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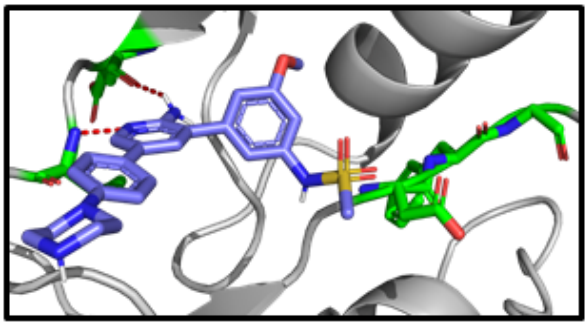
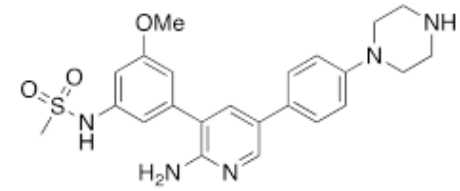
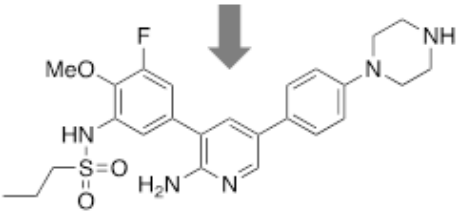




18f



18t

RIPK2 $IC_{50} = 16 \pm 5$ nM

NOD2 cell signaling $IC_{50} = 26 \pm 4$ nM

Receptor-Interacting Protein Kinase 2 (RIPK2) and Nucleotide-Binding Oligomerization Domain (NOD) Cell Signaling Inhibitors Based on a 3,5-Diphenyl-2-aminopyridine Scaffold

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ABSTRACT

Receptor-interacting protein kinase 2 (RIPK2) is a key mediator of nucleotide-binding oligomerization domain (NOD) cell signaling that has been implicated in various chronic inflammatory conditions. A new class of RIPK2 kinase/NOD signaling inhibitors based on a 3,5-diphenyl-2-aminopyridine scaffold was developed. Several co-crystal structures of RIPK2•inhibitor complexes were analyzed to provide insights into inhibitor selectivity versus the structurally related activin receptor-like kinase 2 (ALK2) demonstrating that the inhibitor sits deeper in the hydrophobic binding pocket of RIPK2 perturbing the orientation of the DFG motif. In addition, the structure-activity relationship study revealed that in addition to anchoring to the hinge and DFG via the 2-aminopyridine and 3-phenylsulfonamide, respectively, appropriate occupancy of the region between the gatekeeper and the αC-helix provided by substituents in the 4- and 5-positions of the 3-phenylsulfonamide were necessary to achieve potent NOD cell signaling inhibition. For example, compound **18t** (e.g. CSLP37) displayed potent biochemical RIPK2 kinase inhibition (IC_{50} = 16 ± 5 nM), > 20-fold selectivity versus ALK2 and potent NOD cell signaling inhibition (IC_{50} = 26 ± 4 nM) in the HEKBlue assay. Finally, *in vitro* ADME and pharmacokinetic characterization of **18t** further supports the prospects of the 3,5-diphenyl-2-aminopyridine scaffold for the generation of *in vivo* pharmacology probes of RIPK2 kinase and NOD cell signaling functions.

KEYWORDS

inhibitor, kinase, NOD, nucleotide-binding oligomerization domain, receptor-interacting protein kinase 2, RIPK2

1. Introduction

The nucleotide-binding oligomerization domain (NOD)-containing proteins 1 and 2 are members of the NOD-like receptor (NLR) family that are involved in the innate immune system's detection of bacterial peptidoglycan (PG) derivatives. NOD1 is stimulated by bacterial PG fragments containing diaminopimelic acid (DAP), while NOD2 senses muramyl dipeptide (MDP). NOD1/2 then initiates assembly of signaling complexes by oligomerization through the nucleotide-binding oligomerization domains (NBD), which triggers the recruitment of interacting proteins through homotypic caspase-activated recruitment domain (CARD)-mediated interactions [1-4]. Receptor-interacting protein kinase 2 (RIPK2) is one of the key molecules in NOD-dependent signaling as it plays an essential role in the activation of NF-κB pathway and mitogen-activated protein kinase (MAPK) pathways that ultimately lead to synthesis of pro-inflammatory cytokines and antimicrobial molecules [2, 5].

RIPK2, which has dual serine/threonine and tyrosine kinase function, was identified as an essential mediator of signaling in both innate and adaptive immune systems [6]. In addition, non-kinase activity, particularly X-linked inhibitor of apoptosis (XIAP)-mediated ubiquitination of RIPK2, significantly contributes to the functions of this protein [7-14]. Aberrant RIPK2–NOD signaling pathways appear to play key roles in various inflammatory diseases. Most importantly, positive or negative dysregulation of the NOD2-dependent signaling pathway has been shown to facilitate several chronic inflammatory disorders such as Crohn's disease [15-17], Blau syndrome [18-19], early-onset sarcoidosis [19] and multiple sclerosis [20]. Therefore, RIPK2–NOD has emerged as a crucial mediator of inflammatory pathways and thus a potential therapeutic target for treating an array of inflammatory and autoimmune diseases.

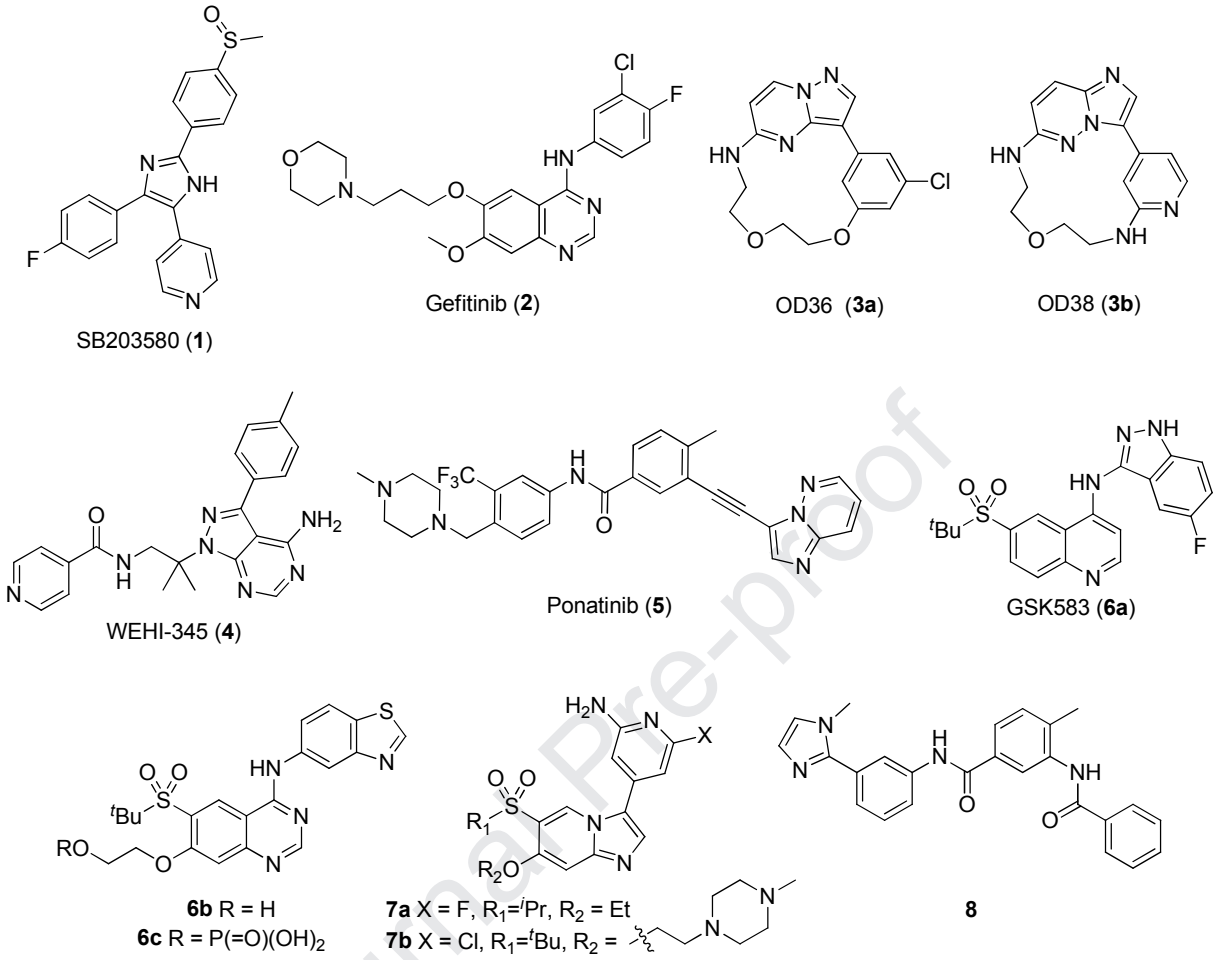


Figure 1. Reported RIPK2 kinase inhibitors.

With growing appreciation of RIPK2–NOD involvement in inflammatory and autoimmune cellular pathways and diseases, interest in RIPK2 small molecule ligands has accelerated. Several compound classes have been reported to inhibit RIPK2's kinase activity (Figure 1), including SB203580 (**1**) [21], gefitinib (**2**) [22], OD36 (**3a**) and OD38 (**3b**) [23], WEHI-345 (**4**) [24], ponatinib (**5**) [25], GSK583 (**6a**) [26], **6b** and its prodrug **6c** [27], **7a** and **7b** [28], and **8** [29]. Several of these compounds (e.g. **1**, **2**, **4**, **6a**, **6b** and **7b**) have been shown to bind the active (DFG-in/αC-helix-in) conformation of RIPK2 via a type I manner, while **5**

demonstrated binding to the inactive (DFG-out/αC-helix-in) conformation via a type II binding mode. These molecules have been shown to inhibit various downstream processes in cells associated with NOD signaling, such as NF-κB activation and MDP stimulated IL-8 or TNFα release. In addition, **3a** and **3b** [23] have demonstrated *in vivo* efficacy in an MDP-induced peritonitis model, **4** [24] and **8** [29] have shown activity in the experimental autoimmune encephalomyelitis model of multiple sclerosis and intestinal and lung inflammation models, respectively, while **7a** [28] inhibited inflammatory cytokine release in the *ex vivo* experiments using human inflammatory bowel disease biopsy samples. Herein we report the structure-activity relationship (SAR) of a new structure class of RIPK2 kinase and NOD cell signaling inhibitors that will be useful as probes for further understanding this protein, its role in NOD cell signaling and potentially as lead compounds for therapeutic development.

2. Design and synthesis

In contemplating a new class of RIPK2 kinase inhibitors we considered two scaffolds (**9a** and **9b**) that had previously been used for activin receptor-like kinase 2 (ALK2) inhibitors. In both cases, RIPK2 was a prevailing off-target revealed by kinome-wide selectivity profiling [30-31]. The 3,5-diphenyl-2-aminopyridine scaffold, exemplified by LDN-214117 (**9a**) [30] that displayed a modest IC_{50} of 100 nM in the RIPK2 ADPGlo kinase assay, was chosen to pursue (Figure 2A, Table I).

To improve potency, we desired to introduce a functional group into the 3,5-diaryl-2-aminopyridine scaffold that would ensure an interaction with the DFG segment of RIPK2. In order to identify a candidate moiety, the Harvard Medical School Library of Integrated Network-based Cellular Signatures (http://lincs.hms.harvard.edu) database was reviewed seeking to find inhibitors with non-overlapping kinase profiles except for RIPK2. Over 160 compounds in the

database displayed RIPK2 inhibition and among them PLX4032 (**10**, vemurafenib, Figure 2A), a B-Raf^{V600E} kinase inhibitor, showed ~96% inhibition at 10 μM. A B-Raf^{V600E}•**10** co-crystal structure reveals a DFG-in type I½ binding mode, a hydrogen bond between the sulfonamide and the backbone NH of Phe595 and Gly596 in the DFG motif and displacement of the αC-helix [32-34].

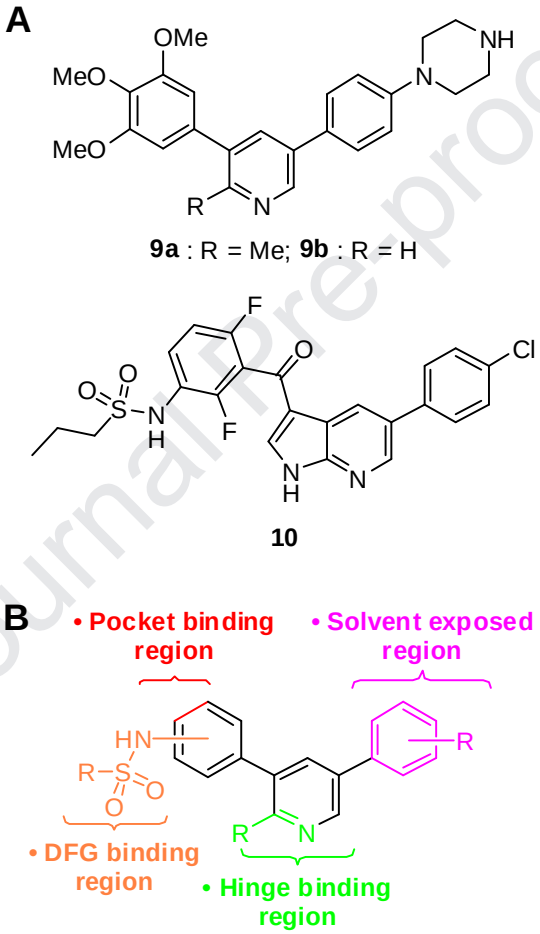


Figure 2. A) Structures of ALK2 inhibitors **9a**–**b** and B-Raf^{V600E} inhibitor **10**, all of which block RIPK2 kinase activity. **B**) RIPK2 inhibitor design incorporating the sulfonamide DFG binding fragment of **10** into scaffold **9**.

Next, **9a** was docked into the DFG-in/αC-helix-in (PDB 5AR4) and DFG-in/αC-helix-out (PDB 5AR8) structures of RIPK2 using AutodockTool-1.5.6. The co-crystal structures of ALK2•**9b** (PDB 4BGG) and B-Raf^{V600E}•**10** (PDB 3OG7) as well as the RIPK2•**9a** docked structures were compared to identify potential positions on **9a** for installation of the sulfonamide from **10** (Figure 3) in order to engage the DFG of RIPK2. The overlay results, with either the DFG-in/αC-helix-in or DFG-in/αC-helix-out conformations, suggested that the sulfonamide should be installed into the 4-position of the 3-phenyl to generate **9a**/**10**-hybrids as a potential new class of RIPK2 inhibitors (Figure 2B).

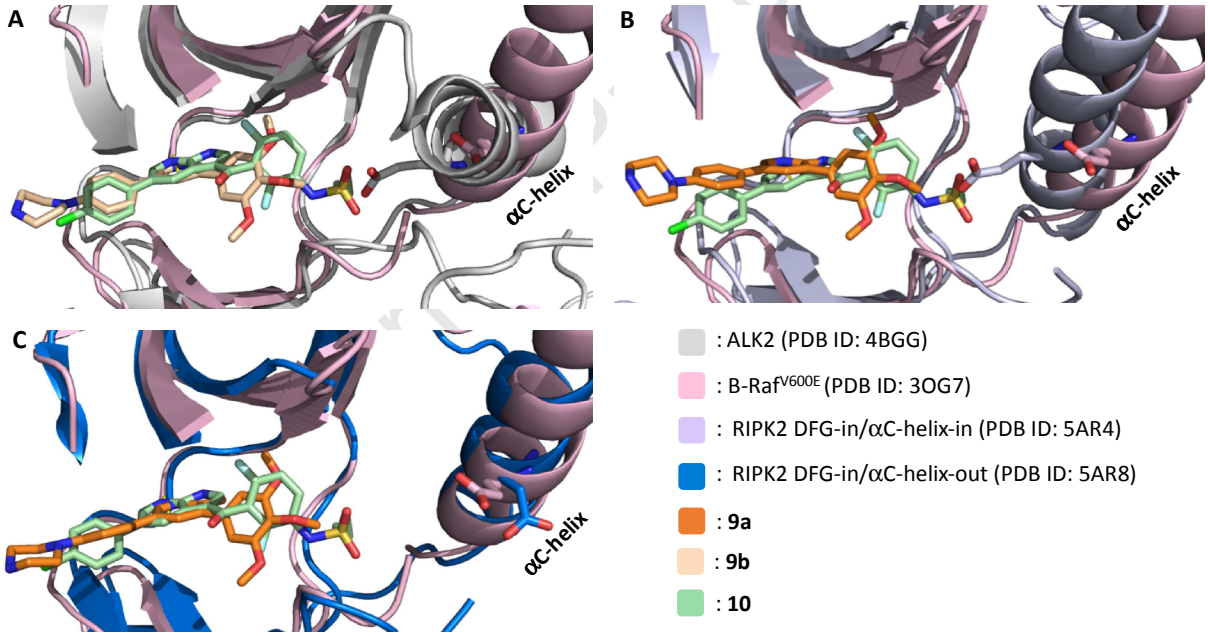
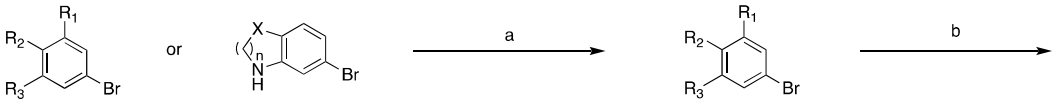


Figure 3. Overlaid structures of **10** *vs* **9b** and **10** *vs* docked **9a** suggested the position to install the sulfonamide moiety on the 3,5-diphenyl-2-aminopyridine scaffold. **A**) Superimposed crystal structures of **10** in B-Raf^{V600E} and **9b** in ALK2; **B**) and **C**) Docking result of **9a** in RIPK2 DFG-in/αC-helix-in and DFG-in/αC-helix-out structures, respectively, overlaid with co-crystal structure of **10** in B-Raf^{V600E}.

