60 °C overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate,

filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 40% ethyl acetate in heptanes to give the title compound (1.23 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 – 7.96 (m, 2H), 7.69 – 7.58 (m, 2H), 7.29 – 7.15 (m, 3H), 7.02 – 6.95 (m, 2H), 6.86 (d, J = 3.0 Hz, 1H), 6.29 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.54 (s, 3H), 3.27 (s, 3H), 1.18 (t, J = 7.1 Hz ,3H). MS (ESI+) m/z 481.3 $(M+H)^+$.

Ethyl 4-(2-fluoro-5-(methylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (86). A mixture of **85** (1.25 g, 2.59 mmol), anisole (0.56 g, 5.18 mmol), and H_2SO_4 (1.105 mL, 20.72 mmol) in TFA (20 mL) was heated at 90 °C for 2 hours. TFA was removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was triturated with 1:1 ethyl acetate/hexanes to give the title compound (0.85 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.07 – 7.94 (m, 2H), 7.62 (dd, J = 10.1, 8.6 Hz, 1H), 7.54 (s, 1H), 6.73 (dd, J = 3.0, 2.1 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.57 (s, 3H), 3.27 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 393.0 $(M+H)^+$.

Ethyl 4-(2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (87). A mixture of **86** (0.405 g, 1.032 mmol), 2,4-difluorophenol (0.161 g, 1.239 mmol), and cesium carbonate (0.404 g, 1.239 mmol) in DMSO (5 mL) was heated at 110 °C overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 1:100 MeOH/ethyl acetate to give the title compound (0.44 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ

12.92 (s, 1H), 7.99 (d, *J* = 2.44 Hz, 1H), 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.72 – 7.46 (m, 2H), 7.37 (td, *J* = 9.2, 5.6 Hz, 1H), 7.16 (dddd, *J* = 9.4, 8.2, 3.1, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.89 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.60 (s, 3H), 3.27 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). MS (ESI+) m/z 503.0 $(M+H)^+$.

4-(2-(2,4-Difluorophenoxy)-5-(methylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (88). A mixture of **87** (0.45 g, 0.896 mmol) and 2 N sodium hydroxide (2.239 mL, 4.48 mmol) in dioxane (10 mL) was heated at 90 °C for three h. After cooling, the reaction mixture was partitioned between 1 N HCl and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to afford the title compound (0.40 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.94 – 7.82 (m, 1H), 7.56 – 7.46 (m, 1H), 7.48 (s, 1H), 7.35 (td, *J* = 9.3, 5.7 Hz, 1H), 7.15 (tdd, *J* = 9.2, 3.0, 1.6 Hz, 1H), 6.98 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.81 (s, 1H), 3.56 (s, 3H), 3.24 (s, 3H). MS (ESI+) m/z 472.2 $(M+H)^+$.

Ethyl 4-(5-(ethylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (90). A 250 mL round-bottomed flask was charged with **78** (2.2053 g, 4.86 mmol), 2-(5-(ethylsulfonyl)-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **89**[53] (1.681 g, 5.35 mmol), potassium phosphate (2.58 g, 12.16 mmol), $Pd_2(dba)_3$ (0.134 g, 0.146 mmol) and 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (0.166 g, 0.569 mmol). The solids were sparged with N_2 for 1 h. Degassed dioxane (19.46 mL) and water (4.86 mL) were added, and the reaction mixture was heated to 60 °C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was

loaded onto a 80 g silica gel column and purified by flash chromatography eluting with a gradient of 20-70% (3:1 EtOAc:EtOH):heptanes over 20 min to provide the title compound (2.51 g, 92%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (m, 2H), 7.98 (dp, J = 7.3, 2.5 Hz, 2H), 7.85 (s, 1H), 7.65 (m, 1H), 7.52 (m, 2H), 6.92 (d, J = 3.1 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.53 (s, 3H), 3.36 (d, J = 7.4 Hz, 2H), 2.43 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.14 (dt, J = 11.6, 7.2 Hz, 3H). MS (ESI+) m/z 561.0 $(M+H)^+$.

***N*-Ethyl-4-(5-(ethylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (91a).** A mixture of **90** (2.05 g, 3.66 mmol), and sodium hydroxide (7.31 mL, 14.63 mmol) in dioxane (15 mL) was heated at 90 °C for 2 h. The reaction mixture was partially concentrated, then quenched with 0.1 N HCl. The solid was collected by filtration to give 4-(5-(ethylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (1.32 g, 3.49 mmol, 95 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.10 (s, 1H), 12.81 (s, 1H), 8.02 (dd, J = 6.9, 2.4 Hz, 1H), 7.97 (ddd, J = 8.5, 4.6, 2.4 Hz, 1H), 7.66 (dd, J = 10.0, 8.6 Hz, 1H), 7.57 (s, 1H), 6.73 (d, J = 2.7 Hz, 1H), 3.60 (s, 3H), 3.39 (q, J = 7.3 Hz, 2H), 1.15 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 379.1 $(M+H)^+$.

A mixture of 4-(5-(ethylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (1.42 g, 3.75 mmol), oxalyl chloride (0.657 mL, 7.51 mmol), and DMF (0.058 mL, 0.751 mmol) in DCM (50 mL) was stirred at rt for 2 h. The solvent was removed, and the residue was dissolved in THF (20 mL) and DMF (10 mL). To this solution was added ethanamine (22.52 mL, 22.52 mmol). The reaction mixture was stirred at rt for another 2 h. The solvent was removed, and residue was subjected to aqueous workup followed by flash chromatography to give the title compound (1.36 g, 89 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.42 (t, J = 5.4 Hz, 1H), 8.02 – 7.90 (m, 2H), 7.64 (dd, J = 10.0, 8.6 Hz, 1H), 7.52

(s, 1H), 6.74 (d, *J* = 2.8 Hz, 1H), 3.57 (s, 3H), 3.36 (q, *J* = 7.3 Hz, 2H), 3.24 (qd, *J* = 7.2, 5.2 Hz, 2H), 1.10 (dt, *J* = 11.2, 7.3 Hz, 6H). MS (ESI+) m/z 406.1 $(M+H)^+$.

4-(5-(Cyclopropylsulfonyl)-2-fluorophenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (91b). To a slurry of **99** (590 mg, 1.511 mmol) in DCM (15 mL) was added 1 drop of DMF and oxalyl chloride (0.397 mL, 4.53 mmol). The reaction mixture was stirred at rt for 3 h, and concentrated. The residue was dissolved in THF (15 mL), 2 M ethanamine in THF (3.78 mL, 7.56 mmol) was added and the mixture was stirred at rt for 1 h. The reaction mixture was partitioned with ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried with anhydrous sodium sulfate, filtered and concentrated to provide the title compound (0.582 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.38 (t, *J* = 5.4 Hz, 1H), 8.06 – 7.94 (m, 2H), 7.67 (dd, *J* = 9.9, 8.6 Hz, 1H), 7.55 (s, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 3.60 (s, 3H), 3.27 (qd, *J* = 7.2, 5.3 Hz, 2H), 2.98 (tt, *J* = 7.8, 4.8 Hz, 1H), 1.27 – 1.16 (m, 2H), 1.19 – 1.09 (m, 3H), 1.08 (ddt, *J* = 6.2, 5.0, 2.5 Hz, 2H). MS (ESI+) m/z 418.0 $(M+H)^+$.

Ethyl 4-(2-(2,4-difluorophenoxy)-5-(ethylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (92). A mixture of **90** (0.561 g, 1 mmol), 2,4-difluorophenol (0.156 g, 1.200 mmol), and cesium carbonate (0.391 g, 1.200 mmol) in DMSO (5 mL) was heated at 110 °C for 16 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 100:5 ethyl acetate/MeOH to give the title compound (0.41 g, 79%). MS (APCI+) m/z 517.4 $(M+H)^+$.

4-(2-(2,4-Difluorophenoxy)-5-(ethylsulfonyl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (93). A mixture of **92** (0.41 g, 0.794 mmol), 2 N sodium hydroxide (1.191 mL, 2.381 mmol) solution, and dioxane (5 mL) was heated at 90 °C for 3 h. The reaction mixture was partitioned between 0.1 N HCl solution and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give the title compound (0.375 g, 97 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 12.65 (s, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.46 (s, 1H), 7.35 (td, J = 9.2, 5.6 Hz, 1H), 7.13 (tdd, J = 9.3, 3.1, 1.5 Hz, 1H), 6.98 (dd, J = 8.5, 1.0 Hz, 1H), 6.79 (s, 1H), 3.55 (s, 3H), 3.31-3.33 (m, 2H), 1.11 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 489.1 $(M+H)^+$.

Cyclopropyl(4-fluorophenyl)sulfane (95). Cesium carbonate (33.0 g, 101 mmol) was added to a solution of 4-fluorobenzenethiol **94** (10 g, 78 mmol) and bromocyclopropane (12.27 g, 101 mmol) in DMSO (150 mL) and the solution was stirred at 70 °C for 4 days. The inorganic salts were filtered off and the filtrate was partitioned between diethyl ether (500 mL) and water (500 mL). The water layer was subsequently extracted with diethyl ether (3 X 250 mL). The combined extracts were washed with water (2 X 500 mL), saturated brine solution, dried with magnesium sulfate, filtered and evaporated to afford the title compound (11 g, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 2H), 7.05 – 6.94 (m, 2H), 2.17 (tt, J = 7.4, 4.3 Hz, 1H), 1.10 – 0.97 (m, 2H), 0.72 – 0.64 (m, 2H).