Various 1-(4-(5-phenylpyridin-3-yl)phenyl)piperazines utilized in this study were prepared using modifications of the reported syntheses of **9a** and **9b** [30]. Primary or secondary bromoanilines **11** and **12**, many of which were commercially available, were used as starting materials. However, several non-commercial anilines were prepared by either nucleophilic aromatic substitution or nitration, followed by iron-mediated nitro reduction. The bromoanilines **11** and **12** were allowed to react with sulfonyl chlorides in the presence of pyridine using slightly modified conditions to provide **13** (Scheme 1). Miyaura borylation reaction of **13** with bis(pinacolato)diboron using either $PdCl_2$(dppf) in THF or $PdCl_2$(dppf) in 1,4-dioxane furnished arylboronic esters **14**. Palladium-catalyzed Suzuki–Miyaura coupling of **14** with 3-bromo-5-iodopyridines **15a**–**c** delivered 3-bromo-5-(phenylalkylsulfonamide)pyridines **16**.

Scheme 1. Synthesis of 3-bromo-5-arylpyridine intermediates **16**.*



11a : R_1 = OMe, R_2 = NH_2, R_3 = H
11b : R_1 = OMe, R_2 = H, R_3 = NH_2
11c : R_1 = H, R_2 = OMe, R_3 = NH_2
11d : R_1 = H, R_2 = Me, R_3 = NH_2
11e : R_1 = OMe, R_2 = Me, R_3 = NH_2
11f : R_1 = F, R_2 = OMe, R_3 = NH_2
11g : R_1 = Me, R_2 = OMe, R_3 = NH_2
11h : R_1 = H, R_2 = OMe, R_3 = CH_2NH_2
11i : R_1 = OEt, R_2 = H, R_3 = NH_2
11j : R_1 = O^{i}Pr, R_2 = H, R_3 = NH_2
11k : R_1 = Cl, R_2 = OMe, R_3 = NH_2
11l : R_1 = R_2 = OMe, R_3 = NH_2
11m : R_1–R_2 = $O(CH_2)_2O$, R_3 = NH_2
11n : R_1 = OEt, R_2 = OMe, R_3 = NH_2
11o : R_1 = H, R_2 = OTBS, R_3 = NH_2

12a : X = CH_2, n = 1
12b : X = O, n = 2

13a : R_1 = OMe, R_2 = $NHSO_2{}^n$Pr, R_3 = H
13b : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Me
13c : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Et
13d : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^n$Pr
13e : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^i$Pr
13f : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Ph
13g : R_1 = H, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13h : R_1 = H, R_2 = Me, R_3 = $NHSO_2{}^n$Pr
13i : R_1 = OMe, R_2 = Me, R_3 = $NHSO_2{}^n$Pr
13j : R_1 = F, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13k : R_1 = Me, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13l : R_1 = H, R_2 = OMe, R_3 = $CH_2NHSO_2{}^n$Pr
13m : R_1 = H, R_2–R_3 = $CH_2CH_2NHSO_2{}^n$Pr
13n : R_1 = H, R_2–R_3 = $OCH_2CH_2NHSO_2{}^n$Pr
13o : R_1 = OEt, R_2 = H, R_3 = $NHSO_2{}^i$Pr
13p : R_1 = O^{i}Pr, R_2 = H, R_3 = $NHSO_2{}^i$Pr
13q : R_1 = Cl, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13r : R_1 = R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13s : R_1–R_2 = $O(CH_2)_2O$, R_3 = $NHSO_2{}^n$Pr
13t : R_1 = OEt, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr
13u : R_1 = H, R_2 = OH, R_3 = $NHSO_2{}^n$Pr
13v : R_1 = F, R_2 = R_3 = OMe

14a–**v**

15a : R_4 = Cl
15b : R_4 = NH_2
15c : R_4 = H

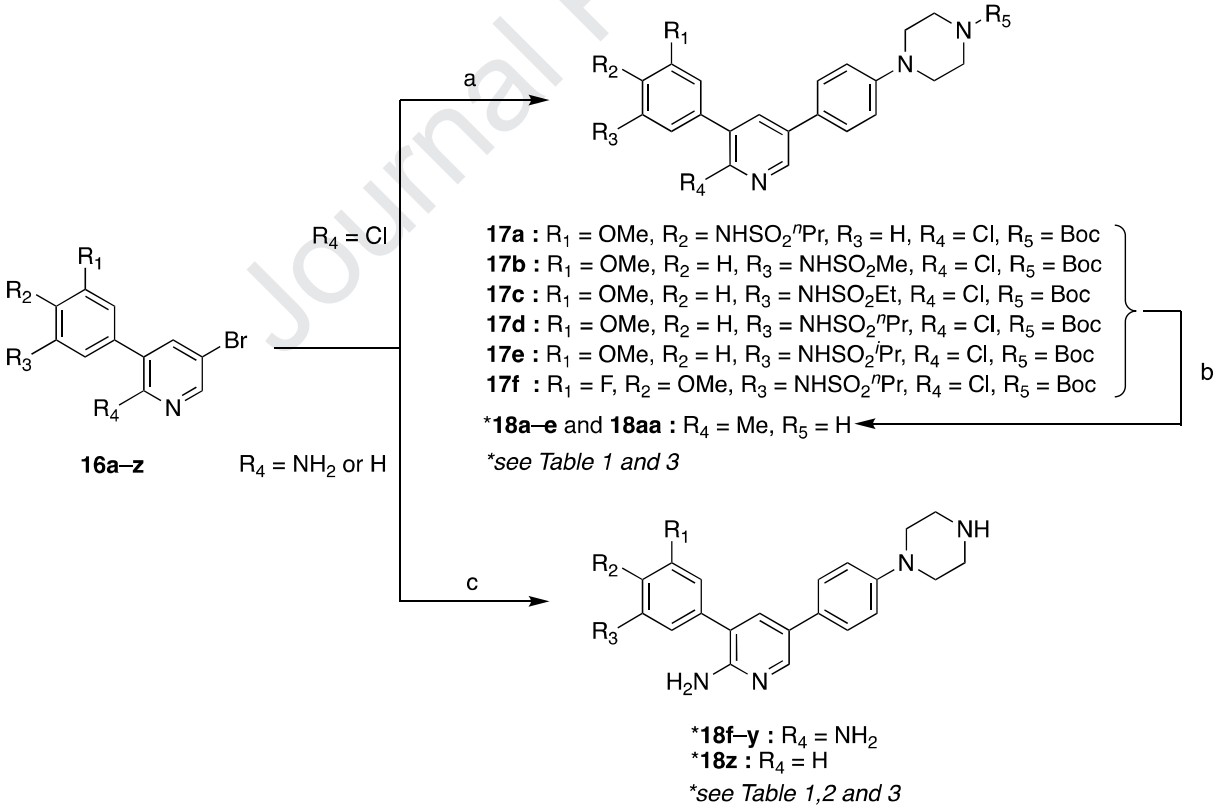
c

16a : R_1 = OMe, R_2 = $NHSO_2{}^n$Pr, R_3 = H, R_4 = Cl
16b : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Me, R_4 = Cl
16c : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Me,, R_4 = NH_2
16d : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Et, R_4 = Cl
16e : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^n$Pr, R_4 = Cl
16f : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16g : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^i$Pr, R_4 = Cl
16h : R_1 = OMe, R_2 = H, R_3 = $NHSO_2{}^i$Pr, R_4 = NH_2
16i : R_1 = OMe, R_2 = H, R_3 = $NHSO_2$Ph, R_4 = NH_2
16j : R_1 = H, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16k : R_1 = H, R_2 = Me, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16l : R_1 = OMe, R_2 = Me, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16m : R_1 = F, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16n : R_1 = Me, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16o : R_1 = H, R_2 = OMe, R_3 = $CH_2NHSO_2{}^n$Pr, R_4 = NH_2
16p : R_1 = H, R_2–R_3 = $CH_2CH_2NHSO_2{}^n$Pr, R_4 = NH_2
16q : R_1 = H, R_2–R_3 = $OCH_2CH_2NHSO_2{}^n$Pr, R_4 = NH_2
16r : R_1 = OEt, R_2 = H, R_3 = $NHSO_2{}^i$Pr, R_4 = NH_2
16s : R_1 = O^{i}Pr, R_2 = H, R_3 = $NHSO_2{}^i$Pr, R_4 = NH_2
16t : R_1 = Cl, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16u : R_1 = R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16v : R_1 = OEt, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16w : R_1 = H, R_2 = OH, R_3 = $NHSO_2{}^n$Pr, R_4 = NH_2
16x : R_1 = F, R_2 = R_3 = OMe, R_4 = NH_2
16y : R_1 = F, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = H
16z : R_1 = F, R_2 = OMe, R_3 = $NHSO_2{}^n$Pr, R_4 = Cl

*Reagents and Conditions: (a) alkyl or phenyl sulfonyl chloride, Method A: pyridine, CH_2Cl_2, rt 16–48 h, Method B: pyridine, cat. DMAP, CH_2Cl_2, rt, 16–48 h, Method C: cat. DMAP, pyridine, 50 ºC, 3 h, Method D: pyridine, 50 ºC, 2.5 h or Method E: pyridine, rt, 16–48 h (30–99%); (b) bis(pinacolato)diboron, Method F: 3 mol% $PdCl_2$(dppf), KOAc, THF, reflux, 16 h or Method G: 10 mol% $PdCl_2$(dppf), KOAc, 1,4-dioxane, 80 ºC, 40 h (24–90%); (c) **15a**, **15b** or **15c**, 10 mol% $Pd(PPh_3)_4$, 1 M Na_2CO_3, MeCN, DMF, 90 ºC, 16 h (38–96%).

2-Chloropyridine intermediates **16** (R_4 = Cl) were subjected to a second Suzuki reaction with 4-(4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester to deliver **17**, which were treated with trimethylboroxine in the presence of a palladium catalyst followed by Boc deprotection using trifluoroacetic acid (TFA) in dichloromethane at room temperature to furnish **18a**–**e** and **18aa** (Scheme 2). Similarly, 2-aminopyridine or pyridine intermediates **16** (R_4 = NH_2 or H) were coupled with 4-(4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester and deprotected to give **18f**–**z**.

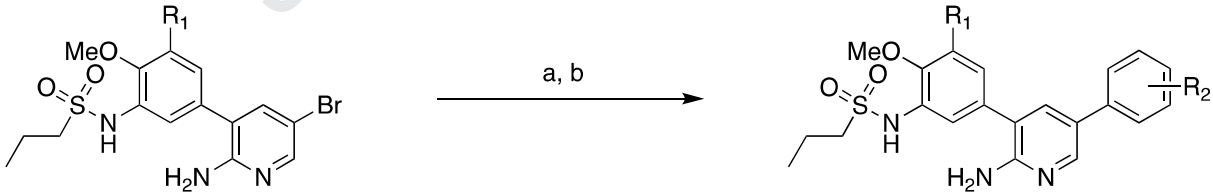
Scheme 2. Synthesis of 1-(4-(5-phenylpyridin-3-yl)phenyl)piperazine derivatives **18a–z** and **18aa**.*



*Reagents and Conditions: (a) 4-(4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester, 15 mol% $Pd(PPh_3)_4$, 1 M Na_2CO_3, DME, 90 ºC, 16 h (79–99%); (b) 1) trimethylboroxine, 20 mol% $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 110 ºC, 16 h; 2) 10% TFA in CH_2Cl_2, rt, 16 h (62–96% over two steps); (c) 1) 4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester, 15 mol% $Pd(PPh_3)_4$, 1 M Na_2CO_3, DME, 90 ºC, 16 h; 2) 10% TFA in CH_2Cl_2, rt, 16 h (18–62% over two steps).

Finally, a set of compounds was prepared with modifications to the solvent exposed region. In this case, intermediate **16j** was coupled with 2-, 3-, and 4-(methanesulfonyl)phenylboronic acid to give **18ab**, **18ac** and **18ad**, respectively (Scheme 3). Similarly, **16m** was coupled with (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid pinacol ester and deprotected to provide **18ae**.

Scheme 3. Synthesis of **18ab**–**18ae**.*



16j : R_1 = H
16m : R_1 = F

18ab : R_1 = H, R_2 = 2-SO_2Me
18ac : R_1 = H, R_2 = 3-SO_2Me
18ad : R_1 = H, R_2 = 4-SO_2Me
18ae : R_1 = F, R_2 = 3-piperazine

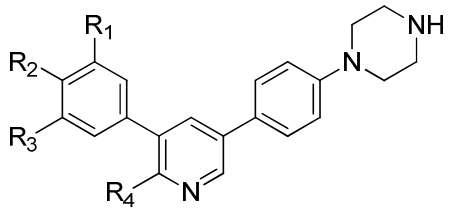
*Reagents and Conditions: (a) 2-, 3-, or 4-(methanesulfonyl)phenylboronic acid or (3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid pinacol ester, 10 mol% $Pd(PPh_3)_4$, 1 M

Na_2CO_3, MeCN, DMF, 90 ºC, 16 h (22–83%); (b) In the case of 3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenyl: 10% TFA in CH_2Cl_2, rt, 16 h (48% over two steps).

3. Results and discussion

As previously mentioned, structure analyses using either the DFG-in/αC-helix-in or DFG-in/αC-helix-out conformations suggested that the sulfonamide should be installed into the *para*-position of the 3-phenyl group occupying the binding pocket region. To test this initial model, a derivative of **9a** containing a 1-propanesulfonamide in this position (e.g. **18a**) was evaluated for RIPK2 inhibitory activity. However, it was not active (Table 1). Therefore, the 1-propanesulfonamide was changed to a methylsulfonamide and moved to the *meta*-position (**18b**) to further test the strategy. Gratifyingly, this compound proved to be a moderately potent inhibitor of RIPK2 (IC_{50} = 296 nM). Since the primary component of these compounds was **9a**, ALK2 kinase activity was chosen as the counter-screen for assessing selectivity [30]. Indeed, **18b** proved to be more potent against ALK2 (IC_{50} = 31 nM). However, these preliminary results indicated that placement of the sulfonamide in the *meta*-position was preferred. Several additional derivatives (**18c**–**e**) examined homologation and branching of the sulfonamide. In general, RIPK2 kinase inhibitory activity was modestly improved, but selectivity versus ALK2 was not significantly altered. Next, an amino group was introduced in place of the methyl at the 2-position of the pyridine to provide better hinge binding interactions. As expected, this set of compounds (**18f**–**h**) was more potent against both RIPK2 and ALK2. In addition, phenylsulfonamide **18i** was found to also be tolerated. Interestingly, increasing the size of the ether to an ethyl or isopropyl (**18j** or **18k**) was allowed by RIPK2, but less so for ALK2.

Table 1. RIPK2 and ALK2 kinases, and NOD2 cell signaling inhibitory activities of **9a** and **18a–k**.



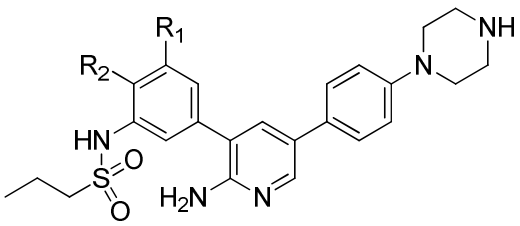
Compounds	R_1	R_2	R_3	R_4	Kinase IC_{50} (nM)		RIPK2/NOD2 Cell Assay IC_{50} (nM)
					RIPK2	ALK2	
9a	OMe	OMe	OMe	Me	100 ± 23	24 [30]	NI
18a	OMe	$NHSO_2{}^nPr$	H	Me	NI	NI	2944 ± 420
18b	OMe	H	$NHSO_2Me$	Me	296 ± 10	31 ± 34	3705 ± 85
18c	OMe	H	$NHSO_2Et$	Me	127 ± 18	86 ± 45	5239 ± 861
18d	OMe	H	$NHSO_2{}^nPr$	Me	164 ± 7	108 ± 92	2669 ± 138
18e	OMe	H	$NHSO_2{}^iPr$	Me	76 ± 12	239 ± 170	523 ± 18
18f	OMe	H	$NHSO_2Me$	NH_2	51 ± 26	5 ± 6	390 ± 22
18g	OMe	H	$NHSO_2{}^nPr$	NH_2	14 ± 0.6	9 ± 3	243 ± 14
18h	OMe	H	$NHSO_2{}^iPr$	NH_2	13 ±	11 ± 10	121 ± 27

					0.04		
18i	OMe	H	$NHSO_2Ph$	NH_2	23 ± 0.5	5 ± 7	53 ± 36
18j	OEt	H	$NHSO_2{}^{i}Pr$	NH_2	21 ± 2	299 ± 180	46 ± 0.5
18k	$O^{i}Pr$	H	$NHSO_2{}^{i}Pr$	NH_2	18 ± 8	NI	323 ± 12

* Values are shown as the mean of two or three determinations ± standard deviation; NI: No inhibition up to 10 μM

Given the previously demonstrated importance of methoxy groups on the 3-phenyl ring of 3,5-diphenyl-2-aminopyridine ALK2 inhibitors, a series of compounds was evaluated that offered changes to this region, while maintaining a 1-propanesulfonamide in the *meta*-position (Table 2) [30]. Installing a methyl in the *para*-position (**18l**) was detrimental for both RIPK2 and ALK2 inhibitory activities. However, moving the methoxy to the *para*-position (**18m**) proved advantageous for improving selectivity (to 86-fold) for RIPK2 versus ALK2. Replacing this group with hydroxyl (**18n**) or methyl (**18o**) resulted in reduced RIPK2 inhibitory activity and selectivity over ALK2.

Table 2. RIPK2 and ALK2 kinase, and NOD2 cell signaling inhibitory activities of **18g** and **18l–o**.



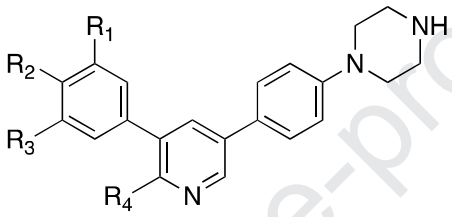
Compounds	R_1	R_2	Kinase IC_{50} (nM)		RIPK2/NOD2 Cell Assay IC_{50} (nM)
			RIPK2	ALK2	
18g	OMe	H	14 ± 0.8	9 ± 4	243 ± 14
18l	OMe	Me	NI	355 ± 318	3347 ± 495
18m	H	OMe	41 ± 19	3545 ± 2114	420 ± 34
18n	H	OH	54 ± 6	387 ± 42	> 5000
18o	H	Me	102 ± 22	2120 ± 509	1064 ± 109

*Values are shown as the mean of two or three determinations ± standard deviation; NI: No inhibition up to 10 μM

Based on the encouraging results with a methoxy group in the *ortho*-position relative to the 3-phenylsulfonamide, additional changes were examined in this region (Table 3). Reintroducing a *meta*-methoxy (**18p**) retained potent RIPK2 inhibitory activity, but predictably resulted in reduced selectivity versus ALK2. Increasing the size to ethoxy (**18q**) or tethering the ethers in an ethylenedioxy (**18r**) resulted in loss of inhibition for both RIPK2 and ALK2. However, replacement with methyl (**18s**), fluoro (**18t**) or chloro (**18u**) was well tolerated with 10 to 20-fold selectivity versus ALK2. Not surprisingly, replacement of the sulfonamide with a methoxy (**18v**) completely abolished selectivity. Installing a methylene between the sulfonamide and phenyl (**18w**) eroded both enzyme inhibitory activity and selectivity. In addition, incorporation of the sulfonamide in a ring (**18x**–**y**) was also not well tolerated. Interestingly,

removal of the 2-amino group on the pyridine of **18t** (e.g. **18z**) did not erode kinase inhibitory activity. However, replacing the amino group with methyl (**18aa**) decreased both RIPK2 and ALK2 inhibitory activities, as expected.

Table 3. RIPK2 and ALK2 kinase, and NOD2 cell signaling inhibitory activities of **18m**, **18p–z** and **18aa**.



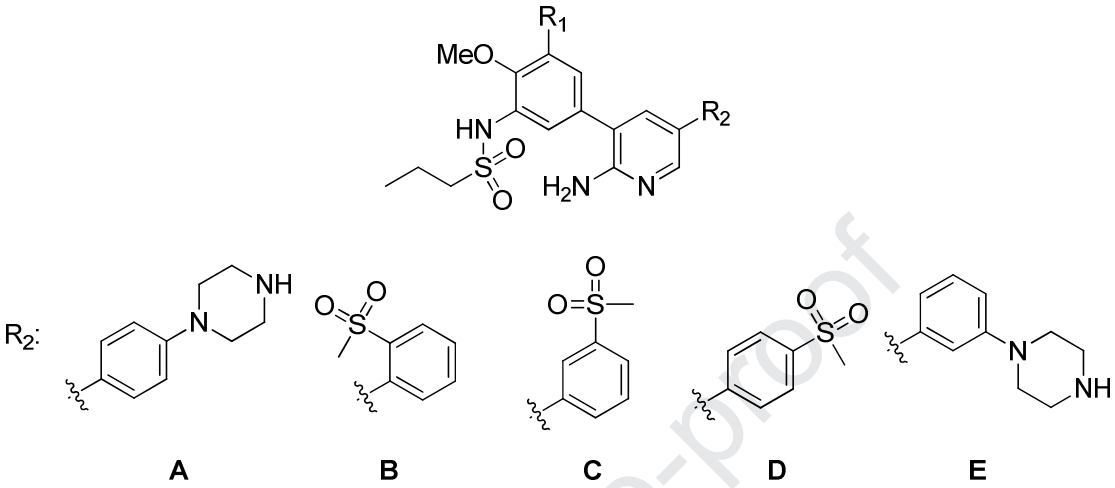
Compounds	**R_1**	**R_2**	**R_3**	**R_4**	**Kinase IC_{50} (nM)**		**RIPK2/NOD 2 Cell Assay IC_{50} (nM)**
					RIPK2	**ALK2**	
18m	H	OMe	$NHSO_2{}^nPr$	NH_2	32 ± 9	3545 ± 2114	476 ± 97
18p	OMe	OMe	$NHSO_2{}^nPr$	NH_2	20 ± 0.8	57 ± 13	1 ± 0.4
18q	OEt	OMe	$NHSO_2{}^nPr$	NH_2	NI	NI	NI
18r	OCH_2CH_2O		$NHSO_2{}^nPr$	NH_2	520 ± 13	NI	2458 ± 309
18s	Me	OMe	$NHSO_2{}^nPr$	NH_2	41 ± 1	395 ± 245	129 ± 38
18t	F	OMe	$NHSO_2{}^nPr$	NH_2	16 ± 5	348 ± 107	26 ± 4

18u	Cl	OMe	$NHSO_2{}^nPr$	NH_2	21 ± 4	202 ± 88	46 ± 0.4
18v	F	OMe	OMe	NH_2	39 ± 4	29 ± 14	595 ± 70
18w	H	OMe	$CH_2NHSO_2{}^nPr$	NH_2	99 ± 20	145 ± 57	1290 ± 94
18x	H	$CH_2CH_2N(SO_2{}^nPr)$		NH_2	185 ± 16	NI	2426 ± 116
18y	H	$OCH_2CH_2N(SO_2{}^nPr)$		NH_2	78 ± 20	NI	1011 ± 27
18z	F	OMe	$NHSO_2{}^nPr$	H	27 ± 2	NT	352 ± 83
18aa	F	OMe	$NHSO_2{}^nPr$	Me	1414 ± 312	NI	2556 ± 253

* Values are shown as the mean of two or three determinations ± standard deviation; NI: No inhibition up to 10 μM; NT: Not tested

Finally, the solvent exposed region of the inhibitor was briefly examined. Previous studies have demonstrated that selectivity for RIPK2 can be improved by introducing functional groups in this area that engage Ser25 in the glycine-rich loop, which is fairly unique to this particular kinase [26]. For example, a co-crystal structure of **6** with RIPK2 reported by Haile and co-worker showed a hydrogen bonding interaction of a methylsulfone with this residue [26]. The potency of the methylsulfone derivative was > 200-fold greater compared with the unsubstituted analog. Based on these observations, (methylsulfonyl)phenyl moieties were introduced to the solvent exposed region of the hybrid series (Table 4). However, the 2-, 3-, and 4-(methylsulfonyl) derivatives (**18ab**, **18ac** and **18ad**) demonstrated significantly less potency. On the other hand, moving the piperazine from the *para*- to *meta*-position (**18ae**) retained potent RIPK2 kinase inhibition and improved selectivity versus ALK2 raising the possible that this group provides a similar interaction with Ser25.

Table 4. RIPK2 and ALK2 kinase, and NOD2 cell signaling inhibitory activities of **18t** and **18ab**–**18ae**.



Compounds	R_1	R_2	Kinase IC_{50} (nM)		RIPK2/NOD2 Cell Assay IC_{50} (nM)
			RIPK2	ALK2	
18t	F	A	16 ± 5	348 ± 76	26 ± 4
18ab	H	B	NI	NI	NI
18ac	H	C	103 ± 16	NI	2655 ± 49
18ad	H	D	264 ± 38	NI	NI
18ae	F	E	11 ± 0.6	522 ± 317	16 ± 0.6

* Values is are shown as the mean of two or three determinations ± standard deviation; NI: No inhibition up to 10 μM

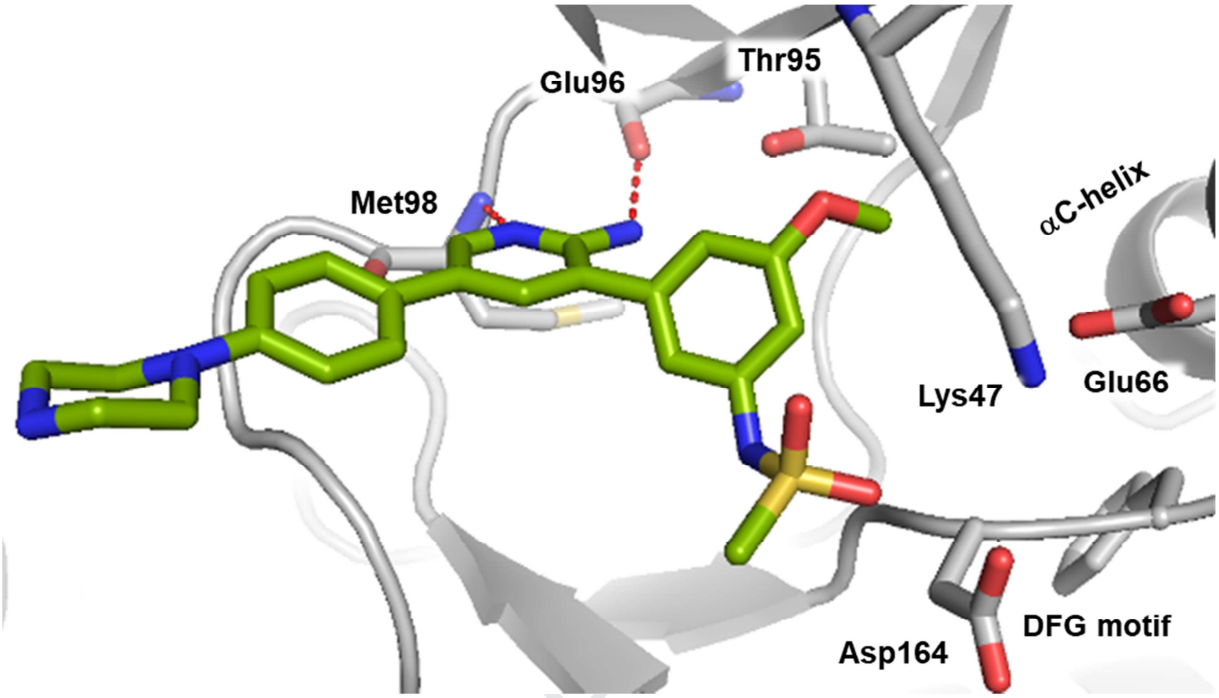


Figure 4. Co-crystal structure of **18f**•RIPK2 (PDB 6S1F). The inhibitor (green) forms hydrogen bonds to backbone NH and carbonyl of Met98 and Glu96, respectively, in the hinge region, while the methylsulfonamide is oriented towards the Asp164 in the DFG motif. Lys47 forms an ionic-ionic interaction with Glu66, in the αC-helix, stabilizing the DFG-in/Glu-in conformation.

In order to understand inhibitor interactions with RIPK2 and to gain insights for preferential binding for a subset of compounds versus ALK2, compound **18f** was co-crystallized with RIPK2 (PDB 6S1F). The **18f**•RIPK2 structure was resolved at a resolution of 3.1 Å (see Table S1 for data collection and refinement statistics) and displayed RIPK2 in an inactive DFG-in/Glu-in conformation with several critical residues misplaced from their active positions, including misorientation of the catalytic residues, perturbation of the R-spine and P-loop, as well

as a disordered activation segment (Figure 4) similar to the **18m**•RIPK2 complex [7]. The 2-aminopyridine formed hydrogen bonds with the backbone NH and carbonyl of hinge residues Met98 and Glu96, respectively. In addition, the 3-phenylsulfonamide of **18f** projected towards the hydrophobic pocket comprised of Val32, Leu70, Leu79, Ile93, Leu153 and Ala163, with the sulfonamide oriented towards Asp164 in the DFG motif. Finally, an ionic-ionic interaction was evident between Lys47 and Glu66 maintains the αC-helix in the Glu-in conformation.

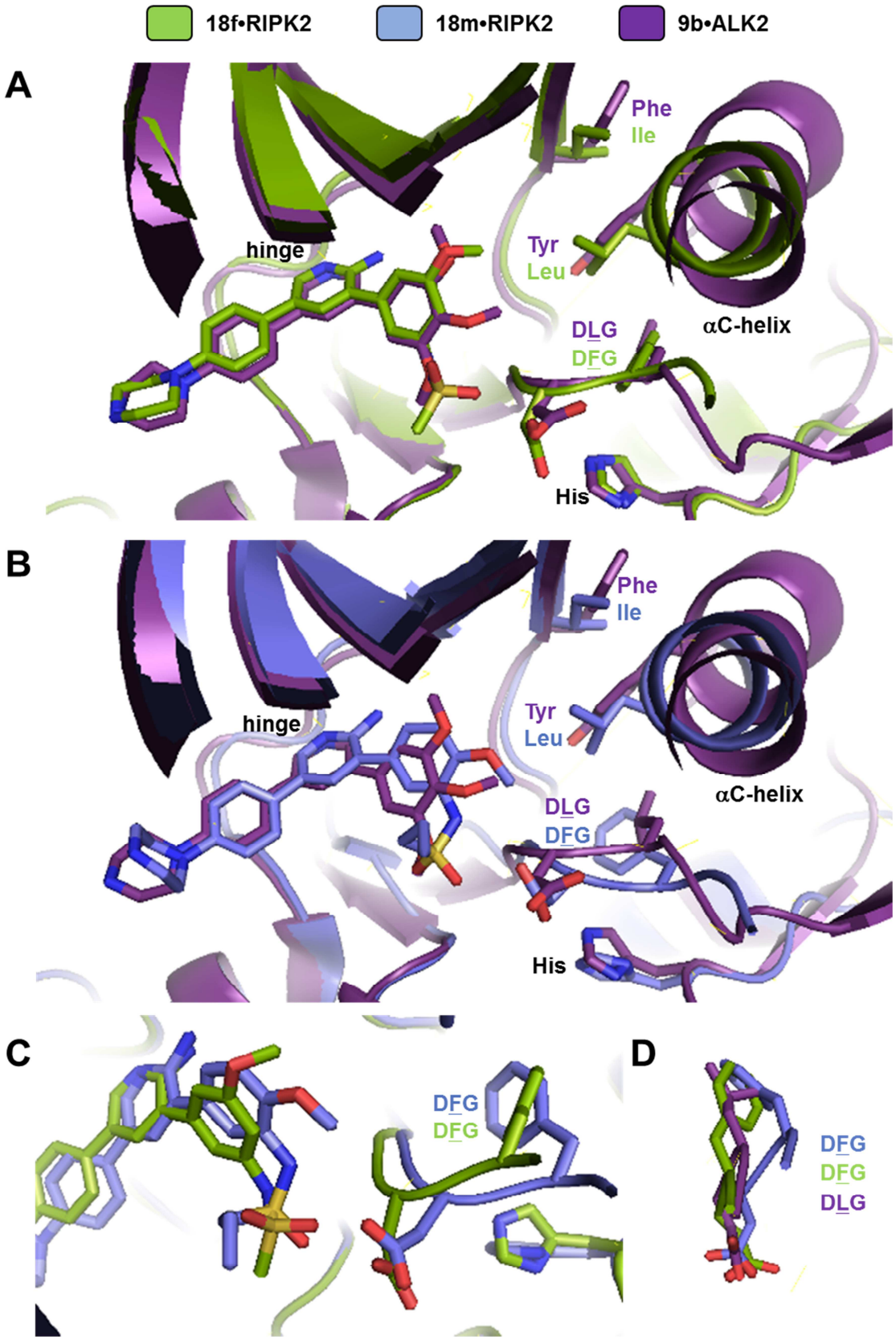

18f•RIPK2
18m•RIPK2
9b•ALK2
A
Phe
Ile
hinge
Tyr
Leu
αC-helix
DLG
DFG
His
B
Phe
Ile
hinge
Tyr
Leu
αC-helix
DLG
DFG
His
C
DFG
DFG
D
DFG
DFG
DLG

Figure 5. (**A**) Alignment of **18f•**RIPK2 (green; PDB 6S1F) and **9b•**ALK2 (light purple; PDB 4BGG) co-crystal structures. Several residues, the DFG and DLG motifs, as well as the αC-helices are labeled. (**B**) Alignment of **18m•**RIPK2 (dark purple; PDB 6FU5) and **9b•**ALK2 (light purple; PDB 4BGG) co-crystal structures. Several residues, the DFG and DLG motifs, as well as the αC-helices are labeled. (**C**) Alignment of **18f•**RIPK2 (green) and **18m•**RIPK2 (dark purple) co-crystal structures. The DFG motifs are labeled. (**D**) Comparison of the DFG and DLG of **18f•**RIPK2 (green) and **9b•**ALK2 (light purple) with the DFG of **18m•**RIPK2 (dark purple).