1-(Cyclopropylsulfonyl)-4-fluorobenzene (96). A solution of **95** (1 g, 5.94 mmol) in DCM (20 mL) was cooled to -10 °C. mCPBA (2.65 g, 13.08 mmol) was added portionwise. The cooling bath was removed and the mixture was stirred at rt for 3 h. The solid was filtered off and discarded and the filtrate was partitioned between DCM (100 mL) and water (100 mL). The

organic phase was washed with sodium hydrogen carbonate solution, saturated brine solution, dried (magnesium sulfate), filtered and the resultant solution evaporated to give the title compound (1.1 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (dd, J = 6.4, 2.3 Hz, 1H), 7.97 (ddd, J = 8.7, 4.6, 2.3 Hz, 1H), 7.67 (m, 1H), 2.99 (ddd, J = 7.9, 4.9, 3.1 Hz, 1H), 1.17 (dd, J = 4.7, 2.6 Hz, 2H), 1.07 (m, 2H). MS (ESI+) m/z 201.1 $(M+H)^+$.

2-Bromo-4-(cyclopropylsulfonyl)-1-fluorobenzene (97). A solution of **96** (8 g, 40 mmol) in H_2SO_4 (80 mL, 1501 mmol) was treated with NBS (10.67 g, 59.9 mmol). The reaction mixture was stirred at 30 °C for 2 days. The reaction mixture was poured into ice-water. The solid was collected by filtration, washed with cold water three times, and dried under vacuum to afford the crude material, which was purifided by silica gel chromatography eluting with petroleum ether/ethyl acetate = 5/1 to provide the title compound (11.6 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 6.2, 2.2 Hz, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.29 (dd, J = 14.5, 6.5 Hz, 1H), 2.47 (tt, J = 7.9, 4.8 Hz, 1H), 1.41 – 1.30 (m, 2H), 1.14 – 1.02 (m, 2H). MS (ESI+) m/z 279.0, 281.0, $M+H)^+$.

Ethyl 4-(5-(cyclopropylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (98). A flask with stirbar was charged with **78** (0.8 g, 1.599 mmol), **97** (0.469 g, 1.679 mmol), $Pd_2(dba)_3$ (0.044 g, 0.048 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante (0.047 g, 0.160 mmol) and potassium phosphate (1.188 g, 5.60 mmol) and sparged with argon for 15 min. Meanwhile a solution of 4:1 dioxane/water (4 mL) was sparged with nitrogen for 15 min and transferred by syringe into the reaction vessel under argon. The mixture was stirred for 4 h under argon at 60 °C, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, treated with 3-mercaptopropyl

functionalized silica gel, filtered and concentrated. Purification by chromatography (silica gel, 20-70% 3:1 ethyl acetate/ethanol in heptanes) afforded the title compound (0.86 g, 94%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 8.34 – 8.21 (m, 2H), 7.99 (dtd, J = 7.2, 3.8, 2.4 Hz, 2H), 7.84 (s, 1H), 7.68 – 7.59 (m, 1H), 7.54 – 7.43 (m, 2H), 6.93 (d, J = 2.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.53 (s, 3H), 2.93 (tt, J = 7.9, 4.8 Hz, 1H), 2.43 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.21 – 1.13 (m, 2H), 1.13 – 1.00 (m, 2H). MS (ESI+) m/z 573.0 $(M+H)^+$.

4-(5-(Cyclopropylsulfonyl)-2-fluorophenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (99). To a solution of **98** (0.86 g, 1.502 mmol) in a mixture of dioxane (17.16 mL) / water (12.87 mL) was added lithium hydroxide (0.719 g, 30.0 mmol). The reaction mixture was heated at 90 °C for 1 h, cooled, diluted with ethyl acetate and the pH was adjusted to 3 by addition of aqueous HCl. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (0.59 g, 100%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.82 – 12.78 (m, 1H), 8.01 (dd, J = 6.9, 2.4 Hz, 1H), 7.96 (ddd, J = 8.6, 4.5, 2.5 Hz, 1H), 7.63 (dd, J = 10.0, 8.7 Hz, 1H), 7.55 (s, 1H), 6.71 (dd, J = 2.9, 1.4 Hz, 1H), 3.58 (s, 3H), 2.96 (tt, J = 7.9, 4.8 Hz, 1H), 1.22 – 1.13 (m, 2H), 1.13 – 1.00 (m, 2H). MS (ESI+) m/z 391.0 $(M+H)^+$.

2-Bromo-4-(ethylsulfonyl)-1-(o-tolyloxy)benzene (101a). A 20 mL microwave tube with stir bar was charged with 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene **100a**[53] (1.0608 g, 3.97 mmol), o-cresol (0.430 mL, 4.17 mmol), and cesium carbonate (1.941 g, 5.96 mmol) in DMSO (13.24 mL) to give a yellow suspension. The reaction was stirred at 90 °C overnight. The reaction was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was taken up into DCM and loaded onto a 40 g silica gel column. The

reaction was purified by flash chromatography using an ISCO Companion, 40 g column (10% (3:1 EtOAc:EtOH):heptanes to 70% (3:1 EtOAc:EtOH):heptanes over 20 min) to provide the title compound (1.338 g, 95%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 8.16 (d, J = 2.2 Hz, 1H), 7.79 (dd, J = 8.7, 2.3 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.30 (tdd, J = 7.5, 1.8, 0.7 Hz, 1H), 7.23 (td, J = 7.4, 1.3 Hz, 1H), 7.07 (dd, J = 8.0, 1.3 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 3.34 (m, 2H), 2.12 (s, 3H), 1.10 (t, J = 7.4 Hz, 3H). MS (ESI+) m/z 355.0, 357.0 $(M+H)^+$.

2-(2-Bromo-4-(ethylsulfonyl)phenoxy)-1-methyl-3-(trifluoromethyl)benzene (101b). A mixture of 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene **100a**[53] (0.267 g, 1 mmol), 2-methyl-6-(trifluoromethyl)phenol (0.176 g, 1.000 mmol), and cesium carbonate (0.326 g, 1.000 mmol) in DMSO (3 mL) was heated at 110 °C overnight and then cooled to ambient temperature. The cooled reaction mixture was poured into water (10 mL), then extracted with ethyl acetate (10 mL) three times. The combined organic layers were dried and the solvent was removed on a rotary evaporator. The crude compound was added to a silica gel column and was eluted with ethyl acetate/petroleum ether = 1/5 to afford the title compound (0.35 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 2.2 Hz, 1H), 7.78 – 7.69 (m, 3H), 7.53 – 7.44 (m, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.33 (m, 2H), 2.01 (s, 3H), 1.08 (m, 3H). MS (ESI+) m/z 424.9, 426.9 $(M+H)^+$.

2-Bromo-1-(3,5-dimethylphenoxy)-4-(ethylsulfonyl)benzene (101c). A mixture of cesium carbonate (0.671 g, 2.059 mmol), 3,5-dimethylphenol (0.172 g, 1.404 mmol) and 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene **100a**[53] (0.25 g, 0.936 mmol) in DMF (2.34 mL) under nitrogen was heated at 60 °C for 2 h, cooled and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by chromatography (silica, 0-50% ethyl acetate in heptanes) afforded the title compound (0.30 g, 87%). MS (APCI+) 410.1, 412.1 $(M+H)^+$.

2-(2-Bromo-4-(methylsulfonyl)phenoxy)-1,3-dimethylbenzene (101d). 2-Bromo-1-fluoro-4-(methylsulfonyl)benzene **100b** (1.0 g, 3.95 mmol), 2,6-dimethylphenol (0.628 g, 5.14 mmol) and cesium carbonate (1.931 g, 5.93 mmol) were combined in DMSO (9.88 mL) under nitrogen and heated at 110 °C for 18 h. The reaction mixture was cooled and diluted into 400 mL of water. The resulting solid was collected by filtration, washed with additional water and dried to afford the title compound (1.39 g, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 8.7, 2.3 Hz, 1H), 7.21 (d, J = 6.2 Hz, 2H), 7.19 – 7.12 (m, 1H), 6.52 (d, J = 8.7 Hz, 1H), 3.22 (s, 3H), 2.02 (s, 6H).

2-(2-Bromo-4-(ethylsulfonyl)phenoxy)-5-fluoro-1,3-dimethylbenzene (101e). To a solution of 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene (0.5 g, 1.872 mmol) and **72 (**0.262 g, 1.872 mmol) in DMSO (10 mL) was added Cs_2CO_3 (1.22 g, 3.74 mmol) at rt. The resulting mixture was stirred at 90 °C for 12 h. The reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate (3 x 25 mL), and the combined organics were washed with H_2O and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to give the title compound (0.6 g, 83 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 2.2 Hz, 1H), 7.73 (dd, J = 8.7, 2.3 Hz, 1H), 7.09 (dt, J = 9.2, 0.7 Hz, 2H), 6.59 (d, J = 8.7 Hz, 1H), 3.30 (q, J = 7.3 Hz, 2H), 2.02 (s, 6H), 1.07 (t, J = 7.3 Hz, 3H). MS (DCI/NH_3+) m/z 404.0, 406.0, M+NH_4)$^+$.

2-Bromo-*N*-(2,6-dimethylphenyl)-4-(methylsulfonyl)aniline (103). A flask was charged with 2-bromo-4-(methylsulfonyl)aniline **102** (0.425 g, 1.7 mmol), $Pd_2(dba)_3$ (0.078 g, 0.085 mmol), cesium carbonate (0.831 g, 2.55 mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (0.098 g, 0.170 mmol) and sparged with argon for 15 min. Meanwhile a solution of 4:1 THF/water (10.0 mL) was sparged with nitrogen for 15 min and transferred by syringe into the reaction vessel under argon. 2-Iodo-1,3-dimethylbenzene (0.592 g,

2.55 mmol) was added via syringe. The mixture was stirred for 48 h under argon at 100 °C, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, treated with 3-mercaptopropyl functionalized silica gel, filtered and concentrated. Purification by chromatography (silica gel, 0-50% ethyl acetate in heptanes) afforded the title compound (0.212 g, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H), 7.52 (dd, J = 8.7, 2.2 Hz, 1H), 7.17 (s, 3H), 6.01 (d, J = 8.7 Hz, 1H), 3.10 (s, 3H), 2.07 (s, 6H). MS (ESI+) m/z 354, 356 $(M+H)^+$.