A number of interactions observed in the **18f•**RIPK2 co-crystal structure were seen for inhibitor **9b** bound to ALK2 with the two inhibitors occupying similar space in their respective kinases (Figure 5A) [30]. Also the DFG (in RIPK2) and DLG (in ALK2) motifs, as well as the αC-helix, were comparable. However, juxtaposition of the **9b•**ALK2 and **18m•**RIPK2 co-crystal structures (Figure 5B) demonstrated that the latter inhibitor, which has the methoxy at the 4-position on the 3-phenylsulfonamide and is more selective for RIPK2 versus ALK2, sits deeper in the hydrophobic pocket. In addition, it perturbs the orientation of the DFG relative to the DLG in ALK2. Interestingly, the DLG in ALK2 appears to be less flexible as evidenced by a lack of disclosed DLG-out ALK2 inhibitors, whereas adoption of a DFG-out conformation in RIPK2 has been previously observed with **5** [25]. The ability of the DFG in RIPK2 to move, in the case of **18m** relative to **18f** in RIPK2 and **9b** in ALK2 (Figures 5C and D), may play a role in its enhanced selectivity for RIPK2 versus ALK2. One additional difference noted for **18m** versus **18f** is rotation of the sulfonamide (Figure 5C) potentially induced by the presence of the methoxy in the 4-position.

Although kinase activity is a function of RIPK2, this protein is also an ubiquitination substrate in response to NOD1/2 stimulation [8-9]. Several ubiquitin (Ub) ligases participate in the conjugation of Ub chains to RIPK2. Particularly critical is XIAP-mediated ubiquitination of RIPK2, which results in recruitment [10] and linear ubiquitin chain assembly complex (LUBAC) mediated Met1-Ub conjugation of RIPK2 [11]. These latter processes are intimately involved in the downstream signaling step leading to the assembly of the NF-κB-activating IKK kinase complex [12]. Disruption of XIAP-RIPK2 interactions through genetic mutations in XIAP [14] or RIPK2 inhibitors mitigates NOD2 inflammatory signaling [7, 13]. Given this array of functional roles of RIPK2, the newly developed kinase inhibitors were assessed in a HEKBlue assay that measures NF-κB activation, downstream of XIAP-mediated RIPK2 ubiquitination, in response to L18-MDP stimulation.

A significant portion of the compounds, despite demonstrating potent RIPK2 kinase inhibition (IC_{50} < 100 nM), either modestly blocked NOD2 signaling in the HEKBlue assay (100 nM < IC_{50} < 1 μM) or were comparatively inactive (IC_{50} > 1 μM), suggesting that inhibition of RIPK2 catalytic activity was not sufficient for inhibition of NOD signaling in cells. In a recently published report, Hrdinka, *et al*. demonstrated that a subset of these 3,5-diaryl-2-aminopyridine based RIPK2 inhibitors (e.g. **18p** and **18t**) engaged RIPK2 to impede XIAP-mediated RIPK2 ubiquitination, leading to efficient inhibition of L18-MDP-induced NOD-dependent signaling responses, e.g. CXCL8 production in U2OS/NOD2 cells and TNFα release from RAW264.7 macrophages. Both **18p** and **18t** interfered with the interaction between GST-BIR2-cIAP1 and RIPK2 blocked XIAP-mediated RIPK2 ubiquitination resulting in disruption of NOD2 signaling similar to ponatinib and GSK583 [7]. Furthermore, **18t** did not block lipopolysaccharide and pan-caspase inhibitor induced RIPK1 and RIPK3 dependent necroptosis [35] in RAW264.7

macrophages at 1 μM (data not shown) demonstrating the compound's selectivity for RIPK2/NOD signaling. The mechanism of how allosteric binding of compounds to the ATP pocket disrupts XIAP-mediated RIPK2 ubiquitination is currently not known. However, the structural features that appear to achieve NOD cell signaling inhibitory function for a subset of compounds in Tables 1-4 as assessed in the NF-κB activation HEKBlue assay were the 2-aminopyridine and 3-phenylsulfonamide anchoring to the hinge and DFG, respectively, as well as appropriate occupancy of the region between the gatekeeper and the αC-helix provided by substituents (e.g. H or OMe) in the 4-position and relatively small substituent (e.g. F, Cl, or OMe) in the 5-positions of the 3-phenylsulfonamide. Absence of this last structural feature was sufficient to eliminate NOD cell signaling, but not kinase inhibitory activity. Further interrogation of this portion of the molecule will likely provide additional insights into the SAR for disruption of NOD cell signaling.

Table 5. Physicochemical properties and pharmacokinetic parameters of **18t**.

Aqueous Solubility at pH 7.4 (μM)	Permeability ($\times 10^{-6}$ cm/s)	Mouse Microsome Stability	
		$t_{1/2}$ (min)	CL_{int} (μL/min/mg)
≥100	2.9	25.6	27

In vivo Pharmacokinetics*					
C_{max} (μM)	T_{max} (h)	$t_{1/2}$ (h)	AUC (min•μg/mL)	V_d (L/kg)	CL (mL/min/kg)

0.55 ± 0.2	1.2	4.7 ± 0.2	175.2 ± 59.9	24.0 ± 6.2	59.7 ± 15.1

* Single 10 mg/kg intraperitoneal administration of **18t** to female C57BL/6 mice.

Since **18t** was among a set of compounds that displayed potent biochemical RIPK2 kinase and NOD cell signaling inhibitory activities, it was selected as a representative compound for further *in vitro* characterization and pharmacokinetic study (Table 5). Its solubility in pH 7.4 PBS buffer was ≥100 μM. The compound also demonstrated both moderate permeability of 2.9×10^{-6} cm/s in the PAMPA and mouse liver microsome stability (CL_{int} = 27 μL/min/mg; $t_{1/2}$ = 25.6 min) assays. After a single 10 mg/kg intraperitoneal administration [6% Captisol® in water formulation] to 8-week old female C57BL/6 mice (n = 5 mice/per group), the compound reached a maximum plasma concentration (C_{max}) of 0.55 ± 0.2 μM in 1.2 h (T_{max}) with a plasma elimination half-life ($t_{1/2}$) of 4.7 ± 0.2 h, an AUC of 175.2 ± 59.9 min•μg/mL, a volume of distribution of 24.0 ± 6.2 L/kg and clearance (CL) of 59.7 ± 15.1 mL/min/kg, well below mouse hepatic blood flow. Overall, these properties support **18t** as a potential useful *in vivo* probe for RIPK2 kinase and NOD cell signaling inhibition.

4. Conclusion

A new class of RIPK2 kinase/NOD cell signaling inhibitors based on a 3,5-diphenyl-2-aminopyridine scaffold was developed. Several co-crystal structures of RIPK2•inhibitor complexes were analyzed to provide insights into inhibitor selectivity versus a related kinase (e.g. ALK2). The inhibitors occupy space further into the hydrophobic binding pocket of RIPK2 altering the position of the DFG motif. The SAR studies also revealed that achieving potent NOD cell signaling inhibition depends on three structural features of the inhibitors: anchoring to the hinge and DFG via the 2-aminopyridine and 3-phenylsulfonamide, respectively, as well as

appropriate occupancy of the region between the gatekeeper and the αC-helix provided by substituents in the 4- and 5-positions of the 3-phenylsulfonamide. For example, a representative compound from the series **18t** demonstrated both potent inhibition of recombinant RIPK2 kinase (IC_{50} = 16 ± 5 nM), > 20-fold selectivity versus ALK2 and NOD cell signaling inhibition (IC_{50} = 26 ± 4 nM). In addition, this compound was found to have *in vitro* ADME and pharmacokinetic characteristics further supporting the use of 3,5-diphenyl-2-aminopyridines (e.g. **18t** – CSLP37 and **18ae** – CSLP58) as the basis for generating *in vivo* pharmacology probes of RIPK2 kinase and NOD cell signaling functions.

5. Experimental section

Unless otherwise stated, all reagents and solvents were obtained from commercial sources and used directly without further purification. All reactions involving air-sensitive reagents were carried out with magnetic stirring and in oven-dried glassware with rubber septa under argon unless otherwise noted. Reactions were monitored by thin-layer chromatography on Baker-flex® silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agent (phosphomolybdic acid stain). Flash chromatography was performed on silica gel (230−400 mesh) utilizing Teledyne ISCO CombiFlash® Rf. The NMR spectra were recorded at 25 ºC using a JEOL ECA (^{1}H NMR at 400, 500, or 600 MHz, and ^{13}C NMR at 100, 125, or 150 MHz). Chemical shifts (δ) are given in parts per million (ppm) with reference to solvent signals [^{1}H-NMR: $CDCl_3$ (7.26 ppm), CD_3OD (3.30 ppm), DMSO-d_6 (2.49 ppm); ^{13}C-NMR: $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm), DMSO-d_6 (39.5 ppm)]. Coupling constants (*J*) are given in Hz. The C-F coupling patterns labeled in ^{13}C-NMR indicate visible patterns in spectra. High resolution mass spectra (HRMS) were carried out using AccuTOF by the Department of Chemistry, The University of Texas at Austin. The spectra were measured using TOF-MS with an ESI ionization

source and reported as *m/z* (relative intensity) for the molecular ion [M]. All tested compounds had a purity ≥95% as determined by high-performance liquid chromatography (HPLC) analyses using a Waters 1525 instrument equipped with a quaternary pump and a Proteo-C12 column (250 mm × 1 mm, 4 μm). UV absorption was monitored at λ = 220 nm. HPLC gradient went from 0% (method A) or 2% (method B) MeCN in H_2O to 90% MeCN in H_2O (both solvents contain 0.1% trifluoroacetic acid) with a total run time of 30 min and a flow rate of 0.5 mL/min.

General Procedure for the Preparation of *N*-(Bromophenyl)sulfonamides (Method A); *N*-(4-bromo-2-methoxyphenyl)propane-1-sulfonamide (13a). To a solution of 4-bromo-2-methoxyaniline (**11a**) (300 mg, 1.48 mmol) in anhydrous CH_2Cl_2 (15 mL) was added pyridine (0.24 mL, 2.97 mmol) and 1-propanesulfonyl chloride (0.18 mL, 1.63 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 16 h. After being quenched with 1 N $HCl_{(aq)}$ (1.0 mL), water and CH_2Cl_2 were added and then the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13a** (490.1 mg, 99%) as a light yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.41 (1 H, d, *J* = 8.6 Hz), 7.08 (1 H, dd, *J* = 8.3, 2.3 Hz), 7.03 (1 H, d, *J* = 2.5 Hz), 6.74 (1 H, br) , 3.88 (3 H, s), 3.02–2.98 (2 H, m), 1.83–1.79 (2 H, m), 1.00 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 149.5, 125.5, 124.2, 121.0, 117.5, 114.3, 56.1, 53.1, 17.1, 12.8.

***N*-(3-Bromo-5-methoxyphenyl)methanesulfonamide (13b).** Prepared from **11b** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **13b** (82%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 6.96–6.95 (2 H, m), 6.86 (1 H, s), 6.75–6.74 (1 H, m), 3.79 (3 H, s), 3.05 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 161.1, 137.8, 123.5, 115.1, 113.8, 105.0, 55.7, 39.5.

***N*-(3-Bromo-5-methoxyphenyl)ethanesulfonamide (13c).** Prepared from **11b** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **13c** (88%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34 (1 H, br), 6.96 (1 H, t, *J* = 1.8 Hz), 6.82 (1 H, t, *J* = 1.8 Hz), 6.75 (1 H, t, *J* = 1.8 Hz), 3.78 (3 H, s), 3.18 (2 H, q, *J* = 7.3 Hz), 1.36 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 161.0, 139.0, 123.4, 114.7, 113.5, 104.5, 55.6, 46.0, 8.1.

***N*-(3-Bromo-5-methoxyphenyl)propane-1-sulfonamide (13d).** Prepared from **11b** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **13d** (86%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34 (1 H, br), 6.96 (1 H, t, *J* = 1.8 Hz), 6.82 (1 H, t, *J* = 1.8 Hz), 6.75 (1 H, d, *J* = 2.3 Hz), 3.78 (3 H, s), 3.13–3.09 (2 H, m), 1.90–1.79 (2 H, m), 1.02 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 161.0, 139.0, 123.4, 114.6, 113.4, 104.5, 55.6, 53.3, 17.1, 12.8.

***N*-(5-Bromo-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (13j).** Prepared from **11e** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13j** (76%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49 (1 H, s), 7.04–7.00 (2 H, m), 3.99 (3 H, d, *J* = 2.3 Hz), 3.12–3.08 (2 H, m), 1.89–1.80 (2 H, m), 1.04 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.6 (d, J_{CF} = 251.4 Hz), 135.7 (d, J_{CF} = 12.7 Hz), 132.1 (d, J_{CF} = 5.9 Hz), 116.7 (d, J_{CF} = 2.9 Hz), 115.7 (d, J_{CF} = 22.5 Hz), 115.4 (d, J_{CF} = 10.8 Hz), 61.6 (d, J_{CF} = 6.8 Hz), 53.6, 17.2, 12.8.

***N*-(5-Bromo-2-methoxy-3-methylphenyl)propane-1-sulfonamide (13k).** Prepared from **11g** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13k** (75%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.51 (1 H, d, *J* = 2.3 Hz), 7.13 (1 H, br), 7.04 (1 H, d, *J* = 1.7 Hz), 3.74 (3 H, s), 3.12–3.09 (2 H, m), 2.26 (3 H, s), 1.86–1.81 (2 H,

m), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 146.2, 133.1, 131.8, 128.9, 118.4, 117.2, 60.6, 53.5, 17.1, 15.9, 12.7.

General Procedure for the Preparation of *N*-(Bromophenyl)sulfonamides (Method B); *N*-(3-bromo-5-methoxyphenyl)propane-2-sulfonamide (13e). To a solution of 3-bromo-5-methoxyaniline (**11b**) (150.0 mg, 0.74 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (8 mL) was added pyridine (0.08 mL, 0.55 mmol) and 2-propanesulfonyl chloride (0.09 mL, 0.82 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 40 h. After being quenched with 1 N $HCl_{(aq)}$ (0.5 mL) and water, CH_2Cl_2 were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **13e** (67.8 mg, 30%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) 7.12 (1 H, br), 6.96 (1 H, t, *J* = 2.1 Hz), 6.81 (1 H, t, *J* = 2.1 Hz), 6.76 (1 H, t, *J* = 2.1 Hz), 3.78 (3 H, s), 3.35 (1 H, sep, *J* = 6.9 Hz), 1.40 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 161.0, 139.4, 123.4, 114.6, 113.3, 104.5, 55.6, 52.8, 16.4.

***N*-(3-Bromo-5-methoxyphenyl)benzenesulfonamide (13f).** Prepared from **11b** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13f** (79%) as a light brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.83 (2 H, d, *J* = 7.3 Hz), 7.57 (1 H, t, *J* = 7.8 Hz), 7.48 (2 H, t, *J* = 7.8 Hz), 7.14 (1 H, br), 6.81 (1 H, s), 6.77 (1 H, s), 6.64 (1 H, t, *J* = 1.8 Hz), 3.71 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.7, 138.5, 138.5, 133.4, 129.2, 127.2, 123.0, 115.9, 113.9, 105.5, 55.6.

***N*-(5-Bromo-2-methoxyphenyl)propane-1-sulfonamide (13g).** Prepared from **11c** and the mixture was stirred at room temperature for 48 h. The reaction was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to give **13g** (85%) as a yellow

solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.65 (1 H, d, *J* = 2.3 Hz), 7.18 (1 H, dd, *J* = 8.6, 2.3 Hz), 6.86 (1 H, br), 6.76 (1 H, d, *J* = 8.6 Hz), 3.86 (3 H, s), 3.05–3.02 (2 H, m), 1.83–1.79 (2 H, m), 1.00 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.7, 127.6, 127.3, 122.0, 113.3, 112.0, 56.0, 53.2, 17.1, 12.7.

***N*-(5-Bromo-2-methylphenyl)propane-1-sulfonamide (13h).** Prepared from **11d** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13h** (96%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.64 (1 H, d, *J* = 2.3 Hz), 7.22 (1 H, dd, *J* = 8.0, 1.7 Hz), 7.07 (1 H, d, *J* = 8.0 Hz), 6.42 (1 H, br), 3.13–3.10 (2 H, m), 2.25 (3 H, s), 1.90–1.82 (2 H, m), 1.05 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 136.3, 132.3, 128.2, 127.7, 123.8, 120.3, 54.0, 17.6, 17.2, 12.9.

***N*-(5-Bromo-3-methoxy-2-methylphenyl)propane-1-sulfonamide (13i).** Prepared from **11e** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90) to give **13i** (78%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.05 (1 H, d, *J* = 2.8 Hz), 6.97 (1 H, d, *J* = 2.8 Hz), 6.71 (1 H, br), 3.76 (3 H, s), 3.09–3.05 (2 H, m), 2.33 (3 H, s), 1.86–1.81 (2 H, m), 1.02 (3 H, t, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 158.2, 136.2, 125.9, 121.6, 115.2, 107.9, 55.6, 53.8, 17.2, 17.1, 12.8.

***N*-(5-Bromo-2-methoxybenzyl)propane-1-sulfonamide (13l).** Prepared from **11h** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13l** (57%) as a clear oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.39–7.38 (2 H, m), 6.77–675 (1 H, m), 5.06 (1 H, br), 4.22 (2 H, d, *J* = 6.3 Hz), 3.83 (3 H, s), 2.84–2.81 (2 H, m), 1.72–1.65 (2 H, m), 0.92 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.4, 132.1, 132.0, 127.4, 112.7, 112.0, 55.6, 54.8, 43.0, 17.2, 12.8.

***N*-(3-Bromo-5-ethoxyphenyl)propane-2-sulfonamide (13o).** Prepared from **11i** and purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 10:90) to give **13o** (58%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.21 (1 H, br), 6.95 (1 H, s), 6.79 (1 H, s), 6.76 (1 H, s), 3.98 (2 H, q, *J* = 7.4 Hz), 3.35 (1 H, sep, *J* = 7.4 Hz), 1.40–1.37 (9 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.4, 139.3, 123.3, 114.4, 113.7, 104.9, 64.0, 52.7, 16.4, 14.6.

Preparation of 6-Bromo-1-(propylsulfonyl)indoline (13m) (Method C). To a solution of 6-bromoindoline (**12a**) (100.0 mg, 0.51 mmol) and a catalytic amount of DMAP in pyridine (2 mL) was added 1-propanesulfonyl chloride (0.09 mL, 0.76 mmol) under an argon atmosphere. The mixture was stirred at 50 ºC for 3 h. After being quenched with 1 N $HCl_{(aq)}$ (1.0 mL) and water, EtOAc were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13m** (102.1 mg, 66%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.50 (1 H, d, *J* = 1.7 Hz), 7.10 (1 H, dd, *J* = 8.0, 1.7 Hz), 7.03 (1 H, d, *J* = 8.0 Hz), 4.02 (2 H, t, *J* = 8.6 Hz), 3.08 (2 H, t, *J* = 8.0 Hz), 3.04–3.00 (2 H, m), 1.92–1.84 (2 H, m), 1.05 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 143.4, 130.0, 126.4, 126.1, 121.2, 116.4, 51.0, 50.6, 27.5, 16.7, 13.0.

Preparation of 6-Bromo-4-(propylsulfonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (13n) (Method D). To a solution of 6-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**12b**) (44.0 mg, 0.22 mmol) in pyridine (1 mL) was added 1-propanesulfonyl chloride (0.04 mL, 0.33 mmol) under an argon atmosphere. The mixture was stirred at 50 ºC for 2.5 h. After being quenched with 1 N $HCl_{(aq)}$ (1.0 mL) and water, EtOAc were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane,

10:90 to 20:80) to give **13n** (49.6 mg, 70%) as a brown solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.76 (1 H, d, *J* = 2.3 Hz), 7.13 (1 H, dd, *J* = 8.6, 2.3 Hz), 6.79 (1 H, d, *J* = 8.6 Hz), 4.26 (2 H, t, *J* = 4.6 Hz), 3.85 (2 H, t, *J* = 4.6 Hz), 3.09–3.06 (2 H, m), 1.92–1.85 (2 H, m), 1.06 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 145.0, 128.1, 125.6, 124.3, 119.2, 113.0, 64.7, 54.0, 44.0, 17.0, 12.9.

General Procedure for the Preparation of *N*-(Bromophenyl)sulfonamides (Method E); *N*-(3-bromo-5-isopropoxyphenyl)propane-2-sulfonamide (13p). To a solution of 3-bromo-5-isopropoxyaniline (**11j**) (108.5 mg, 0.47 mmol) in pyridine (2.5 mL) was added 2-propanesulfonyl chloride (0.08 mL, 0.71 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 24 h. After being quenched with 1 N $HCl_{(aq)}$ (1.0 mL), water and EtOAc were added, the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13p** (73.1 mg, 46%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.31 (1 H, s), 6.94 (1 H, t, *J* = 1.7 Hz), 6.78 (1 H, t, *J* = 1.7 Hz), 6.75 (1 H, t, *J* = 1.7 Hz), 4.49 (1 H, sep, *J* = 5.7 Hz), 3.35 (1 H, sep, *J* = 6.9 Hz), 1.39 (6 H, d, *J* = 6.9 Hz), 1.31 (6 H, d, *J* = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.4, 139.4, 123.3, 114.9, 114.3, 105.9, 70.5, 52.7, 21.8, 16.4.

***N*-(5-Bromo-3-chloro-2-methoxyphenyl)propane-1-sulfonamide (13q).** Prepared from **11k** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13q** (58%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.61 (1 H, d, *J* = 2.3 Hz), 7.25 (1 H, d, *J* = 2.3 Hz), 7.10 (1 H, br), 3.90 (3 H, s), 3.14–3.11 (2 H, m), 1.88–1.83 (2 H, m), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 144.1, 133.2, 128.4, 127.8, 119.4, 117.4, 61.2, 53.9, 17.2, 12.8.

***N*-(5-Bromo-2,3-dimethoxyphenyl)propane-1-sulfonamide (13r).** Prepared from **11l** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **13r** (85%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33 (1 H, d, *J* = 1.8 Hz), 7.01 (1 H, br), 6.80 (1 H, d, *J* =2.3 Hz), 3.86 (6 H, s), 3.10–3.06 (2 H, m), 1.86–1.80 (2 H, m), 1.02 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 152.8, 136.6, 131.9, 116.8, 113.3, 111.3, 60.9, 56.0, 53.3, 17.1, 12.7.

***N*-(7-Bromo-2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)propane-1-sulfonamide (13s).** Prepared from **11m** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **13s** (80%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.25 (1 H, d, *J* = 2.3 Hz), 6.82 (1 H, d, *J* = 1.8 Hz), 6.67 (1 H br), 4.31–4.29 (2 H , m), 4.28–4.26 (2 H, m), 3.10–3.06 (2 H, m), 1.88–1.79 (2 H, m), 1.03 (3 H, t, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 144.2, 132.3, 127.3, 116.0, 114.3, 113.2, 64.6, 64.2, 53.4, 17.2, 12.8.

***N*-(5-Bromo-3-ethoxy-2-methoxyphenyl)propane-1-sulfonamide (13t).** Prepared from **11n** and purified by column chromatography on silica gel (EtOAc/hexane, 15:85) to give **13t** (87%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.22 (1 H, s), 6.98 (1 H, s), 6.51 (1 H, s), 4.04 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 3.01–2.97 (2 H, m), 1.88–1.78 (2 H, m), 1.44 (3 H, t, *J* = 6.9 Hz), 0.99 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 149.3, 146.8, 127.7, 115.8, 107.6, 105.9, 64.8, 56.1, 53.6, 17.1, 14.6, 12.9.

***N*-(5-Bromo-2-hydroxyphenyl)propane-1-sulfonamide (13u).** *N*-(5-Bromo-2-((*tert*-butyldimethylsilyl)oxy)phenyl)propane-1-sulfonamide was prepared from **11o** and purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 10:90) as a brown oil (86%); ^{1}H NMR ($CDCl_3$, 400 MHz) 7.65 (1 H, d, *J* = 2.3 Hz), 7.08 (1 H, dd, *J* = 8.5, 2.3 Hz), 6.72 (1 H, d, *J* = 8.2 Hz), 6.75 (1 H, br), 3.08–3.04 (2 H, m), 1.86–1.77 (2 H, m), 1.03–0.99 (12 H, m), 0.27 (6

H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 143.5, 129.8, 127.0, 121.4, 119.1, 114.0, 53.3, 25.6, 18.1, 17.2, 12.7, -4.3. To a solution of *N*-(5-bromo-2-((*tert*-butyldimethylsilyl)oxy)phenyl)propane-1-sulfonamide (35.0 mg, 0.09 mmol) in anhydrous THF (1 mL) were added 1 M tetrabutylammonium fluoride in THF (0.17 mL, 0.17 mmol) at 0 ºC. The mixture was stirred at 0 ºC for 1 h. After being quenched with saturated aqueous NH_4Cl (5 mL), EtOAc were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70) to give **13u** (23.6 mg, 93%) as a brown oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.46 (1 H, d, *J* = 2.3 Hz), 7.21 (1 H, dd, *J* = 8.6, 2.3 Hz), 6.82 (1 H, d, *J* = 8.6 Hz), 6.47 (1 H, br), 3.09–3.06 (2 H, m), 1.90–1.86 (2 H, m), 1.05 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 147.1, 129.3, 125.3, 125.2, 117.6, 112.6, 53.1, 17.0, 12.8.

General Procedure for the Preparation of *N*-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonamides (Method F); *N*-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14a). To a mixture of **13a** (50.0 mg, 0.16 mmol), bis(pinacolato)diboron (49.4 mg, 0.20 mmol), KOAc (47.7 mg, 0.49 mmol) and $PdCl_2$(dppf) (3.6 mg, 0.005 mmol) was added anhydrous THF (1.5 mL) under argon. The reaction was stirred at room temperature for 10 min then was refluxed for 16 h. After being quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to afford **14a** (46.6 mg, 81%) as a white solid; ; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.53 (1 H, d, *J* = 7.8 Hz), 7.41 (1 H, d, *J* = 7.8 Hz), 7.29 (1 H, s), 6.99 (1 H, br), 3.91 (3 H,

s), 3.04–3.00 (2 H, m), 1.82–1.74 (2 H, m), 1.33 (12 H, s), 0.97 (1 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 147.6, 129.2, 128.3, 117.8, 116.0, 83.9, 55.8, 52.9, 24.8, 17.1, 12.8.

***N*-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methane sulfonamide (14b).** Prepared from **13b** and purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **14b** (90%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.37 (1 H, br), 7.14 (1 H, d, *J* = 1.7 Hz), 7.10 (1 H, d, *J* = 2.9 Hz), 6.99, (1 H, t, *J* = 2.3 Hz), 3.78 (3 H, s), 2.98 (3 H, s), 1.30 (12 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.9, 137.6, 118.8, 115.8, 110.0, 84.0, 55.3, 39.0, 24.6.

***N*-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanesulfonamide (14c).** Prepared from **13c** and purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 20:80) to give **14c** (74%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.10–7.09 (2 H, m), 7.01 (1 H, t, *J* = 2.3 Hz), 6.93 (1 H, br), 7.02 (1 H, s), 3.81 (3 H, s), 3.13 (2 H, q, *J* = 7.4 Hz), 1.36–1.32 (15 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.1, 137.6, 118.5, 115.5, 109.6, 84.1, 55.4, 45.8, 24.8, 8.2.

***N*-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14d).** Prepared from **13d** and purified by column chromatography on silica gel (EtOAc/hexane, 15:85) to give **14d** (78%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.11–7.10 (1 H, m), 7.06 (1 H, s), 7.02 (1 H, s), 6.68 (1 H, br), 3.82 (3 H, s), 3.09–3.05 (2 H, m), 1.89–1.79 (2 H, m), 1.33 (12 H, s), 1.00 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.1, 137.6, 118.4, 115.5, 109.5, 84.1, 55.5, 53.2, 24.8, 17.2, 12.8.

***N*-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-2-sulfonamide (14e).** Prepared from **13e** and purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 20:80) to give **14e** (69%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500

MHz) 7.09–7.07 (2 H, m), 7.06–7.05 (1 H, m), 6.76 (1 H, br), 3.81 (3 H, s), 3.32 (1 H, sep, *J* = 6.9 Hz), 1.38 (6 H, d, *J* = 6.9 Hz), 1.33 (12 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.1, 137.9, 118.2, 115.2, 109.4, 84.1, 55.4, 52.4, 24.8, 16.5.

***N*-(3-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (14f).** Prepared from **13f** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **14f** (86%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.79 (2 H, d, *J* = 7.3 Hz), 7.51 (1 H, t, *J* = 7.3 Hz), 7.42 (2 H, t, *J* = 7.3 Hz), 7.04 (1 H, s), 6.93–6.92 (3 H, m), 3.75 (3 H, s), 1.29 (12 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 159.8, 138.9, 137.1, 133.0, 129.0, 127.2, 119.5, 115.8, 110.2, 84.0, 55.4, 24.8.

***N*-(2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14g).** Prepared from **13g** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **14g** (82%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.90 (1 H, s), 7.58 (1 H, d, *J* = 8.0 Hz), 6.89 (1 H, d, *J* = 8.0 Hz), 6.72 (1 H, br), 3.90 (3 H, s), 3.04–3.03 (2 H, t, *J* = 8.0 Hz), 1.82 (2 H, sex, *J* = 7.4 Hz), 1.32 (12 H, s), 0.99 (3 H, t, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 151.6, 132.4, 126.4, 125.7, 109.9, 83.8, 55.8, 53.0, 24.8, 17.2, 12.8.

***N*-(2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14h)**. Prepared from **13h** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **14h** (78%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.77 (1 H, s), 7.56 (1 H, d, *J* = 7.4 Hz), 7.23 (1 H, d, *J* = 7.4 Hz), 6.43 (1 H, br), 3.13–3.10 (2 H, m), 2.36 (3 H, s), 1.88 (2 H, sex, *J* = 8.0 Hz), 1.32 (12 H, s), 1.04 (3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 135.0, 134.4, 132.6, 130.7, 129.4, 83.9, 53.9, 24.8, 18.5, 17.3, 12.9.

***N*-(3-Methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14i).** Prepared from **13i** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90) to give **14i** (54%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.20 (1 H, d, J = 2.7 Hz), 7.14 (1 H, d, J = 2.7 Hz), 6.31 (1 H, br), 3.80 (3 H, s), 3.06–3.03 (2 H, m), 2.42 (3 H, s), 1.87–1.79 (2 H, m), 1.34 (12 H, s), 1.01 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.7, 135.9, 126.4, 117.5, 110.1, 83.9, 55.4, 53.6, 24.8, 17.2, 15.5, 12.9.

***N*-(3-Fluoro-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14j).** Prepared from **13j** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **14j** (68%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.67 (1 H, s), 7.29 (1 H, dd, J = 12.0, 1.2 Hz), 6.90 (1 H, s), 4.03 (3 H, d, J = 2.9 Hz), 3.10–3.07 (2 H, m), 1.87–1.80 (2 H, m), 1.31 (12 H, s), 1.02 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 153.8 (d, J_{CF} = 248.6 Hz), 139.2 (d, J_{CF} = 12.3 Hz), 130.4 (d, J_{CF} = 3.7 Hz), 120.6 (d, J_{CF} = 2.5 Hz), 118.7 (d, J_{CF} = 17.2 Hz), 84.2, 61.4 (d, J_{CF} = 8.6 Hz), 53.3, 24.8, 17.2, 12.8.