2-(2-Bromobenzyl)-1,3-dimethylbenzene (106).[54] A mixture of (2-bromophenyl)boronic acid **104** (0.402 g, 2 mmol), 2-(bromomethyl)-1,3-dimethylbenzene **105** (0.398 g, 2.000 mmol), $Pd(PPh_3)_4$ (0.069 g, 0.060 mmol), and 2 M sodium carbonate solution (1.1 mL, 2.2 mmol) in EtOH (3 mL), toluene (4 mL), and water (1.8 mL) was subjected to vacuum and nitrogen cycle several times to remove oxygen. The reaction mixture was then heated at 90 °C overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was then extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 1% ethyl acetate in heptanes to give the title compound (0.38 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (dd, J = 7.7, 1.5 Hz, 1H), 7.17 (td, J = 7.4, 1.6 Hz, 1H), 7.16 – 7.06 (m, 2H), 7.07 (d, J = 5.1 Hz, 2H), 6.45 (dd, J = 7.5, 1.9 Hz, 1H), 3.96 (s, 2H), 2.10 (s, 6H).

2-(2-(Ethylcarbamoyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridin-4-yl)-4-(ethylsulfonyl)phenyl trifluoromethanesulfonate (107). A solution of **91** (0.5 g, 1.233 mmol) in DMSO (12 mL) was treated with potassium hydroxide solution (5 M aqueous) (2 mL, 10 mmol) and heated with stirring at 90 °C for 2.25 h. The reaction mixture was cooled to rt, acidified with

2 N HCl solution and exhaustively extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 20 to 100% of a 3:1 mixture of ethyl acetate/ethanol in heptanes. The obtained material was triturated with methanol, filtered and dried in a vacuum oven at 70 °C to provide *N*-ethyl-4-(5-(ethylsulfonyl)-2-hydroxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (0.3 g, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 10.73 (s, 1H), 8.34 (t, *J* = 5.3 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.34 (s, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 6.69 (s, 1H), 3.58 (s, 3H), 3.30 - 3.16 (m, 4H), 1.12 (td, *J* = 7.3, 3.7 Hz, 6H). MS (ESI+) m/z 404.1 $(M+H)^+$.

N-ethyl-4-(5-(ethylsulfonyl)-2-hydroxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (0.1735 g, 0.420 mmol) in DMF (4.3 mL) was treated with *N*-ethyl-*N*-isopropylpropan-2-amine (0.22 mL, 1.26 mmol) and stirred for 10 min. *N,N*-bis(trifluoromethansulfonyl)aniline (0.158 g, 0.441 mmol) was added and the mixture was stirred at ambient temperature for 1 h. Water was added to induce precipitation. The solid was collected by filtration and rinsed with additional water. The solid was dried to provide the title compound (0.2067, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.36 (t, *J* = 5.2 Hz, 1H), 8.15 - 8.07 (m, 2H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 6.71 (s, 1H), 3.60 (s, 3H), 3.47 (q, *J* = 7.3 Hz, 2H), 3.29 - 3.21 (m, 2H), 1.17 (t, *J* = 7.3 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 536.0 $(M+H)^+$.

Ethyl 4-(5-(ethylsulfonyl)-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (108). A mixture of **78** (0.31 g, 0.62 mmol), **101e** (0.2 g, 0.516 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.018 g, 0.06 mmol), $Pd_2(dba)_3$ (0.014 g, 0.015 mmol), and potassium

phosphate (0.274 g, 1.291 mmol) in dioxane (4 mL) and water (1 mL) was degassed and back-filled with nitrogen several times. The reaction mixture was heated at 60 °C for 16 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 90% ethyl acetate in hexanes to give the title compound (0.35 g, 100 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (dd, J = 22.1, 8.5 Hz, 2H), 7.88 (d, J = 2.4 Hz, 1H), 7.81 (m, 2H), 7.50 (m, 3H), 7.04 (d, J = 9.0 Hz, 2H), 6.99 (s, 1H), 6.64 (d, J = 8.7 Hz, 1H), 4.34 (dq, J = 11.7, 7.1 Hz, 2H), 3.55 (s, 3H), 3.28 (d, J = 7.4 Hz, 2H), 2.41 (s, 3H), 2.00 (s, 6H), 1.29 (dt, J = 9.3, 7.1 Hz, 3H), 1.09 (m, 3H). MS (ESI+) m/z 681.0 $(M+H)^+$.

2-(2-Bromo-4-(ethylsulfonyl)phenoxy)-3-methylbenzaldehyde (109). A mixture of 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene **100a**[53] (1.202 g, 4.5 mmol), 2-hydroxy-3-methylbenzaldehyde (1.225 g, 9.00 mmol), and cesium carbonate (2.93 g, 9.00 mmol) in DMSO (10 mL) was heated at 110 °C overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (10-100% EtOAc:heptanes) to provide the title compound (1.62 g, 94%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 9.99 (d, J = 0.6 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 7.82 (ddd, J = 7.6, 1.8, 0.6 Hz, 1H), 7.77 (ddd, J = 7.6, 1.8, 0.8 Hz, 1H), 7.72 (dd, J = 8.7, 2.3 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 3.33 (t, J = 7.4 Hz, 2H), 2.08 (s, 3H), 1.09 (m, 3H).

***N*-Ethyl-4-(5-(ethylsulfonyl)-2-(2-formyl-6-methylphenoxy)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (110).** A mixture of **70a** (0.518 g,

1.500 mmol), **109** (0.575 g, 1.5 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.051 g, 0.176 mmol), $Pd_2(dba)_3$ (0.041 g, 0.045 mmol), and sodium carbonate (0.636 g, 6.00 mmol) in THF (6 mL) and water (1.5 mL) was degassed and back-filled with nitrogen several times. The reaction was heated at 60 °C for 4 h. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was triturated with 1:1 ethyl acetate/hexanes to give the title compound (0.66 g, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.99 (s, 1H), 8.31 (t, J = 5.3 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.75 (ddd, J = 11.3, 8.2, 2.1 Hz, 2H), 7.70 – 7.64 (m, 1H), 7.56 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 6.83 (s, 1H), 6.69 (d, J = 8.7 Hz, 1H), 3.57 (s, 3H), 3.34 – 3.19 (m, 4H), 2.06 (s, 3H), 1.21 – 1.05 (m, 6H). MS (ESI+) m/z 522.1 $(M+H)^+$.

3-Bromo-4-(2,6-dimethylphenoxy)benzoic acid (111). A mixture of methyl 3-bromo-4-fluorobenzoate (**73**) (10.8 g, 46.3 mmol), 2,6-dimethylphenol (6.24 g, 51.1 mmol) and cesium carbonate (16.6 g, 50.9 mmol) in DMSO (95 mL) was heated at 190 °C for 20 h. The mixture was allowed to cool, then poured into 400 mL of brine, acidified with HCl and extracted with 500 mL of ethyl acetate. The organic extracts were washed with brine and dried over anhydrous magnesium sulfate. After filtration, the crude material was adsorbed on silica gel and chromatographed on a 220 g silica cartridge eluting with 10-70 % 3:1 ethyl acetate:ethanol/heptanes to provide the title compound (13.54 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.6, 2.1 Hz, 1H), 7.20 (d, J = 6.3 Hz, 2H), 7.20 – 7.11 (m, 1H), 6.42 (d, J = 8.6 Hz, 1H), 2.03 (s, 6H). MS (DCI/NH_3) m/z 338, 340 $(M+NH_4)^+$.

3-Bromo-4-(2,6-dimethylphenoxy)-*N*-methoxy-*N*-methylbenzamide (112). A 20 mL flask with stirbar was charged with **111** (1.008 g, 3.14 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.74 g, 3.86 mmol), 1*H*-benzo[d][1,2,3]triazol-1-ol hydrate (0.70 g, 4.57 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.51 g, 5.23 mmol) and 4-methylmorpholine (1.4 mL, 12.73 mmol) in DCM (16 mL). The mixture was stirred at ambient temperature for 5.5 h. The mixture was diluted with 40 mL of DCM, washed with water and aqueous sodium bicarbonate and dried over magnesium sulfate. After filtration and solvent removal, the crude material was chromatographed on a 40 g silica cartridge eluting with a gradient of 0-50% EtOAc/heptane to provide the title compound (1.056 g, 92%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.94 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 8.6, 2.1 Hz, 1H), 7.20 (dq, J = 7.6, 0.6 Hz, 2H), 7.15 (dd, J = 8.4, 6.4 Hz, 1H), 6.38 (d, J = 8.6 Hz, 1H), 3.55 (s, 3H), 3.23 (s, 3H), 2.06 (s, 6H). MS (APCI+) m/z 364, 366 $(M+H)^+$.

1-(3-Bromo-4-(2,6-dimethylphenoxy)phenyl)ethanone (113). A 100 mL flask with stirbar was charged with **112** (1.19 g, 3.27 mmol) in THF (24 mL) and sealed. Methylmagnesium chloride, 3.0 M solution in THF (1.4 mL, 4.2 mmol) was added by syringe and the mixture stirred at ambient temperature. After 90 min, the solution was poured into aqueous ammonium chloride and extracted into EtOAc (100 mL). The organics were dried over sodium sulfate. After filtration and solvent removal, the residue was chromatographed on a 40 g silica cartridge eluting with 0-100% EtOAc/heptane to provide the title compound (0.631g, 61%) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 8.6, 2.1 Hz, 1H), 7.17 (dd, J = 7.4, 1.6 Hz, 2H), 7.15 – 7.08 (m, 1H), 6.39 (d, J = 8.6 Hz, 1H), 2.49 (s, 3H), 2.02 (s, 6H). MS (DCI/NH_3) m/z 336, 338 $(M+NH_4)^+$.