***N*-(2-Methoxy-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14k).** Prepared from **13k** and purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 20:80) to give **14k** (24%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.73 (1 H, s), 7.39 (1 H, s), 6.89 (1 H, s), 3.77 (3 H, s), 3.15–3.11 (2 H, m), 2.30 (3 H, s), 1.90–1.80 (2 H, m), 1.00 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 150.0, 133.5, 130.4, 130.1, 122.2, 83.9, 60.5, 53.4, 24.8, 17.2, 16.0, 12.8.

***N*-(2-Methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)propane-1-sulfonamide (14l).** Prepared from **13l** and purified by column chromatography on silica gel (EtOAc/hexane, 2.5:97.5) to give **14l** (71%) as a clear oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.77 (1 H, dd, J = 8.0, 1.7 Hz), 7.68 (1 H, d, J = 1.7 Hz), 6.89 (1 H, d, J = 8.6 Hz), 4.28 (2 H, d, J = 6.9

Hz), 3.88 (3 H, s), 2.82–2.79 (2 H, m), 1.68–1.60 (2 H, m), 1.33 (12 H, s), 0.87 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.0, 136.8, 136.2, 124.4, 109.8, 83.7, 55.4, 54.6, 43.7, 24.8, 17.2, 12.8.

1-(Propylsulfonyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (14m). Prepared from **13m** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90) to give **14m** (70%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.74 (1 H, s), 7.46 (1 H, d, *J* = 7.4 Hz), 7.20 (1 H, d, *J* = 7.4 Hz), 4.02 (2 H, t, *J* = 8.6 Hz), 3.14 (2 H, t, *J* = 8.6 Hz), 3.05–3.02 (2 H, m), 1.92–1.84 (2 H, m), 1.32 (12 H, s), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 141.7, 134.5, 130.2, 124.8, 118.9, 83.8, 50.9, 50.2, 28.2, 24.8, 16.7, 13.1.

4-(Propylsulfonyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (14n). Prepared from **13n** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90) to give **14n** (74%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.95 (1 H, d, *J* = 1.2 Hz), 7.48 (1 H, dd, *J* = 8.3, 1.2 Hz), 6.90 (1 H, d, *J* = 8.6 Hz), 4.30 (2 H, t, *J* = 4.6 Hz), 3.86 (2 H, t, *J* = 4.6 Hz), 3.13–3.09 (2 H, m), 1.93–1.85 (2 H, m), 1.31 (12 H, s), 1.05 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 148.7, 132.2, 129.0, 124.0, 117.2, 83.7, 65.1, 54.4, 44.0, 24.8, 17.0, 13.0.

***N*-(3-Ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-2-sulfonamide (14o).** Prepared from **13o** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to afford **14o** (63%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.09–7.08 (1 H, m), 7.05–7.04 (2 H, m), 6.63 (1 H, br), 4.04 (2 H, q, *J* = 6.9 Hz), 3.32 (1 H, sep, *J* = 6.9 Hz), 1.40−1.37 (9 H, m), 1.32 (12 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.5, 137.8, 118.2, 116.0, 109.9, 84.0, 63.6, 52.3, 24.8, 16.5, 14.7.

***N*-(3-Isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-2-sulfonamide (14p).** Prepared from **13p** and purified by column chromatography on silica gel (EtOAc/hexane, 2.5:97.5) to give **14p** (34%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.09 (1 H, d, *J* = 2.3 Hz), 7.04 (1 H, t, *J* = 2.3 Hz), 7.00 (1 H, d, *J* = 1.7 Hz), 6.04 (1 H, s), 4.59 (1 H, sep, *J* = 5.7 Hz), 3.32 (1 H, sep, *J* = 6.9 Hz), 1.38 (6 H, d, *J* = 6.9 Hz), 1.32–1.31 (18 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.4, 137.8, 118.0, 117.7, 111.0, 84.0, 70.0, 52.3, 24.8, 22.0, 16.5.

***N*-(3-Chloro-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14q).** Prepared from **13q** and purified by column chromatography on silica gel (EtOAc/hexane, 2.5:97.5) to give **14q** (46%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.79 (1 H, d, *J* = 1.2 Hz), 7.56 (1 H, d, *J* = 1.2 Hz), 6.96 (1 H, br), 3.92 (3 H, s), 3.15–3.12 (2 H, m), 1.88–1.83 (2 H, m), 1.32 (12 H, s), 1.03 (3 H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.6, 132.1, 131.8, 127.1, 122.9, 84.3, 61.1, 53.7, 24.8, 17.2, 12.8

***N*-(2,3-Dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14r).** Prepared from **13r** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **14r** (25%) as a clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.56 (1 H, d, *J* = 0.9 Hz), 7.12 (1 H, d, *J* = 1.4 Hz), 6.92 (1 H, br), 3.91 (3 H, s), 3.90 (3 H, s), 3.11–3.07 (2 H, m), 1.88–1.78 (2 H, m), 1.32 (12 H, s), 1.00 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 151.6, 140.3, 130.5, 117.3, 113.9, 84.0, 60.9, 55.9, 53.2, 24.8, 17.2, 12.8.

***N*-(7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)propane-1-sulfonamide (14s).** Prepared from **13s** and purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 25:75) to give **14s** (56%) as a white solid; ^{1}H NMR ($CDCl_3$, 600 MHz) 7.48 (1 H, s), 7.13 (1 H, s), 6.57 (1 H, s), 4.33–4.32 (2 H, m), 4.26–4.24 (2 H, m), 3.08–3.06 (2 H, m), 1.84 (2 H, sex, *J* = 8.2 Hz), 1.30 (12 H, s), 1.01 (3 H, t, *J* = 7.6 Hz); ^{13}C

NMR ($CDCl_3$, 150 MHz) 143.1, 136.3, 125.8, 119.9, 118.7, 83.8, 64.9, 63.9, 53.2, 24.8, 17.2, 12.8.

***N*-(2-Hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14u).** Prepared from **13u** and purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to give **14u** (73%) as a clear oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.67 (1 H, d, J = 1.2 Hz), 7.56 (1 H, dd, J = 8.0, 1.2 Hz), 6.94 (1 H, d, J = 8.0 Hz), 6.60 (1 H, s), 3.06–3.03 (2 H, m), 1.90–1.83 (2 H, m), 1.32 (12 H, s), 1.00 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 152.6, 134.6, 131.0, 123.0, 116.4, 83.9, 52.5, 24.8, 17.0, 12.8.

2-(3-Fluoro-4,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14v). Prepared from 5-bromo-1-fluoro-2,3-dimethoxybenzene (**13v**) and purified by column chromatography on silica gel (EtOAc/hexane, 5:95) to give **14v** (66%) as a clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.16 (1 H, dd, J = 10.8, 1.4 Hz), 7.09 (1 H, s), 3.94 (3 H, d, J = 1.4 Hz), 3.90 (3 H, s), 1.32 (12 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 155.4 (d, J_{CF} = 245.5 Hz), 153.0 (d, J_{CF} = 4.9 Hz), 139.6 (d, J_{CF} = 12.7 Hz), 115.4 (d, J_{CF} = 18.6 Hz), 113.2 (d, J_{CF} = 2.0 Hz), 84.0, 61.3 (d, J_{CF} = 4.9 Hz), 56.3, 24.8.

Preparation of *N*-(3-Ethoxy-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-sulfonamide (14t) (Method G). To a mixture of **13t** (60.0 mg, 0.17 mmol), bis(pinacolato)diboron (64.9 mg, 0.26 mmol), KOAc (50.0 mg, 0.51 mmol) and $PdCl_2$(dppf) (12.4 mg, 0.017 mmol) was added anhydrous 1,4-dioxane (0.9 mL) under argon. The reaction was put into a preheated oil bath (80 ºC) and stirred for 40 h. After being quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane,

10:90) to afford **14t** (19.8 mg, 29%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.24 (1 H, s), 7.26 (1 H, s), 7.18 (1 H, s), 4.10 (2 H, q, *J* = 6.9 Hz), 3.89 (3 H, s), 2.98–2.95 (2 H, m), 1.82–1.74 (2 H, m), 1.45 (3 H, t, *J* = 6.9 Hz), 1.34 (12 H, s), 0.95 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 153.0, 144.7, 138.7, 119.0, 103.4, 84.4, 64.5, 55.9, 52.5, 24.8. 17.0, 14.8, 12.9.

General Procedure for the Preparation of 3-Bromo-5-phenylpyridines; *N*-(4-(5-bromo-2-chloropyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (16a). To a mixture of **14a** (46.6 mg, 0.13 mmol), **15a** (41.7 mg, 0.13 mmol) and $Pd(PPh_3)_4$ (3.1 mg, 0.002 mmol) was added anhydrous acetonitrile (1 mL) and anhydrous DMF (0.5 mL) under argon. The reaction was stirred at room temperature for 10 min then 1 M Na_2CO_3 (0.3 mL, 0.30 mmol) was added. The mixture was put into a preheated oil bath (90 ºC) and stirred for 16 h. After being quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to afford **16a** (31.5 mg, 57%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.44 (1 H, d, *J* = 2.3 Hz), 7.81 (1 H, d, *J* = 2.3 Hz), 7.61 (1 H, d, *J* = 8.0 Hz), 7.02–6.99 (2 H, m), 6.94 (1 H, br), 3.92 (3 H, s), 3.11–3.08 (2 H, m), 1.89–1.84 (2 H, m), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 149.1, 148.2, 148.1, 141.7, 137.6, 132.4, 127.1, 122.3, 119.0, 118.8, 111.6, 56.0, 53.5, 17.2, 12.8.

***N*-(3-(5-Bromo-2-chloropyridin-3-yl)-5-methoxyphenyl)methanesulfonamide (16b).** Prepared from **14b** and **15a**, and then purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to give **16b** (88%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.45 (1 H, s), 7.80 (1 H, s), 7.45 (1 H, s), 6.88 (2 H, s), 6.74 (1 H, s), 3.83 (3 H, s), 3.08 (3

H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 165.0, 149.5, 147.9, 141.7, 138.4, 138.2, 137.4, 119.1, 112.9, 111.6, 106.2, 55.6, 39.4.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-methoxyphenyl)methanesulfonamide (16c)**. Prepared from **14b** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 60:40) to give **16c** (38%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.08 (1 H, s), 7.44 (1 H, d, *J* = 1.8 Hz), 6.88–6.87 (1 H, m), 6.85 (1 H, s), 6.72 (1 H, s), 4.79 (2 H, br), 3.81 (3 H, s), 3.05 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 161.1, 154.4, 147.8, 139.7, 139.2, 139.0, 122.6, 112.3, 110.5, 108.2, 105.7, 55.6, 39.7.

***N*-(3-(5-Bromo-2-chloropyridin-3-yl)-5-methoxyphenyl)ethanesulfonamide (16d).** Prepared from **14c** and **15a**, and then purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 25:75) to give **16d** (81%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.47 (1 H, d, *J* = 2.3 Hz), 7.80 (1 H, d, *J* = 2.9 Hz), 7.00 (1 H, br), 6.87 (1 H, t, *J* = 1.7 Hz), 6.86 (1 H, t, *J* = 1.7 Hz), 6.72 (1 H, t, *J* = 2.3 Hz), 3.84 (3 H, s), 3.20 (2 H, q, *J* = 7.4 Hz), 1.40 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.6, 149.5, 148.0, 141.7, 138.5, 138.3, 137.4, 119.1, 112.6, 111.3, 105.9, 55.6, 46.1, 8.3.

***N*-(3-(5-Bromo-2-chloropyridin-3-yl)-5-methoxyphenyl)propane-1-sulfonamide (16e).** Prepared from **14d** and **15a**, and then purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to give **16e** (96%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.46 (1 H, d, *J* = 2.3 Hz), 7.80 (1 H, d, *J* = 2.9 Hz), 7.28 (1 H, s), 6.87 (1 H, t, *J* = 1.7 Hz), 6.86 (1 H, t, *J* = 1.7 Hz), 6.72 (1 H, t, *J* = 1.7 Hz), 3.84 (3 H, s), 3.16–3.13 (2 H, m), 1.91–1.82 (2 H, m), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.5, 149.5, 148.0, 141.7, 138.4, 138.3, 137.4, 119.1, 112.6, 111.3, 105.8, 55.6, 53.4, 17.2, 12.8.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-methoxyphenyl)propane-1-sulfonamide (16f).** Prepared from **14d** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 45:55) to give **16f** (65%) as a pale yellow solid; ^{1}H NMR (CD_3OD, 500 MHz) 7.98 (1 H, d, *J* = 2.3 Hz), 7.50 (1 H, d, *J* = 2.3 Hz), 6.87 (1 H, t, *J* = 1.7 Hz), 6.84 (1 H, t, *J* = 1.7 Hz), 6.74 (1 H, t, *J* = 1.7 Hz), 3.82 (3 H, s), 3.13–3.10 (2 H, m), 1.81 (2 H, sex, *J* = 7.4 Hz), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 162.6, 148.2, 141.6, 141.0, 140.2, 124.7, 112.9, 110.6, 108.1, 107.9, 106.4, 56.0, 54.0, 18.4, 13.1.

***N*-(3-(5-Bromo-2-chloropyridin-3-yl)-5-methoxyphenyl)propane-2-sulfonamide (16g).** Prepared from **14e** and **15a**, and then purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 20:80) to give **16g** (92%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.46 (1 H, d, *J* = 2.9 Hz), 7.80 (1 H, d, *J* = 2.3 Hz), 7.19 (1 H, br), 6.90 (1 H, t, *J* = 2.3 Hz), 6.88 (1 H, t, *J* = 1.7 Hz), 6.70 (1 H, t, *J* = 1.7 Hz), 3.84 (3 H, s), 3.38 (1 H, sep, *J* = 6.9 Hz), 1.42 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.5, 149.5, 148.0, 141.7, 138.6, 138.4, 137.5, 119.0, 112.5, 111.1, 105.8, 55.6, 52.8, 16.5.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-methoxyphenyl)propane-2-sulfonamide (16h).** Prepared from **14e** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 45:55) to give **16h** (88%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.08 (1 H, d, *J* = 1.7 Hz), 7.76 (1 H, br), 7.45 (1 H, d, *J* = 2.3 Hz), 6.85 (1 H, t, *J* = 1.7 Hz), 6.84 (1 H, t, *J* = 1.7 Hz), 6.69 (1 H, t, *J* = 2.3 Hz), 4.82 (2 H, br), 3.82 (3 H, s), 3.36 (1 H, sep, *J* = 6.9 Hz), 1.41 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 161.2, 154.5, 147.8, 139.7, 139.5, 138.9, 122.7, 111.9, 110.1, 108.1, 105.5, 55.6, 53.0, 16.5.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-methoxyphenyl)benzenesulfonamide (16i).** Prepared from **14f** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane,