2-(3-Bromo-4-(2,6-dimethylphenoxy)phenyl)propan-2-ol (114). To a solution of **113** (0.365 g, 1.144 mmol) in THF (10 mL) was added by syringe methylmagnesium chloride (3.0 M solution in THF, 1 mL, 3.0 mmol), and the mixture was stirred at ambient temperature. After 3.5 h, the solution was partitioned between saturated aqueous ammonium chloride (50 mL) and ethyl acetate (75 mL). The organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0-100% ethyl acetate/heptane) to provide the title compound (0.247 g, 64%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.73 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 2.2 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.10 (dd, J = 8.4, 6.5 Hz, 1H), 6.23 (d, J = 8.5 Hz, 1H), 5.05 (s, 1H), 2.02 (s, 6H), 1.37 (s, 6H). MS (DCI/NH_3) m/z 317, 319 $(M\text{-}H_2O)^+$.

(3-Bromo-4-(2,6-dimethylphenoxy)phenyl)methanol (115). To a solution of **111** (3 g, 8.95 mmol) in DCM (10 mL was added diisobutylaluminum hydride (22.38 mL, 22.38 mmol) dropwise at 0 °C. The mixture was stirred for 4 h at rt. The reaction mixture was quenched with 1 M H_2SO_4 until all of the solid dissolved. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The solvent was evaporated *in vacuo* and purified by flash column chromatography over silica gel (hexane/ethyl acetate from 50/1 to 5/1) to afford the title compound (2.0 g, 73 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, J = 2.0 Hz, 1H), 7.14 - 7.04 (m, 4H), 6.34 (d, J = 8.4 Hz, 1H), 4.61 (s, 2H), 2.13 (s, 6H).

3-Bromo-4-(2,6-dimethylphenoxy)-*N*-ethylbenzamide (116). To a solution of **111** (0.957 g, 2.98 mmol) in DCM (2.4 mL) and DMF (2.4 mL) was added HATU (1.360 g, 3.58 mmol) under nitrogen, followed by dropwise addition of *N*-ethyl-*N*-isopropylpropan-2-amine (5.28 mL, 29.8 mmol). The mixture was stirred at rt for 1 h, then ethanamine hydrochloride (0.729 g, 8.94 mmol) was added. The reaction mixture was stirred at this temperature for 24 h. The reaction

mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel to give the title product (1.008 g, 97 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.53 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.17 – 7.05 (m, 3H), 6.38 (d, *J* = 8.6 Hz, 1H), 6.06 (s, 1H), 3.47 (qd, *J* = 7.2, 5.5 Hz, 2H), 2.11 (s, 6H), 1.24 (t, *J* = 7.2 Hz, 3H).

***N*-Ethyl-4-(2-fluoro-5-nitrophenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (117).** A flask was charged with **70a** (0.25 g, 0.839 mmol), (2-fluoro-5-nitrophenyl)boronic acid (0.233 g, 1.258 mmol), $Pd_2(dba)_3$ (0.038 g, 0.042 mmol), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (0.037 g, 0.126 mmol) and sodium carbonate (0.382 g, 3.61 mmol) and sparged with nitrogen for 30 min. To this were added nitrogen-sparged 1,4-dioxane (4.2 mL) and water (1.05 mL) via syringe. The reaction mixture was stirred at 60 °C for 7 h. The reaction mixture was cooled to ambient temperature and diluted with water to further induce precipitation. The solid was collected by filtration, washed with 75 mL of water and dried overnight in a vacuum oven at 70 °C. The solid was dissolved in a mixture of DCM, methanol and ethyl acetate (7:2:1, 400 mL) with gentle heating at 45 °C. The solution was treated with 3-mercaptopropyl-functionalized silica gel for 20 min, dried over anhydrous magnesium sulfate, filtered through a plug of Celite® and concentrated. The residue was triturated with ethyl acetate. The solid was collected by filtration, rinsed with ethyl acetate and dried overnight in a vacuum oven at 70 °C to afford the title compound (0.22 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1 H), 8.36 (m, 3 H), 7.68 (t, *J* = 9.31 Hz, 1 H), 7.59 (m, 1 H), 6.81 (d,

J = 2.44 Hz, 1 H), 3.60 (s, 3 H), 3.27 (m, 2 H), 1.13 (t, *J* = 7.17 Hz, 3 H). MS (ESI+) m/z 359.1 $(M+H)^+$.

4-(2-(2,6-Dimethylphenoxy)-5-nitrophenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (118). A solution of **117** (0.073 g, 0.204 mmol), 2,6-dimethylphenol (0.037 g, 0.306 mmol) and cesium carbonate (0.133 g, 0.407 mmol) in DMSO (1 mL) was heated at 50 °C for 90 min. After cooling to rt, water was added to induce precipitation. The solid was collected by filtration, washed with 30 mL of water and dried in a vacuum oven at 70 °C to afford the title compound (0.0919 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.36 - 8.29 (m, 2H), 8.20 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.52 (s, 1H), 7.23 - 7.10 (m, 3H), 6.87 (s, 1H), 6.59 (d, *J* = 9.1 Hz, 1H), 3.61 (s, 3H), 3.30 - 3.22 (m, 2H), 2.03 (s, 6H), 1.12 (t, *J* = 7.2 Hz, 3H). MS (ESI+) m/z 461.1 $(M+H)^+$.

4-(5-Amino-2-(2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (119a). A solution of **118** (0.0919 g, 0.200 mmol) in a mixture of THF (1 mL), ethanol (0.5 mL) and water (0.25 mL) was treated with zinc dust (0.196 g, 2.99 mmol) and ammonium chloride (0.107 g, 1.996 mmol) and stirred at ambient temperature for 35 min. The reaction mixture was filtered through Celite® rinsing with 3:1 ethyl acetate / methanol. The filtrate was concentrated to form a solid. The solid was slurried in water, collected by filtration, rinsed with additional water and dried overnight in a vacuum oven at 70 °C to provide the title compound (0.0709 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) d 12.17 (s, 1 H), 8.35 (t, *J* = 5.19 Hz, 1 H), 7.31 (s, 1 H), 7.07 (m, 2 H), 6.99 (m, 1 H), 6.91 (d, *J* = 1.6 Hz, 1 H), 6.70 (d, *J* = 2.44 Hz, 1 H), 6.42 (dd, *J* = 8.54, 2.75 Hz, 1 H), 6.08 (d, *J* = 8.54 Hz, 1 H), 4.78 (s, 2 H), 3.58 (s, 3 H), 3.26 (m, 2 H), 2.00 (s, 6 H), 1.12 (t, *J* = 7.17 Hz, 3 H). MS (ESI+) m/z 431.1 $(M+H)^+$.

4-(5-Amino-2-(4-fluoro-2,6-dimethylphenoxy)phenyl)-*N*-ethyl-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxamide (119b). A 20-mL microwave tube was charged with **122** (0.5043 g, 1.626 mmol), **70a (**0.510 g, 1.478 mmol), sodium carbonate (0.548 g, 5.17 mmol), $Pd_2(dba)_3$ (0.068 g, 0.074 mmol), and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (0.073 g, 0.251 mmol). The solids were flow purged with nitrogen for 30 min. Degassed THF (11.82 mL) and water (2.96 mL) were added. The reaction mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to rt and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography using an ISCO Companion, 24 g column (10% (3:1 EtOAc:EtOH):heptanes to 70% (3:1 EtOAc:EtOH):heptanes over 20 min, then to 100% (3:1 EtOAc:EtOH) over 5 min, then 3:1 EtOAc:EtOH for 30 min to provide the title compound (0.589 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.33 (t, J = 5.4 Hz, 1H), 7.28 (s, 1H), 6.95 - 6.84 (m, 3H), 6.67 (d, J = 2.7 Hz, 1H), 6.42 (dd, J = 8.7, 2.8 Hz, 1H), 6.08 (d, J = 8.7 Hz, 1H), 4.79 (s, 2H), 3.56 (s, 3H), 3.31 - 3.19 (m, 2H), 1.98 (d, J = 5.8 Hz, 6H), 1.10 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 449.1 $(M+H)^+$.

2-(2-Bromo-4-nitrophenoxy)-5-fluoro-1,3-dimethylbenzene (121). A microwave tube was charged with 2-bromo-1-fluoro-4-nitrobenzene **120** (1.088 g, 4.95 mmol), **72 (**0.728 g, 5.19 mmol), and cesium carbonate (2.418 g, 7.42 mmol) in DMSO (16.49 mL) to give an orange suspension. The reaction mixture was stirred at 90 °C overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was taken up into DCM and loaded onto a 40 g silica gel column. The reaction mixture was purified by flash chromatography using an ISCO Companion,

40 g column (100% heptanes to 50% (3:1 EtOAc:EtOH):heptanes over 20 min) to provide the title compound (1.44 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 2.7 Hz, 1H), 8.13 (dd, J = 9.1, 2.8 Hz, 1H), 7.12 (d, J = 9.1 Hz, 2H), 6.59 (d, J = 9.1 Hz, 1H), 2.04 (s, 6H).

3-Bromo-4-(4-fluoro-2,6-dimethylphenoxy)aniline (122). A 250-mL round-bottomed flask was charged with **121** (1.4384 g, 4.23 mmol) in ethanol (38.4 mL) and water (3.84 mL) to give a yellow solution. Iron powder (1.181 g, 21.14 mmol) and ammonium chloride (1.131 g, 21.14 mmol) were added. The flask was fitted with a reflux condenser and heated to 90 °C for 2.5 h. The reaction mixture was filtered through a 2 g Celite® SPE column and rinsed with ethyl acetate. The filtrate was made basic (pH 10) using saturated sodium bicarbonate solution and was then extracted 2x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound (1.24 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 2.6 Hz, 1H), 6.39 (dd, J = 8.7, 2.6 Hz, 1H), 6.06 (d, J = 8.7 Hz, 1H), 4.94 (s, 2H), 2.03 (s, 6H).

4-(2,6-Dimethylphenoxy)-3-nitrobenzenesulfonamide (124). To a stirred solution of 2,6-dimethylphenol (3.33 g, 27.3 mmol) in DMF (25 mL) was added sodium hydride (1.09 g, 27.3 mmol) at 10 °C. After stirring for 15 min, 4-fluoro-3-nitrobenzenesulfonamide **123** (1.5 g, 6.81 mmol) was added. The reaction mixture was stirred at rt for 1.5 h. The reaction mixture was quenched by the addition of 0.5 M HCl until the pH = 6. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (ethyl acetate/petroleum ether = 30/70) to give the title compound (2.0 g, 6.2 mmol, 91 % yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (m, 1H), 7.91 (d, 1H), 7.16 (m, 3H), 6.70 (d, 1H), 5.08 (bds, 2H), 2.14 (s, 6H).

3-Amino-4-(2,6-dimethylphenoxy)benzenesulfonamide (125). A mixture of **124** (2 g, 6.2 mmol) and Pd/C (0.33 g, 0.31 mmol) in methanol (15 mL) and ethyl acetate (15 mL) was stirred under hydrogen (3 atm) at rt for 2 h. The reaction mixture was filtered, concentrated under vacuum and triturated with ethyl acetate and petroleum ether to give the title compound (1.6 g, 5.47 mmol, 88 % yield) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21 (m, 3H), 7.10 (m, 3H), 6.86 (d, 1H), 6.13 (d, 1H), 5.53 (bds, 2H), 2.06 (s, 6H).

4-(2,6-Dimethylphenoxy)-3-iodobenzenesulfonamide (126). A solution of **125** (1.0 g, 3.42 mmol) in dioxane (10 mL) was treated with conc HCl (0.312 mL, 10.26 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. To this solution was added sodium nitrite (0.283 g, 4.10 mmol) in water (1 mL). The reaction mixture was stirred at 0 °C for another 30 min. To this solution was added potassium iodide (1.136 g, 6.84 mmol) in water (2 mL). The reaction mixture was stirred for 1 h at 10 °C. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried, filtered and concentrated. The residue was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate = 10/1 to provide the title compound (1.2 g, 2.98 mmol, 87 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.71 (m, 1H), 7.16 (m, 3H), 6.36 (m, 1H), 4.91 (bds, 2H), 2.10 (s, 6H).

2-(2-Bromo-4-iodophenoxy)-5-fluoro-1,3-dimethylbenzene (128). A mixture of 2-bromo-1-fluoro-4-iodobenzene **127** (3.01 g, 10 mmol), **72 (**1.472 g, 10.5 mmol), and cesium carbonate (3.42 g, 10.5 mmol) in DMSO (20 mL) was heated at 110 °C overnight. After cooling to ambient temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The

residue was purified by column chromatography on silica gel eluting with heptanes to give the title compound (3.21 g, 76% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 8.7, 2.1 Hz, 1H), 7.03 (dt, J = 9.1, 0.8 Hz, 2H), 6.15 (d, J = 8.6 Hz, 1H), 2.00 (s, 6H). MS (APCI+) m/z 419.8, 421.8 $(M+H)^+$.

1-(3-Bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)cyclobutan-1-ol (129a). To a solution of **128** (0.421 g, 1.0 mmol) in hexane (10 mL) at -78 °C was added 1.7 M t-butyllithium (0.647 mL, 1.1 mmol). The reaction mixture was stirred at -78 °C for 1 h. Then toluene (3 mL) was added, and the solution became clear. To this solution was added cyclobutanone (0.105 g, 1.5 mmol) in toluene (1 mL). The reaction mixture was allowed to warm up to ambient temperature slowly overnight. The reaction mixture was quenched with saturated NH_4Cl. It was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate in heptanes to give the title compound (0.086 g, 24% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.71 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 8.5, 2.3 Hz, 1H), 7.05 (dt, J = 9.0, 0.8 Hz, 2H), 6.32 (d, J = 8.5 Hz, 1H), 5.52 (s, 1H), 2.34 (m, 2H), 2.22 (m, 2H), 2.04 (s, 6H), 1.88 (dtt, J = 10.9, 9.5, 5.4 Hz, 1H), 1.61 (m, 1H). MS (APCI+) 347.3, 349.3 $(M-H_2O)^+$.

3-(3-Bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)oxetan-3-ol (129b). A solution of **128** (0.421 g, 1.0 mmol) in hexanes (6 mL) and toluene (3 mL) was cooled to -78 °C. To this solution was added tert-butyllithium (1.7 M in pentane, 0.735 mL, 1.25 mmol) at -78 °C. The reaction was stirred at -78 °C for 1 h. To this solution was added oxetan-3-one (0.144 g, 2 mmol) in toluene (1 mL). The reaction was allowed to warm up to ambient temperature overnight. The

reaction mixture was quenched with saturated NH_4Cl. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate in heptanes to give the title compound (0.049 g, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.6, 2.2 Hz, 1H), 7.06 (d, J = 9.1 Hz, 2H), 6.39 (t, J = 4.3 Hz, 1H), 4.71 (d, J = 6.5 Hz, 2H), 4.63 (d, J = 6.5 Hz, 2H), 2.04 (s, 6H).

4-(3-Bromo-4-(4-fluoro-2,6-dimethylphenoxy)phenyl)tetrahydro-2*H*-pyran-4-ol (129c). A solution of **128** (0.842 g, 2 mmol) in hexanes (20 mL) was cooled to -78 °C. To this solution was added tert-butyllithium (1.7 M in pentane, 1.35 mL, 2.30 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. Then the reaction mixture was allowed to warm to ambient temperature and was stirred at ambient temperature for 1 h. The reaction mixture was cooled back to -78 °C again. To this solution was added dihydro-2*H*-pyran-4(3H)-one (0.2 g, 2 mmol) in toluene (1 mL). The reaction mixture was allowed to warm up to ambient temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 10% ethyl acetate in heptanes) to give the title compound (0.14 g, 18%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.76 (d, J = 2.2 Hz, 1H), 7.30 (dd, J = 8.6, 2.3 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.31 (d, J = 8.6 Hz, 1H), 5.08 (d, J = 1.0 Hz, 1H), 3.77 – 3.54 (m, 4H), 2.6 (s, 6H), 1.89 (td, J = 12.7, 5.2 Hz, 2H), 1.58 (td, J = 12.6, 5.9 Hz, 2H). MS (ESI-) m/z 394.9 $(M-H)^-$.

Ethyl 4-(2-(4-fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (130). A flask charged with **77** (3.506 g, 7.01 mmol), cesium carbonate (3.11 g, 9.55 mmol), $Pd_2(dba)_3$ (65 mg, 0.071 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (84 mg, 0.287 mmol) was sealed and purged with nitrogen for 15 min, followed by addition of a degassed solution of **75** (2.056 g, 5.82 mmol) in THF (40 mL)/ water (10 mL). The mixture was heated at 60 °C for 5 h. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried over anhydrous sodium sulfate. After filtration and solvent removal, the residues were chromatographed on an 80 g silica cartridge eluting with 0-100 % ethyl acetate/heptanes to provide the title compound (3.21g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.30 (m, 2H), 7.69 (s, 1H), 7.53 – 7.44 (m, 4H), 6.97 (d, J = 9.0 Hz, 2H), 6.92 (s, 1H), 6.31 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.56 (s, 3H), 2.41 (s, 3H), 1.98 (d, J = 9.7 Hz, 6H), 1.41 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 647.1 $(M+H)^+$.

4-(2-(4-Fluoro-2,6-dimethylphenoxy)-5-(2-hydroxypropan-2-yl)phenyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylic acid (131). A mixture of **130** (3.21 g, 4.96 mmol) and lithium hydroxide monohydrate (2.13 g, 50.8 mmol) in a mixture of 1,4-dioxane (75 mL) and water (25 mL) was heated at 70 °C for 2 h, then cooled to ambient temperature and adjusted to pH 2-3 with 1 M HCl. The mixture was diluted with 400 mL of ice water, extracted with 2 x 200 mL of methyl tert-butyl ether. The combined organics were dried over anhydrous sodium sulfate. After filtration and solvent removal, the residues were chromatographed on a 40 g HP silica column eluting with 10-100 % 3:1 ethyl acetate:ethanol/heptanes to provide the title compound (1.95g, 85%). ^{1}H NMR (501 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.52 (d, J = 2.4 Hz,

1H), 7.35 (s, 1H), 7.29 (dd, J = 8.6, 2.4 Hz, 1H), 6.96 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 2.1 Hz, 1H), 6.29 (d, J = 8.7 Hz, 1H), 3.58 (s, 3H), 2.00 (s, 6H), 1.42 (s 6H). MS (DCI+) m/z 465.1 $(M+H)^+$.

2-(4-(4-Fluoro-2,6-dimethylphenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (132). A 2 L three-necked flask equipped with mechanical stirrer was charged with a solution of **75** (24 g, 67.9 mmol) in THF (453 mL) and was cooled to -78 °C. nBuLi (2.5 M in hexanes) (82 mL, 204 mmol) was added slowly so that the internal temperature did not exceed -70 °C. The reaction was stirred for 30 min. Neat 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (43.0 mL, 211 mmol) was added and after 10 min, the cold bath was removed and the reaction was allowed to warm up. The reaction was quenched after a total of 1 h by adding saturated aq $NaHCO_3$ and extracted with EtOAc. The crude material was purified via chromatography on a Grace Reveleris X2 MPLC (10-25% EtOAc/heptanes) to provide the title compound (14.4 g, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 2.5 Hz, 1H), 7.31 (dd, J = 8.7, 2.5 Hz, 1H), 6.96 (d, J = 9.1 Hz, 2H), 6.15 (d, J = 8.7 Hz, 1H), 4.90 (s, 1H), 2.01 (s, 6H), 1.34 (s, 6H), 1.27 (s, 12H). MS (ESI+) m/z 383.3 $(M-H_2O)^+$.