40:60) to give **16i** (85%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.98 (1 H, s), 7.79 (2 H, d, *J* = 8.0 Hz), 7.53 (1 H, t, *J* = 7.4 Hz), 7.43 (2 H, t, *J* = 7.4 Hz), 7.30 (1 H, d, *J* = 2.3 Hz), 6.72 (1 H, s), 6.62 (1 H, s), 6.58 (1 H, s), 3.73 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.8, 154.3, 147.3, 139.8, 139.0, 139.0, 138.2, 133.0, 129.0, 127.1, 122.8, 112.5, 110.4, 107.9, 106.2, 55.4.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (16j).** Prepared from **14g** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **16j** (92%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.08 (1 H, s), 7.59 (1 H, d, *J* = 1.7 Hz), 7.44 (1 H, d, *J* = 2.3 Hz), 7.17 (2 H, dd, *J* = 8.6, 2.3 Hz), 6.99 (1 H, d, *J* = 8.6 Hz), 6.89 (1 H, s), 4.65 (2 H, br), 3.94 (3 H, s), 3.08–3.04 (2 H, m), 1.90–1.83 (2 H, m), 1.03 (3 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.6, 148.8, 147.6, 139.7, 132.0, 129.8, 128.4, 127.0, 125.1, 119.9, 111.3, 56.0, 53.8, 17.2, 12.9.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2-methylphenyl)propane-1-sulfonamide (16k).** Prepared from **14h** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **16k** (82%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.06 (1 H, d, *J* = 2.3 Hz), 7.51 (1 H, d, *J* = 1.4 Hz), 7.46 (1 H, d, *J* = 2.3 Hz), 7.31 (1 H, d, *J* = 7.8 Hz), 7.17 (1 H, dd, *J* = 7.8, 1.4 Hz), 6.80 (1 H, br), 4.75 (2 H, br), 3.15–3.11 (2 H, m), 2.36 (3 H, s), 1.90 (2 H, sex, *J* = 7.8 Hz), 1.06 (3 H, t, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.6, 147.7, 139.7, 135.7, 135.7, 132.0, 129.9, 125.6, 122.4, 122.1, 108.3, 54.7, 17.8, 17.3, 12.9.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-3-methoxy-2-methylphenyl)propane-1-sulfonamide (16l).** Prepared from **14i** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to give **16l** (81%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.10 (1 H, d, *J* = 2.3 Hz), 7.37 (1 H, d, *J* = 2.8 Hz), 7.13 (1 H, d, *J* = 2.8 Hz), 6.80 (1 H,

br), 6.57 (1 H, d, *J* = 2.3 Hz), 4.48 (2 H, br), 3.79 (3 H, s), 3.16–3.12 (2 H, m), 2.02 (3 H, s), 1.93–1.84 (2 H, m), 1.06 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.5, 154.5, 148.0, 139.7, 137.7, 137.0, 122.6, 119.8, 112.0, 107.9, 107.8, 55.5, 54.1, 17.3, 13.8, 12.9.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (16m)**. Prepared from **14j** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **16m** (83%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz) 8.09 (1 H, d, *J* = 1.4 Hz), 7.43 (1 H, d, *J* = 1.4 Hz), 7.37 (1 H, s), 7.24 (1 H, s), 6.96 (1 H, d, *J* = 11.7 Hz), 4.75 (2 H, s), 4.06 (3 H, d, *J* = 2.1 Hz), 3.12–3.10 (2 H, m), 1.87 (2 H, sex, *J* = 7.6 Hz), 1.05 (3 H, t, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 154.5 (d, J_{CF} = 248.4 Hz), 154.4, 148.2, 139.7, 136.6 (d, J_{CF} = 11.8 Hz), 132.2 (d, J_{CF} = 8.9 Hz), 131.7 (d, J_{CF} = 5.9 Hz), 121.2, 114.6, 112.7 (d, J_{CF} = 20.7 Hz), 108.3, 61.6 (d, J_{CF} = 7.4 Hz), 54.2, 17.2, 12.8.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2-methoxy-3-methylphenyl)propane-1-sulfonamide (16n).** Prepared from **14k** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to give **16n** (87%) as a light brown solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.08 (1 H, d, *J* = 2.3 Hz), 7.44 (1 H, d, *J* = 2.3 Hz), 7.37 (1 H, d, *J* = 1.7 Hz), 7.04 (1 H, br), 6.97 (1 H, d, *J* = 1.2 Hz), 4.72 (2 H, br), 3.82 (3 H, s), 3.15–3.12 (2 H, m), 2.35 (3 H, s), 1.92–1.86 (2 H, m), 1.05 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.5, 147.7, 147.2, 139.7, 133.1, 132.3, 131.3, 126.6, 122.5, 116.0, 108.3, 60.7, 54.2, 17.3, 16.3, 12.9.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2-methoxybenzyl)propane-1-sulfonamide (16o).** Prepared from **14l** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **16o** (78%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.98 (1 H, s), 7.39–7.33 (3 H, m), 6.96 (1 H, d, *J* = 8.6 Hz), 5.45 (1 H, t, *J* = 6.3 Hz), 4.72 (2 H, br), 4.29 (2 H, d, *J* = 6.3 Hz), 3.90 (3 H, s), 2.91–2.88 (2 H, m), 1.79–1.72 (2 H, m), 0.96 (3

H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.2, 154.8, 147.2, 139.6, 129.7, 129.6, 128.9, 126.3, 122.7, 111.0, 108.2, 55.6, 54.8, 43.2, 17.3, 12.9.

5-Bromo-3-(1-(propylsulfonyl)indolin-6-yl)pyridin-2-amine (16p). Prepared from **14m** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to give **16p** (70%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.07 (1 H, d, *J* = 2.3 Hz), 7.43 (1 H, d, *J* = 2.3 Hz), 7.39 (1 H, d, *J* = 1.2 Hz), 7.27 (1 H, d, *J* = 8.6 Hz), 7.04 (1 H, dd, *J* = 7.4, 1.2 Hz), 4.67 (2 H, br), 4.08 (2 H, t, *J* = 8.6 Hz), 3.18 (2 H, t, *J* = 8.6 Hz), 3.06–3.03 (2 H, m), 1.93–1.85 (2 H, m), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.5, 147.8, 143.0, 139.7, 136.6, 131.2, 126.0, 123.4, 123.0, 113.2, 108.2, 51.4, 50.4, 27.8, 16.7, 13.0.

5-Bromo-3-(4-(propylsulfonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)pyridin-2-amine (16q). Prepared from **14n** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to give **16q** (85%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.07 (1 H, s), 7.60 (1 H, d, *J* = 1.8 Hz), 7.45 (1 H, d, *J* = 1.4 Hz), 7.08 (1 H, d, *J* = 8.7, 1.8 Hz), 7.00 (1 H, d, *J* = 8.7 Hz), 7.24 (1 H, s), 4.72 (2 H, br), 4.33 (2 H, t, *J* = 4.1 Hz), 3.87 (2 H, t, *J* = 4.6 Hz), 3.15–3.11 (2 H, m), 1.91 (2 H, sex, *J* = 7.8 Hz), 1.07 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.7, 147.5, 146.0, 139.6, 129.2, 125.6, 124.6, 122.3, 118.6, 65.0, 54.8, 44.0, 17.1, 12.9.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-ethoxyphenyl)propane-2-sulfonamide (16r).** Prepared from **14o** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 35:65) to afford **16r** (85%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.07 (1 H, d, *J* = 2.3 Hz), 7.80 (1 H, br), 7.45 (1 H, d, *J* = 2.3 Hz), 6.85 (1 H, s), 6.82 (1 H, br), 6.68(1 H, s), 4.84 (2 H, br), 4.03 (2 H, q, *J* = 6.9 Hz), 3.36 (1 H, sep, *J* = 6.9 Hz), 1.43−1.40

(9 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.5, 154.5, 147.6, 139.7, 139.4, 138.8, 122.8, 111.7, 110.6, 108.1, 105.9, 63.9, 52.9, 24.8, 16.5, 14.6.

***N*-(3-(2-Amino-5-bromopyridin-3-yl)-5-isopropoxyphenyl)propane-2-sulfonamide (16s).** Prepared from **14p** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **16s** (81%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.08 (1 H, s), 7.68 (1 H, s), 7.45 (1 H, d, *J* = 2.3 Hz), 6.84 (1 H, t, *J* = 2.3 Hz), 6.80 (1 H, s), 6.68 (1 H, s), 4.84 (2 H, br), 4.56 (1 H, sep, *J* = 5.7 Hz), 3.36 (1 H, sep, *J* = 6.9 Hz), 1.41 (6 H, d, *J* = 6.9 Hz), 1.34 (6 H, d, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.5, 154.5, 147.6, 139.7, 139.5, 138.9, 122.8, 111.7, 111.6, 108.1, 107.0, 70.3, 52.9, 21.9, 16.5.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-3-chloro-2-methoxyphenyl)propane-1-sulfonamide (16t).** Prepared from **14q** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70) to give **16t** (78%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.11 (1 H, d, *J* = 2.3 Hz), 7.50 (1 H, d, *J* = 1.7 Hz), 7.44 (1 H, d, *J* = 2.3 Hz), 7.19 (1 H, d, *J* = 2.3 Hz), 7.13 (1 H, br), 4.68 (2 H, br), 3.97 (3 H, s), 3.16–3.13 (2 H, m), 1.93–1.86 (2 H, m), 1.06 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.3, 148.4, 144.9, 130.7, 134.0, 132.9, 128.3, 125.5, 121.0, 116.9, 108.4, 61.3, 54.5, 17.3, 12.8.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2,3-dimethoxyphenyl)propane-1-sulfonamide (16u).** Prepared from **14r** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70) to give **16u** (69%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.09 (1 H, d, *J* = 2.3 Hz), 7.46 (1 H, d, *J* = 2.3 Hz), 7.20 (1 H, d, *J* = 1.7 Hz), 7.12 (1 H, br), 6.72 (1 H, d, *J* = 2.3 Hz), 4.72 (2 H, br), 3.93 (3 H, s), 3.90 (3 H, s), 3.12–3.09 (2 H, m), 1.90–1.83 (2 H, m), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.5, 152.8, 147.8, 139.6, 137.5, 132.9, 131.6, 122.6, 110.8, 108.2, 61.0, 56.0, 54.0, 17.2, 12.8.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-3-ethoxy-2-methoxyphenyl)propane-1-sulfonamide (16v).** Prepared from **14t** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to give **16v** (89%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.19 (1 H, d, *J* = 2.3 Hz), 7.50 (1 H, d, *J* = 2.3 Hz), 7.21 (1 H, s), 6.88 (1 H, s), 6.70 (1 H, s), 4.52 (2 H, br), 4.14–4.02 (2 H, m), 3.92 (3 H, s), 2.76–2.69 (1 H, m), 2.60–2.53 (1 H, m), 1.60–1.51 (1 H, m), 1.47 (3 H, t, *J* = 6.9 Hz), 1.29–1.20 (1 H, m), 0.84 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.2, 150.2, 148.8, 147.3, 140.8, 127.2, 121.5, 121.0, 113.8, 110.0, 109.5, 64.8, 56.2, 53.8, 17.1, 14.7, 12.9.

***N*-(5-(2-Amino-5-bromopyridin-3-yl)-2-hydroxyphenyl)propane-1-sulfonamide (16w).** Prepared from **14u** and **15b**, and then purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 1:99 to 3:97) to give **16w** (61%) as a brown solid; ^{1}H NMR (CD_3OD, 500 MHz) 7.93 (1 H, s), 7.46 (1 H, d, *J* = 2.3 Hz), 7.43 (1 H, d, *J* = 1.7 Hz), 7.11 (1 H, dd, *J* = 7.7, 2.9 Hz), 6.97 (1 H, d, *J* = 8.6 Hz), 3.07–3.04 (2 H, m), 1.86 (2 H, sex, *J* = 8.0 Hz), 1.00 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.9, 151.4, 147.4, 141.0, 129.2, 127.8, 126.6, 126.2, 124.8, 117.1, 108.2, 25.0, 18.3, 13.2.

5-Bromo-3-(3-fluoro-4,5-dimethoxyphenyl)pyridin-2-amine (16x). Prepared from **14v** and **15b**, and then purified by column chromatography on silica gel (EtOAc/hexane, 30:70) to give **16x** (39%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.09 (1 H, d, *J* = 2.3 Hz), 7.45 (1 H, d, *J* = 2.3 Hz), 6.81 (1 H, dd, *J* = 10.9, 2.3 Hz), 6.73 (1 H, s), 4.68 (2 H, br), 3.97 (3 H, s), 3.90 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.0 (d, J_{CF} = 246.1 Hz), 154.4, 154.1 (d, J_{CF} = 6.2 Hz), 147.9, 139.6, 137.0 (d, J_{CF} = 13.5 Hz), 131.7 (d, J_{CF} = 9.8 Hz), 122.2, 109.3 (d, J_{CF} = 20.9 Hz), 108.3, 108.0 (d, J_{CF} = 2.5 Hz), 61.5 (d, J_{CF} = 3.7 Hz), 56.4.

***N*-(5-(5-Bromopyridin-3-yl)-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (16y).** Prepared from **14j** and **15c**, and then purified by column chromatography on silica gel (EtOAc/hexane, 0:100 to 25:75) to give **16y** (89%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz) 8.69 (1 H, s), 8.67 (1 H, s), 7.96 (1 H, s), 7.54 (1 H, s), 7.09–7.05 (2 H, m), 4.08 (3 H, d, J = 2.4 Hz), 3.11 (2 H, t, J = 8.1 Hz), 1.95–1.84 (2 H, sex, J = 7.8 Hz), 1.06–1.03 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 153.7 (d, J_{CF} = 247.1 Hz), 149.9, 146.1, 136.9 (d, J_{CF} = 19.5 Hz), 136.7, 136.3, 132.0 (d, J_{CF} = 9.0 Hz), 131.7 (d, J_{CF} = 6.0 Hz), 121.0, 112.8, 111.2 (d, J_{CF} = 19.5 Hz), 61.6 (d, J_{CF} = 7.2 Hz), 53.7, 17.3, 12.9.

***N*-(5-(5-Bromo-2-chloropyridin-3-yl)-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (16z).** Prepared from **14j** and **15a**, and then purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85) to give **16z** (85%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz) 8.46 (1 H, d, J = 2.1 Hz), 7.78 (1 H, d, J = 2.1 Hz), 7.41 (1 H, s), 7.06 (1 H, s), 6.96 (1 H, dd, J = 12.4, 1.4 Hz), 4.09 (3 H, d, J = 2.1 Hz), 3.13 (2 H, t, J = 7.6 Hz), 1.87 (2 H, sex, J = 7.6 Hz), 1.04 (3 H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 153.8 (d, J_{CF} = 246.9 Hz), 149.6, 148.0, 141.6, 136.8 (d, J_{CF} = 11.8 Hz), 136.4, 131.4 (d, J_{CF} = 8.9 Hz), 131.1 (d, J_{CF} = 4.4 Hz), 119.1, 114.8, 113.3 (d, J_{CF} = 22.2 Hz), 108.3, 61.6 (d, J_{CF} = 7.4 Hz), 53.7, 17.2, 12.8.

General Procedure for the Preparation of *tert*-Butyl 4-(4-(6-chloro-5-phenylpyridin-3-yl)phenyl)piperazine-1-carboxylate; ***tert*-butyl 4-(4-(6-chloro-5-(3-methoxy-4-(propylsulfonamido)phenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17a).** To a mixture of **16a** (31.0 mg, 0.07 mmol), 4-(4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester (31.6 mg, 0.08 mmol) and $Pd(PPh_3)_4$ (12.8 mg, 0.01 mmol) was added anhydrous DME (2 mL) under argon. The reaction was stirred at room temperature for 10 min then 1 M Na_2CO_3 (0.15 mL, 0.15 mmol) was added. The mixture was refluxed for 16 h. After being

quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **17a** (35.6 mg, 80%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.56 (1 H, d, *J* = 2.3 Hz), 7.80 (1 H, d, *J* = 2.3 Hz), 7.62 (1 H, d, *J* = 8.6 Hz), 7.51 (2 H, d, *J* = 8.6 Hz), 7.07–7.05 (2 H, m), 7.00 (2 H, d, *J* = 9.2 Hz), 6.93 (1 H, s), 3.92 (3 H, s), 3.61–3.59 (4 H, m), 3.22–3.21 (4 H, m), 3.12–3.08 (2 H, m), 1.92–1.84 (2 H, m), 1.48 (9 H, s), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.6, 151.3, 148.2, 147.2, 145.9, 137.1, 135.8, 135.5, 134.0, 127.7, 127.0, 126.5, 122.3, 119.1, 116.2, 111.9, 80.0, 56.0, 53.4, 48.6, 28.3, 17.2, 12.8.

***tert*-Butyl 4-(4-(6-chloro-5-(3-methoxy-5-(methylsulfonamido)phenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17b).** Prepared from **16b** and purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 60:40) to give **17b** (83%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.56 (1 H, d, *J* = 2.3 Hz), 7.79 (1 H, d, *J* = 2.3 Hz), 7.53 (1 H, br), 7.49 (2 H, d, *J* = 8.7 Hz), 6.98 (2 H, d, *J* = 8.7 Hz), 6.95–6.94 (1 H, m), 6.91 (1 H, t, *J* = 2.3 Hz), 6.81–6.80 (1 H, m), 3.84 (3 H, s), 3.60–3.58 (4 H, m), 3.21–3.19 (4 H, m), 3.08 (3 H, s), 1.48 (9 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.4, 154.7, 151.3, 147.0, 146.2, 139.8, 138.2, 137.1, 135.7, 135.6, 127.8, 126.8, 116.5, 113.2, 111.7, 105.8, 80.1, 55.6, 48.6, 39.4, 28.4.

***tert*-Butyl 4-(4-(6-chloro-5-(3-(ethylsulfonamido)-5-methoxyphenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17c).** Prepared from **16d** and purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 45:55) to give **17c** (99%) as a white solid; ^{1}H NMR ($CDCl_3$, 600 MHz) 8.57 (1 H, d, *J* = 2.1 Hz), 7.79 (1 H, d, *J* = 2.1 Hz), 7.49 (2 H, d, *J* = 8.9 Hz), 7.47 (1 H, s), 6.99 (2 H, d, *J* = 8.9 Hz), 6.94 (1 H, s), 6.91 (1 H, s), 6.78 (1 H, s), 3.84 (3

H, s), 3.59–3.59 (4 H, m), 3.21–3.19 (6 H, m), 1.48 (9 H, s), 1.39 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 160.4, 154.6, 151.3, 147.0, 146.2, 139.8, 138.3, 137.0, 135.7, 135.5, 127.8, 126.9, 116.5, 113.0, 111.4, 105.5, 80.0, 55.6, 55.5, 48.6, 45.9, 28.4, 8.22.