Associated Content

Supporting Information

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

Binding affinity of compound **46** for non-BET family bromodomains, additional information on the TR-FRET binding assays including reference agents and representative dose-response curves for compound **46**, X-ray data collection and refinement statistics, electron density maps, HPLC

methods used to asses compound purity and HPLC traces (PDF). Molecular formula strings (CSV).

Accession Codes

Atomic coordinates of BRD4 BD1 bound to compounds **8** (PDB code 5UVW), **18** (PDB code 6VIW) and **27** (PDB code 6VIZ), of BRD4 BD2 bound to compound **18** (PDB code 6VIX), of BRD2 BD1 bound to compound **46** (PDB code 6ONY), and of BRD2 BD2 bound to compound **27** (PDB code 6VIY) and compound **46** (PDB code 6E6J) have been deposited with the Protein Data Bank. Authors will release the atomic coordinates and experimental data upon article publication

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Notes

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‡Former AbbVie employee.

Abbreviations used

BET, Bromodomain and ExtraTerminal; PAPh, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane; PROTAC, proteolysis targeting chimera; ITC, isothermal titration calorimetry; FP, fluorescence polarization; DAST, diethylaminosulfur trifluoride; HATU, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; DIPEA, *N*,*N*-diisopropylethylamine; HOBT, hydroxybenzotriazole; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; NMM, *N*-methylmorpholine; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; Xphos Pd precatalyst G2, Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II); B_2Pin_2, bis(pinacolato)diboron; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; iProBPin, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; TCEP, tris(2-carboxyethyl)phosphine; AR, androgen receptor; MSR, minimum significant ratio; IVIVE, *in vitro* to *in vivo* extrapolation; TPSA, total polar surface area

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References

1) Liu, Z.; Wang, P.; Chen, H.; Wold, E. A.; Tian, B.; Brasier, A. R.; Zhou, J. Drug Discovery Targeting Bromodomain-Containing Protein 4. *J. Med. Chem.* **2017**, *60*, 4533−4558.

2) Romero, F. A.; Taylor, A. M.; Crawford, T. D.; Tsui, V.; Côté, A.; Magnuson, S. Disrupting Acetyl-Lysine Recognition: Progress in the Development of Bromodomain Inhibitors. *J. Med. Chem.* **2016**, *59*, 1271−1298.

3) Filappakopoulos, P., Picaud, S., Mangos, M., Keates, T., Lambert, J-P., Barsyte-Lovejoy, D., Felletar, I., Volkmer, R., Muller, S., Pawson, T., Gingras, A-C., Arrowsmith, C. H., and Knapp, S. Histone Recognition and Large-Scale Structural Analysis of the Human Bromodomain Family" *Cell* **2012**, *149*, 214-231.

4) Love´n, J.; Hoke, H. A.; Lin, C. Y.; Lau, A.; Orlando, D. A.; Vakoc, C. R.; Bradner, J. E.; Lee, T. I.; Young, R. A. Selective Inhibition of Tumor Oncogenes by Disruption of Super-Enhancers. *Cell* **2013**, *153*, 320–334.

5) Brown, J. D.; Lin, C. Y.; Duan, Q.; Griffin, G.; Federation, A. J.; Paranal, R. M.; Bair, S.; Newton, G.; Lichtman, A. H.; Kung, A. L.; Yang, T.; Wang, H.; Luscinskas, F. W.; Croce, K. J.; Bradner, J. E.; Plutzky, J. NF-kB Directs Dynamic Super Enhancer Formation in Inflammation and Atherogenesis. *Mol. Cell*, **2014**, *56*, 219–231.

6) Cochran, A. G.; Conery, A. R.; Simms, R. J. Bromodomains: a New Target Class for Drug Development. *Nat. Rev. Drug Discov.* **2019**, *18*, 609-628.

7) Huang, B.; Yang, X.-D.; Zhou, M.-M.; Ozato, K.; Chen, L.-F. Brd4 Coactivates Transcriptional Activation of NF-B via Specific Binding to Acetylated RelA. *Mol. Cell Biol.* **2009**, *29*, 1375-1387.

8) Gacias, M.; Gerona-Navarro, G.; Plotnikov, A. N.; Zhang, G.; Zeng, L.; Kaur, J.; Moy, G.; Rusinova, E.; Rodriguez, Y.; Matikainen, B.; Vincek, A.; Joshua, J.; Casaccia, P.; Zhou, M.-M. Selective Chemical Modulation of Gene Transcription Favors Oligodendrocyte Lineage Progression. *Chem. Biol.* **2014**, *21*, 841–854.

9) Cheung, K.; Lu, G.; Sharma, R.; Vincek, A.; Zhang, R.; Plotnikov, A. N.; Zhang, F.; Zhang, Q.; Ju, Y.; Hu, Y.; Zhao, L.; Han, X.; Meslamani, J.; Xu, F.; Jaganathan, A.; Shen, T.; Zhu, H.; Rusinova, E.; Zeng, L.; Zhou, J.; Yang, J.; Peng, L.; Ohlmeyer, M.; Walsh, M. J.; Zhang, D. Y.; Xiong, H.; Zhou, M.-M. BET *N*-Terminal Bromodomain Inhibition Selectively Blocks Th17 Cell Differentiation and Ameliorates Colitis in Mice. *Proc. Natl. Acad. Sci. U. S. A* **2017**, *114*, 2952-2959.

10) Shi, J.; Wang, Y.; Zeng, L.; Wu, Y.; Deng, J.; Zhang, Q.; Lin, Y.; Li, J.; Kang, T.; Tao, M.; Rusinova, E.; Zhang, G.; Wang, C.; Zhu, H.; Yao, J.; Zeng, Y.-X.; Evers, B. M.; Zhou, M.-

M.; Zhou, B. P. Disrupting the Interaction of BRD4 with Diacetylated Twist Suppresses Tumorigenesis in Basal-like Breast Cancer. *Cancer Cell* **2014**, *25*, 210-225.

11) Tyler, D. S.; Vappiani, J.; Cañeque, T.; Lam, E. Y. N.; Ward, A.; Gilan, O.; Chan, Y.-C.; Hienzsch, A.; Rutkowska, A.; Werner, T.; Wagner, A. J.; Lugo, D.; Gregory, R.; Ramirez Molina, C.; Garton, N.; Wellaway, C. R.; Jackson, S.; MacPherson, L.; Figueiredo, M.; Stolzenburg, S.; Bell, C. C.; House, C.; Dawson, S.-J.; Hawkins, E. D.; Drewes, G.; Prinjha, R. K.; Rodriguez, R.; Grandi, P.; Dawson, M. A. Click Chemistry Enables Preclinical Evaluation of Targeted Epigenetic Therapies. *Science* **2017**, *356*, 1397-1401.

12) Runcie, A. C.; Zengerle, M.; Chan, K.-H.; Testa, A.; van Beurden, L.; Baud, M. G. J.; Epemolu, O.; Ellis, L. C. J.; Read, K. D.; Coulthard, V.; Brien, A.; Ciulli, A. Optimization of a "Bump-and-hole" Approach to Allele-selective BET Bromodomain Inhibition. *Chem. Sci*. **2018**, *9*, 2452-2468.

13) Lamonica, J. M.; Deng, W.; Kadauke, S.; Campbell, A. E.; Gamsjaeger, R.; Wang, H.; Cheng, Y.; Billin, A. N.; Hardison, R. C.; Mackay, J. P.; Blobel, G. A. Bromodomain Protein Brd3 Associates with Acetylated GATA1 to Promote its Chromatin Occupancy at Erythroid Target Genes. *Proc. Natl. Acad. Sci. U. S. A* **2011**, *108*, E159-E168.

14) Noel, J. K; Iwata, K.; Ooike, S.; Sugahara, K.; Nakamura, H.; Daibata, M. Development of the BET Bromodomain Inhibitor OTX015. *Mol. Cancer Ther*. **2013**, *12(11 Suppl)*, C244. **DOI:** 10.1158/1535-7163.TARG-13-C244.

15) Shapiro, G. I.; Dowlati, A.; LoRusso, P. M.; Eder, J. P.; Anderson, A.; Do, K. T.; Kagey, M. H.; Sirard, C.; Bradner, J. E.; Landau, S. B. Abstract A49: Clinically Efficacy of the BET

Bromodomain Inhibitor TEN-010 in an Open-label Substudy with Patients with Documented NUT-Midline Carcinoma (NMC). *Mol. Cancer Ther.* **2015**, *14*, A49−A49.

16) Nicodeme, E.; Jeffrey, K. L.; Schaefer, U.; Beinke, S.; Dewell, S.; Chung, C.-W.; Chandwani, R.; Marazzi, I.; Wilson, P.; Coste, H.; White, J.; Kirilovsky, J.; Rice, C. M.; Lora, J. M.; Prinjha, R. K.; Lee, K.; Tarakhovsky, A. Suppression of Inflammation by a Synthetic Histone Mimic. *Nature* **2010**, *468*, 1119−1123.

17) Albrecht, B. K.; Gehling, V. S.; Hewitt, M. C.; Vaswani, R. G.; Cote, A.; Leblanc, Y.; Nasveschuk, C. G.; Bellon, S.; Bergeron, L.; Campbell, R.; Cantone, N.; Cooper, M. R.; Cummings, R. T.; Jayaram, H.; Joshi, S.; Mertz, J. A.; Neiss, A.; Normant, E.; O'Meara, M.; Pardo, E.; Poy, F.; Sandy, P.; Supko, J.; Sims, R. J.; Harmange, J.-C.; Taylor, A. M.; Audia, J. E. Identification of a Benzoisoxazoloazepine Inhibitor (CPI-0610) of the Bromodomain and Extra-Terminal (BET) Family as a Candidate for Human Clinical Trials. *J. Med. Chem.* **2016**, *59*, 1330-1339.

18) McDaniel, K. F.; Wang, L.; Soltwedel, T.; Fidanze, S. D.; Hasvold, L. A.; Liu, D.; Mantei, R. A.; Pratt, J. K.; Sheppard, G. S.; Bui, M. H.; Faivre, E. J.; Huang, X.; Li, L.; Lin, X.; Wang, R.; Warder, S. E.; Wilcox, D.; Albert, D. H.; Magoc, T. J.; Rajaraman, G.; Park, C. H.; Hutchins, C. W.; Shen, J. J.; Edalji, R. P.; Sun, C. C.; Martin, R.; Gao, W.; Wong, S.; Fang, G.; Elmore, S. W.; Shen, Y.; Kati, W. M. Discovery of *N*-(4-(2,4-Difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridin-4-yl)phenyl)ethanesulfonamide (ABBV-075/Mivebresib), a Potent and Orally Available Bromodomain and Extraterminal Domain (BET) Family Bromodomain Inhibitor. *J. Med. Chem.* **2017**, *60*, 8369-8384.

19) Gavai, A. V.; Norris, D.; Tortolani, D.; O'Malley, D.; Zhao, Y.; Quesnelle, C.; Gill, P.; Vaccaro, W.; Huynh, T.; Ahuja, V.; Dodd, D.; Mussari, C.; Harikrishnan, L.; Kamau, M.; Tokarski, J. S.; Sheriff, S.; Rampulla, R.; Wu, D.-R.; Li, J.; Zhang, H.; Li, P.; Sun, D.; Yip, H.; Zhang, Y.; Mathur, A.; Zhang, H.; Huang, C.; Yang, Z.; Ranasinghe, A.; D'Arienzo, C.; Su, C.; Everlof, G.; Zhang, L. Discovery of Clinical Candidate BMS-986158, an Oral BET Inhibitor, for the Treatment of Cancer. *Cancer Res.* **2018**, *13(13 Suppl)*: Abstract 5789. **DOI:** 10.1158/1538-7445.AM2018-5789.

20) Liu, P. C. C.; Liu, X. M.; Stubbs, M. C.; Maduskuie, T.; Sparks, R.; Zolotarjova, N.; Li, J.; Wen, X.; Favata, M.; Feldman, P.; Volgina, A.; DiMatteo, D.; Collins, R.; Falahatpisheh, N.; Polam, P.; Li, Y.; Covington, M.; Diamond-Fosbenner, S.; Wynn, R.; Burn, T.; Vaddi, K.; Yeleswaram, S.; Combs, A. P.; Yao, W.; Huber, R.; Scherle, P.; Hollis, G. Abstract 3523: Discovery of a Novel BET inhibitor INCB054329. *Cancer Res*. **2015**, *75*, 3523. Combs, A. P. Invention of INCB054329 and INCB057643, Two Potent and Selective BET Inhibitors in Clinical Trials for Oncology. ACS Spring 2018 255th National Meeting, March 18-22, 2018 , New Orleans LA, Abstract MEDI 306.

21) Stubbs, M. C.; Maduskuie, T.; Burn, T.; Diamond-Fosbenner, S.; Falahatpisheh, N.; Volgina, A.; Zolotarjova, N.; Wen, X.; Feldman, P.; Rupar, M.; Collins, R.; Marando, C.; Ruggeri, B.; Covington, M.; Liu, X. M.; Wynn, R.; Yeleswaram, S.; Yao, W.; Huber, R.; Hollis, G.; Scherle, P.; Combs, A. P.; Liu, P. C. Abstract 5071: Preclinical Characterization of the Potent and Selective BET Inhibitor INCB057643 in Models of hematologic malignancies. *Cancer Res.* **2017**;*77*, 5071.

22) Ozer, H. G.; El-Gamal, D.; Powell, B.; Hing, Z. A.; Blachly, J. S.; Harrington, B.; Mitchell, S.; Grieselhuber, N. R.; Williams, K.; Lai, T.-H.; Alinari, L.; Baiocchi, R. A.; Brinton, L.; Baskin, E.; Cannon, M.; Beaver, L.; Goettl, V. M.; Lucas, D. M.; Woyach, J. A.; Sampath, D.; Lehman, A. M.; Yu, L.; Zhang, J.; Ma, Y.; Zhang, Y.; Spevak, W.; Shi, S.; Severson, P.; Shellooe, R.; Carias, H.; Tsang, G.; Dong, K.; Ewing, T.; Marimuthu, A.; Tantoy, C.; Walters, J.; Sanftner, L.; Rezaei, H.; Nespi, M.; Matusow, B.; Habets, G.; Ibrahim, P.; Zhang, C.; Mathé, E. A.; Bollag, G.; Byrd, J. C.; Rosa Lapalombella, R. BRD4 Profiling Identifies Critical Chronic Lymphocytic Leukemia Oncogenic Circuits and Reveals Sensitivity to PLX51107, a Novel Structurally Distinct BET Inhibitor. *Cancer Disc.* **2018**, *8*, 458-477. .

23) Ouyang, L.; Zhang, L.; Liu, J.; Fu, L.; Yao, D.; Zhao, Y.; Zhang, S.; Wang, G.; He, G.; Liu, B. Discovery of a Small-Molecule Bromodomain-Containing Protein 4 (BRD4) Inhibitor That Induces AMP-Activated Protein Kinase-Modulated Autophagy-Associated Cell Death in Breast Cancer. *J. Med. Chem.* **2017**, *60*, 9990−10012.

24) Liu, Z.; Tian, B.; Chen, H.; Wang, P.; Brasier, A. R.; Zhou, J. Discovery of Potent and Selective BRD4 Inhibitors Capable of Blocking TLR3-Induced Acute Airway Inflammation. *Eur. J. Med. Chem.* **2018**, *151*, 450-461.

25) Zhang, G.; Plotnikov, A. N.; Rusinova, E.; Shen, T.; Morohashi, K.; Joshua, J.; Zeng, L.; Mujtaba, S.; Ohlmeyer, M.; Zhou, M.-M. Structure-Guided Design of Potent Diazobenzene Inhibitors for the BET Bromodomains. *J. Med. Chem.* **2013**, *56*, 9251−9264.

26) Raux, B.; Voitovich, Y.; Derviaux, C.; Lugari, A.; Rebuffet, E.; Milhas, S.; Priet, S.; Roux, T.; Trinquet, E.; Guillemot, J.-C.; Knapp, S.; Brunel, J.-M.; Fedorov, A. Y.; Collette, Y.; Roche, P.; Betzi, S.; Combes, S.; Morelli, X. Exploring Selective Inhibition of the First

Bromodomain of the Human Bromodomain and Extra-terminal Domain (BET) Proteins. *J. Med. Chem.* **2016**, *59*, 1634−1641.

27) Ma, J.; Chen, H.; Yang, J.; Yu, Z.; Huang, P.; Yang, H.; Zheng, B.; Liu, R.; Li, Q.; Chen, Z. Binding Pocket-based Design, Synthesis and Biological Evaluation of Novel Selective BRD4-BD1 Inhibitors. *Bioorg. Med. Chem.* **2019**, *27*, 1871-1881.

28) Divakaran, A.; Talluri, S. K.; Ayoub, A. M.; Mishra, N. K.; Cui, H.; Widen, J. C.; Berndt, N.; Zhu, J.-Y.; Carlson, A. S.; Topczewski, J. J.; Schonbrunn, E. K.; Harki, D. A.; Pomerantz, W. C. K. Molecular Basis for the N-Terminal Bromodomain-and-Extra-Terminal-Family Selectivity of a Dual Kinase–Bromodomain Inhibitor. *J. Med. Chem.* **2018**, *61*, 9316-9334.

29) Picaud, S.; Wells, C.; Felletar, I.; Brotherton, D.; Sarah Martin, S.; Savitskya, P.; Diez-Dacal, B.; Philpott, M.; Bountra, C.; Lingard, H.; Fedorov, O.; Müller, S.; Brennan, P. E.; Knapp, S.; Filippakopoulos, P. RVX-208, an Inhibitor of BET Transcriptional Regulators with Selectivity for the Second Bromodomain. *Proc. Natl. Acad. Sci. U. S. A* **2013**, *110*, 19754-19759.

30) Kharenko, O. A.; Gesner, E. M.; Patel, R. G.; Norek, K.; White, A.; Fontano, E.; Suto, R. K.; Young, P. R.; McLure, K. G.; Hansen, H. C. RVX-297- a Novel BD2 Selective Inhibitor of BET Bromodomains. *Biochem. Biophys. Res. Commun.* **2016**, *477*, 62-67.

31) Sharp, P. P.; Garnier, J.-M.; Hatfaludi, T.; Xu, Z.; Segal, D.; Jarman, K. E.; Jousset, H.; Garnham, A.; Feutrill, J. T.; Cuzzupe, A.; Hall, P.; Taylor, S.; Walkley, C. R.; Tyler, D.; Dawson, M. A.; Czabotar, P.; Wilks, A. F.; Glaser, S.; Huang, D. C. S.; Burns, C. J.; Design,

Synthesis, and Biological Activity of 1,2,3-Triazolobenzodiazepine BET Bromodomain Inhibitors. *ACS Med. Chem. Lett.* **2017**, *8*, 1298−1303.

32) Shadrick, W. R.; Slavish, P. J.; Chai, S. C.; Waddell, B.; Connelly, M.; Low, J. A.; Tallant, C.; Young, B. M.; Bharatham, N.; Knapp, S.; Boyd, V. A.; Morfouace, M.; Roussel, M. F.; Chen, T.; Lee, R. E.; Guy, R. K.; Shelat, A. A.; Potter, P. M. Exploiting a Water Network to Achieve Enthalpy-driven, Bromodomain-selective BET Inhibitors. *Bioorg. Med. Chem.* **2018**, *26*, 25-36.

33) Law, R. P.; Atkinson, S. J.; Bamborough, P.; Chung, C.; Demont, E. H.; Gordon, L. J.; Lindon, M.; Prinjha, R. K.; Watson, A. J. B.; Hirst, D. J. Discovery of Tetrahydroquinoxalines as Bromodomain and Extra-Terminal Domain (BET) Inhibitors with Selectivity for the Second Bromodomain. *J. Med. Chem.* **2018**, *61*, 4317-4334.

34) Baud, M. G. J.; Lin-Shiao, E.; Zengerle, M.; Tallant, C.; Ciulli, A. New Synthetic Routes to Triazolo-benzodiazepine Analogues: Expanding the Scope of the Bump-and-Hole Approach for Selective Bromo and Extra-Terminal (BET) Bromodomain Inhibition. *J. Med. Chem.* **2016**, *59*, 1492−1500.

35) Chen, D.; Lu, T.; Yan, Z.; Lu, W.; Zhou, F.; Lyu, X.; Xu, B.; Jiang, H.; Chen, K.; Luo, C.; Zhao, Y. Discovery, Structural Insight, and Bioactivities of BY27 as a Selective Inhibitor of the Second Bromodomains of BET Proteins. *Eur. J. Med. Chem.* **2019**, *182*, 111633.

36) Ujjinamatada, R. K.; Samajdar, S.; Abbineni, C.; Mukherjee, S.; Linnanen, T.; Wohlfahrt, G. Spiro[cyclobutane-1,3'-indolin]-2'-one Derivatives as Bromodomain Inhibitors. WO2016203112, December 22, 2016.

37) Amans, D.; Bamborough, P.; Barker, M. D.; Bit, R. A.; Brown, J. A.; Campbell, M.; Garton, N. S.; Lindon, M. J.; Shipley, T. J.; Theodoulou, N. H.; Wellaway, C. R.; Westaway, S. M. Furopyridines as Bromodomain Inhibitors. U. S. Patent 9,670,221, June 6, 2017.

38) Bamborough, P.; Chung, C.-W. Process for the Identification of a Compound Which Inhibits the Binding of the First Bromodomain of each of Human BRD-2, BRD-3, and BRD-4. U. S. Patent 9,753,034, September 5, 2017.

39) Seitzberg, J. G.; Kronborg, T. T. A.; Poljak, V.; Friberg, G.; Teuber, L. Compounds Active Towards Bromodomains. US20170349607, December 7, 2017.

40) Baxter, A.; Brown, J. A.; Hirst, D.; Humphreys, P.; Jones, K. L.; Patel, V. K. Imidazole Derivatives and Their Use in the Treatment of Autoimmune or Inflammatory Diseases or Cancers. WO2018041947, March 8, 2018.

41) Baxter, A.; Bit, R. A.; Brown, J. A.; Hirst, D.; Humphreys, P.; Jones, K. L.; Patel, V. K. Imidazole Derivatives and Their Use in the Treatment of Autoimmune or Inflammatory Diseases or Cancers. WO2018041964, March 8, 2018.

42) Atkinson, S. J.; Demont, E. H.; Harrison, L. A.; Preston, A. G.; Seal, J. T.; Wall, I. D.; Watson, R. J.; Woolven, J. M. Benzo[b]furans as Bromodomain Inhibitors. WO2017174620, October 12, 2017.

43) Atkinson, S. J.; Demont, E. H.; Harrison, L. A.; Levernier, E.; Preston, A. G.; Seal, J. T.; Wall, I. D.; Watson, R. J.; Woolven, J. M. Pyridyl Derivatives as Bromodomain Inhibitors. WO2017174621, October 12, 2017.

44) Fidanze, S. D.; Hasvold, L. A.; Liu, D.; McDaniel, K. F.; Pratt, J.; Schrimpf, M.; Sheppard, G. S.; Wang, L.; Li, B. Bromodomain Inhibitors. WO2017177955, October 19, 2017.

45) Atkinson, S. J.; Demont, E. H.; Harrison, L. A.; Levernier, E.; Preston, A. G.; Seal, J. T.; Wall, I. D.; Watson, R. J.; Woolven, J. M. Pyridyl Derivatives as Bromodomain Inhibitors. WO2018158210, September 7, 2018.

46) Atkinson, S. J.; Demont, E. H.; Harrison, L. A.; Liwicki, G. M.; Lucas, S. C. C.; Preston, A. G.; Seal, J. T.; Wall, I. D.; Watson, R. J. Pyrazole Derivatives as Bromodomain Inhibitors. WO2018158212, September 7, 2018.

47) Gadd, M. S.; Testa, A.; Lucas, X.; Chan, K.-H.; Chen, W.; Lamont, D. J.; Zengerle, M.; Ciulli, A. Structural Basis of PROTAC Cooperative Recognition for Selective Protein Degradation. *Nature Chem. Biol.* **2017**, *13*, 514-521.

48) Bui, M. H.; Lin, X.; Albert, D. H.; Li, L.; Lam, L. T.; Faivre, E. J.; Warder, S. E.; Huang, X.; Wilcox, D. Donawho, C. K.; Sheppard, G. S.; Wang, L.; Fidanze, S.; Pratt, J. K; Liu, D.; Hasvold, L.; Uziel, T.; Lu, X.; Kohlhapp, F.; Gang, G.; Elmore, S. W.; Rosenberg, S. H.; McDaniel, K. F.; Kati, W. M.; Shen, Y. Preclinical Characterization of BET Family Bromodomain Inhibitor ABBV-075 Suggests Combination Therapeutic Strategies. *Cancer Res.* **2017**, *77*, 2976-2989.

49) Machleidt, T.; Woodroofe, C. C.; Schwinn, M. K.; Mendez, J.; Robers, M. B.; Zimmerman, K.; Otto, P.; Daniels, D. L.; Kirkland, T. A.; Wood, K. V. NanoBRET-A Novel BRET Platform for the Analysis of Protein-Protein Interactions. *ACS Chem. Biol.* **2015**, *10*,1797-1804.

50) Gierse, J. K.; McDonald, J. J.; Hauser, S. D.; Rangwala, S. H.; Koboldt, C. M.; Seibert, K. A Single Amino Acid Difference between Cyclooxygenase-1 (COX-1) and -2 (COX-2) Reverses the Selectivity of COX-2 Specific Inhibitors *J. Bio. Chem.* **1996**, *271*, 15810–15814.

51) Faivre, E.; McDaniel, K. F.; Albert, D.H.; Mantena, S. R.; Plotnik, J. P.; Wilcox, D.; Zhang, L.; Bui, M. H.; Sheppard, G. S.; Wang, L.; Sehgal, V.; Lin, X.; Huang, X.; Lu, X.; Uziel, T.; Hessler, P.; Lam, L. T.; Bellin, R. J.; Mehta, G.; Fidanze, S.; Pratt, J. K.; Liu, D.; Hasvold, L. A.; Sun, C.; Panchal, S. C.; Nicolette, J. J.; Fossey, S. L.; Park, C. H.; Longenecker, K.; Bigelow, L.; Torrent, M.; Rosenberg, S. H.; Kati, W. M.; Shen, Y. Selective Inhibition of the BD2 Bromodomain of BET proteins in prostate cancer. *Nature* **2020**, *578*, 306-310.

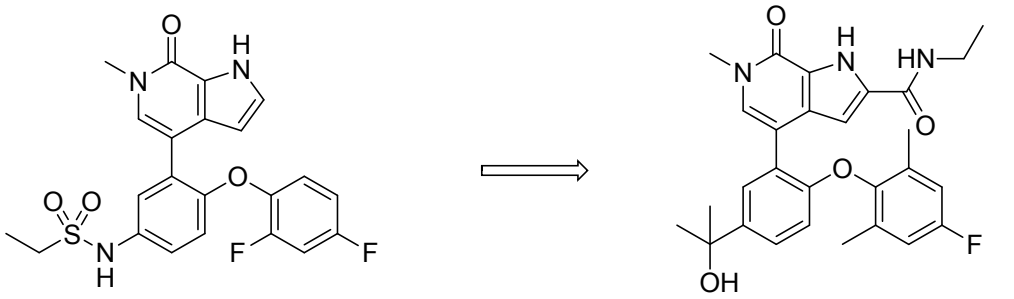
52) Zhang, L.; Cai, T.; Lin, X.; Huang, X.; Bui, M. H.; Bellin, R.; Faivre, E.; Kuruvilla, V.; Lam, L.; Uziel, T.; Zhang, Q.; Cavazos, A.; Han, L.; Ferguson, D. C.; Albert, D. H.; McDaniel, K.; Kati, W.; Konopleva, M.; Shen, Y.., unpublished results.

53) Wang, L.; Pratt, J. K.; Soltwedel, T.; Sheppard, G. S.; Fidanze, S. D.; Liu, D.; Hasvold, L. A.; Mantei, R. A.; Holms, J. H.; McClellan, W. J.; Wendt, M. D.; Wada, C.; Frey,R.; Hansen, T. M.; Hubbard, R.; Park, C. H.; Li, L.; Magoc, T. J.; Albert, D. A.; Lin, X.; Warder, S. E.; Kovar, P.; Huang, X.; Wilcox, D.; Wang, R.; Rajaraman, G.; Petros, A. M.; Hutchins, C. W.; Panchal, S. C.; Sun, C.; Elmore, S. W.; Shen, Y.; Kati, W. M.; McDaniel, K. F. Fragment-Based, Structure-Enabled Discovery of Novel Pyridones and Pyridone Macrocycles as Potent Bromodomain and Extra-Terminal Domain (BET) Family Bromodomain Inhibitors. *J. Med. Chem.* **2017**, *60*, 3828-3850.

54) Previously reported by another route in Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. Unsymmetrical Diarylmethanes by Ferroceniumboronic Acid

Catalyzed Direct Friedel-Crafts Reactions with Deactivated Benzylic Alcohols: Enhanced Reactivity due to Ion-Pairing Effects. *J. Am. Chem, Soc.* **2015**, *137*, 9694-9703.

Table of Contents Graphic



5 (ABBV-075, mivebresib)
BRD4 BD1/BRD4 BD2 = 2

46 (ABBV-744)
BRD4 BD1/BRD4 BD2 = 330