***tert*-Butyl 4-(4-(6-chloro-5-(3-methoxy-5-(propylsulfonamido)phenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17d).** Prepared from **16e** and purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 40:60) to give **17d** (95%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.57 (1 H, d, *J* = 2.9 Hz), 7.79 (1 H, d, *J* = 2.9 Hz), 7.49 (2 H, d, *J* = 8.6 Hz), 7.47 (1 H, br), 6.99 (2 H, d, *J* = 8.6 Hz), 6.93 (1 H, s), 6.90 (1 H, t, *J* = 1.7 Hz), 6.78–6.77 (1 H, m), 3.84 (3 H, s), 3.60–3.58 (4 H, m), 3.21–3.19 (4 H, m), 3.16–3.13 (2 H, m), 1.91–1.84 (2 H, m), 1.48 (9 H, s), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.4, 154.7, 151.3, 147.0, 146.2, 139.8, 138.3, 137.0, 135.7, 135.5, 127.8, 126.9, 116.5, 112.9, 111.3, 105.5, 80.1, 55.5, 53.3, 48.6, 28.4, 24.8, 17.2, 12.8.

***tert*-Butyl 4-(4-(6-chloro-5-(3-methoxy-5-(1-methylethylsulfonamido)phenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17e).** Prepared from **16g** and purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 50:50) to give **17e** (79%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.57 (1 H, d, *J* = 2.7 Hz), 7.79 (1 H, d, *J* = 2.3 Hz), 7.49 (2 H, d, *J* = 8.6 Hz), 7.37 (1 H, s), 6.99 (2 H, d, *J* = 8.6 Hz), 6.95 (1 H, s), 6.92 (1 H, t, *J* = 2.3 Hz), 6.76–6.75 (1 H, m), 3.83 (3 H, s), 3.60–3.58 (4 H, m), 3.39 (1 H, sep, *J* = 6.9 Hz), 3.21–3.20 (4 H, m), 1.48 (9 H, s), 1.42 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.4, 154.6, 151.3, 147.0, 146.2, 139.7, 138.6, 137.0, 135.8, 135.5, 127.8, 126.9, 116.5, 112.9, 111.2, 105.4, 80.0, 55.5, 52.6, 48.6, 30.9, 28.4, 16.5.

***tert*-Butyl 4-(4-(6-chloro-5-(3-fluoro-4-methoxy-5-(propylsulfonamido)phenyl)pyridin-3-yl)phenyl)piperazine-1-carboxylate (17f).** Prepared from **16z** and purified by column

chromatography on silica gel (EtOAc/hexane, 20:80) to give **17f** (69%) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.57 (1 H, d, J = 2.3 Hz), 7.82 (1 H, d, J = 2.3 Hz), 7.51 (2 H, d, J = 8.6 Hz), 7.39 (1 H, t, J = 8.0 Hz), 7.07 (1 H, dd, J = 6.6, 1.7 Hz), 7.03, 7.02 (1 H, d, J = 2.3, 1.7 Hz), 7.01–6.99 (3 H, m), 3.85 (3 H, s), 3.61–3.59 (4 H, m), 3.21 (4 H, br), 1.49 (9 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.6, 153.9 (d, J_{CF} = 248.6 Hz), 151.4, 147.0, 146.4, 137.0, 136.4 (d, J_{CF} = 12.3 Hz), 135.7, 134.6, 133.0 (d, J_{CF} = 8.6 Hz), 131.0 (d, J_{CF} = 4.9 Hz), 127.8, 126.9, 116.5, 114.8 (d, J_{CF} = 2.5 Hz), 113.4 (d, J_{CF} = 20.9 Hz), 80.0, 61.6 (d, J_{CF} = 7.4 Hz), 53.6, 48.6, 28.4, 17.2, 12.9.

General Procedure for the Preparation of 1-(4-(6-methyl-5-phenylpyridin-3-yl)phenyl)piperazines; ***N*-(2-methoxy-4-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)propane-1-sulfonamide (18a).** To a mixture of **17a** (35.0 mg, 0.06 mmol), K_2CO_3 (16.0 mg, 0.12 mmol) and $Pd(PPh_3)_4$ (13.4 mg, 0.01 mmol) was added anhydrous 1,4-dioxane (1.5 mL) and trimethylboroxine (0.03 mL, 0.23 mmol) under argon. The reaction was stirred at room temperature for 10 min then the mixture was refluxed for 16 h. After being quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 70:30) to afford the methylated pyridine product then anhydrous CH_2Cl_2 (3 mL) and trifluoroacetic acid (0.3 mL) were added. The mixture was stirred at room temperature for 16 h. After being quenched with saturated aqueous $NaHCO_3$ (5 mL), CH_2Cl_2 were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95 to 15:85) to give **18a** (24.7 mg, 89%) as a

yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.70 (1 H, d, *J* = 1.8 Hz), 7.67 (1 H, d, *J* = 1.8 Hz), 7.60 (1 H, d, *J* = 8.2 Hz), 7.52 (2 H, d, *J* = 8.7 Hz), 7.00 (2 H, d, *J* = 8.7 Hz), 6.96 (2 H, dd, *J* = 8.2, 1.8 Hz), 6.88 (1 H, d, *J* = 1.4 Hz), 3.90 (3 H, s), 3.24–3.22 (4 H, m), 3.11–3.07 (5 H, m), 2.53 (3 H, s), 1.88 (2 H, sex, *J* = 7.8 Hz), 1.04 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 153.5, 151.3, 148.6, 145.8, 136.8, 136.0, 134.8, 133.7, 128.3, 127.6, 125.7, 122.0, 119.6, 116.2, 111.5, 55.9, 53.3, 49.6, 45.7, 23.0, 17.2, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{33}N_4O_3S$ 481.2268; found 481.2274; Purity (method A) >99%, t_R = 14.8 min.

***N*-(3-Methoxy-5-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)methanesulfonamide (18b).** Prepared from **17b** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 20:80) to give **18b** (81%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.71 (1 H, d, *J* = 2.3 Hz), 7.65 (1 H, s), 7.50 (2 H, d, *J* = 8.6 Hz), 6.99 (2 H, d, *J* = 8.6 Hz), 6.86 (1 H, s), 6.77 (1 H, s), 6.70 (1 H, s), 3.84 (3 H, s), 3.24–3.22 (4 H, m), 3.09–3.07 (7 H, m), 2.52 (3 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.6, 153.3, 151.4, 146.0, 142.6, 138.2, 135.9, 134.6, 133.7, 128.2, 127.6, 116.2, 113.0, 111.5, 105.1, 55.6, 49.6, 45.8, 39.6, 22.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{24}H_{29}N_4O_3S$ 453.1955; found 453.1963; Purity (method A) 98%, t_R = 13.2 min.

***N*-(3-Methoxy-5-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)ethanesulfonamide (18c).** Prepared from **17c** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 20:80) to give **18c** (62%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) 8.70 (1 H, d, *J* = 1.8 Hz), 7.64 (1 H, d, *J* = 1.8 Hz), 7.51 (2 H, d, *J* = 8.7 Hz), 7.00 (2 H, d, *J* = 8.7 Hz), 6.86 (1 H, s), 6.77 (1 H, s), 6.68 (1 H, s), 3.84 (3 H, s), 3.31–3.28 (4 H, m), 3.22–3.16 (6 H, m), 2.52 (3 H, s), 1.40 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.6, 153.4, 151.0, 146.1, 142.5, 138.2, 135.9, 134.7, 133.7, 128.7, 127.7,

116.5, 112.8, 111.2, 104.8, 55.6, 49.0, 46.1, 45.3, 22.9, 8.3; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{31}N_4O_3S$ 467.2111; found 467.2116; Purity (method A) 98%, t_R = 13.9 min.

***N*-(3-Methoxy-5-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)propane-1-sulfonamide (18d).** Prepared from **17d** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 10:90 to 20:80) to give **18d** (65%) as a yellow solid; ^1H NMR ($CDCl_3$, 500 MHz) 8.71 (1 H, d, *J* = 2.3 Hz), 7.65 (1 H, d, *J* = 2.3 Hz), 7.50 (2 H, d, *J* = 8.6 Hz), 7.00 (2 H, d, *J* = 8.6 Hz), 6.85 (1 H, t, *J* = 2.3 Hz), 6.75 (1 H, t, *J* = 1.7 Hz), 6.68 (1 H, t, *J* = 2.3 Hz), 3.84 (3 H, s), 3.23–3.21 (4 H, m), 3.15–3.12 (2 H, m), 3.08–3.06 (4 H, m), 2.52 (3 H, s), 1.92–1.84 (2 H, m), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.6, 153.3, 151.4, 146.0, 142.6, 138.2, 135.9, 134.6, 133.8, 128.2, 127.6, 116.2, 112.8, 111.2, 105.8, 55.5, 53.5, 49.8, 45.9, 22.9, 17.3, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{33}N_4O_3S$ 481.2268; found 481.2274; Purity (method A) 98%, t_R = 15.0 min.

***N*-(3-Methoxy-5-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)propane-2-sulfonamide (18e).** Prepared from **17e** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18e** (96%) as a yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.62 (1 H, d, *J* = 2.3 Hz), 7.81 (1 H, d, *J* = 2.3 Hz), 7.58 (2 H, d, *J* = 8.6 Hz), 7.08 (2 H, d, *J* = 9.2 Hz), 6.91 (1 H, t, *J* = 1.7 Hz), 6.84, (1 H, t, *J* = 1.7 Hz), 6.70 (1 H, t, *J* = 1.2 Hz), 3.82 (3 H, s), 3.35–3.29 (1 H, m), 3.23–3.21 (4 H, m), 3.02–3.00 (4 H, m), 2.48 (3 H, s), 1.35 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 162.2, 154.1, 153.0, 145.9, 143.0, 141.2, 138.5, 136.3, 135.9, 129.1, 128.6, 117.6, 113.4, 111.2, 105.6, 56.0, 53.5, 50.3, 46.3, 22.4, 16.7; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{33}N_4O_3S$ 481.2268; found 481.2273; Purity (method B) 98%, t_R = 15.8 min.

***N*-(3-Fluoro-2-methoxy-5-(2-methyl-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)propane-1-sulfonamide (18aa).** Prepared from **17f** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 10:90) to give **18aa** (90%) as a yellow solid; ^1H NMR ($CDCl_3$, 600 MHz) 8.71 (1 H, d, J = 2.1 Hz), 7.63 (1 H, d, J = 2.1 Hz), 7.50 (2 H, d, J = 8.9 Hz), 7.34 (1 H, s), 7.01 (2 H, d, J = 8.2 Hz), 6.88 (1 H, dd, J = 11.7, 1.4 Hz), 4.08 (3 H, d, J = 1.4 Hz), 3.23–3.22 (4 H, m), 3.12–3.10 (2 H, m), 3.08–3.06 (4 H, m), 2.53 (3 H, s), 1.87 (2 H, sex, J = 7.6 Hz), 1.04 (3 H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 154.1 (d, J_{CF} = 246.9 Hz), 153.3, 151.5, 146.2 (d, J_{CF} = 3.0 Hz), 135.9 (d, J_{CF} = 10.4 Hz), 135.8 (d, J_{CF} = 8.9 Hz), 134.8, 134. 6, 133.9, 131.0 (d, J_{CF} = 5.9 Hz), 128.1, 127.6, 116.2, 114.8, 113.1 (d, J_{CF} = 20.7 Hz), 61.6, 53.8, 49.8, 45.9, 23.0, 17.2, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{32}FN_4O_3S$ 499.2174; found 499.2181, Purity (method A) 97%, t_R = 15.4 min.

General Procedure for the Preparation of 3-phenyl-5-(4-(piperazin-1-yl)phenyl)pyridin-2-amines; ***N*-(3-(2-amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-methoxyphenyl)methanesulfonamide (18f).** To a mixture of **16c** (26.0 mg, 0.07 mmol), 4-(4-*tert*-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester (29.8 mg, 0.08 mmol) and $Pd(PPh_3)_4$ (13.4 mg, 0.01 mmol) was added anhydrous DME (1.5 mL) under argon. The reaction was stirred at room temperature for 10 min then 1 M Na_2CO_3 (0.14 mL, 0.14 mmol) was added. The mixture was refluxed for 16 h. After being quenched by the addition of water, the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 70:30) to afford the coupling product then anhydrous CH_2Cl_2 (3 mL), and trifluoroacetic acid (0.3 mL) were added. The mixture was stirred at room temperature for 16 h. After being quenched with saturated aqueous

$NaHCO_3$ (5 mL), CH_2Cl_2 were added, and the layers were separated. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 10:90 to 30:70) to give **18f** (9.9 mg, 31%) as a yellow solid; m.p. 155 - 157°C; ^{1}H NMR (CD_3OD, 500 MHz) 8.15 (1 H, d, *J* = 2.3 Hz), 7.62 (1 H, d, *J* = 2.3 Hz), 7.48 (2 H, d, *J* = 8.6 Hz), 7.06 (2 H, d, *J* = 8.6 Hz), 6.92 (1 H, s), 6.89 (1 H, t, *J* = 1.7 Hz), 6.83 (1 H, s), 3.84 (3 H, s), 3.30–3.27 (4 H, m), 3.17–3.15 (4 H, m), 3.02 (3 H, s); ^{13}C NMR (CD_3OD, 125 MHz) 162.6, 156.4, 151.6, 144.9, 141.5, 141.4, 137.4, 131.2, 128.3, 127.8, 123.1, 118.1, 113.5, 111.2, 106.3, 66.9, 56.0, 45.7, 39.4; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{23}H_{28}N_5O_3S$ 454.1907; found 454.1913; Purity (method A) 98%, t_R = 13.2 min.

***N*-(3-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-methoxyphenyl)propane-1-sulfonamide (18g).** Prepared from **16f** and purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95 to 15:85) to give **18g** (49%) as a yellow solid; ^{1}H NMR (CD_3OD, 500 MHz) 8.15 (1 H, d, *J* = 2.3 Hz), 7.62 (1 H, d, *J* = 2.3 Hz), 7.48 (2 H, d, *J* = 8.6 Hz), 7.06 (2 H, d, *J* = 8.6 Hz), 6.92 (1 H, t, *J* = 1.7 Hz), 6.87 (1 H, t, *J* = 1.7 Hz), 6.81 (1 H, t, *J* = 1.7 Hz), 3.83 (3 H, s), 3.33–3.29 (4 H, m), 3.22–3.20 (4 H, m), 3.14–3.10 (2 H, m), 1.82 (2 H, sex, *J* = 7.4 Hz), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 161.2, 154.2, 150.8, 145.1, 140.5, 139.1, 136.0, 129.1, 127.7, 126.9, 120.9, 116.4, 112.3, 110.1, 105.1, 55.6, 53.7, 50.0, 45.9, 17.3, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{32}N_5O_3S$ 482.2220; found 482.2225; Purity (method A) 99%, t_R = 14.6 min.

***N*-(3-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-methoxyphenyl)propane-2-sulfonamide (18h).** Prepared from **16g** and purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 5:95 to 15:85) to give **18h** (31%) as a yellow solid; ^{1}H NMR (CD_3OD, 500

MHz) 8.14 (1 H, d, *J* = 1.7 Hz), 7.60 (1 H, d, *J* = 1.7 Hz), 7.45 (2 H, d, *J* = 8.6 Hz), 7.02 (2 H, d, *J* = 8.6 Hz), 6.93 (1 H, s), 6.89 (1 H, s), 6.78 (1 H, s), 3.82 (3 H, s), 3.37–3.30 (1 H, m), 3.21–3.19 (4 H, m), 3.06–3.04 (4 H, m), 1.35 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 162.5, 156.3, 152.0, 144.9, 141.7, 141.4, 137.4, 130.8, 128.4, 127.7, 123.1, 118.0, 113.0, 110.7, 105.9, 55.9, 53.4, 50.3, 46.2, 16.7; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{32}N_5O_3S$ 482.2220; found 482.2225; Purity (method A) >99%, t_R = 14.4 min.

***N*-(3-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-methoxyphenyl)benzenesulfonamide (18i).** Prepared from **16i** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18i** (24%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.23 (1 H, d, *J* = 1.7 Hz), 7.85 (2 H, d, *J* = 7.4 Hz), 7.55 (1 H, t, *J* = 7.4 Hz), 7.47 (2 H, t, *J* = 7.4 Hz), 7.43 (1 H, d, *J* = 2.3 Hz), 7.38 (2 H, d, *J* = 8.6 Hz), 6.95 (2 H, d, *J* = 8.6 Hz), 6.78 (1 H, t, *J* = 1.7 Hz), 6.74 (1 H, s), 6.69 (1 H, s), 4.55 (2 H, br), 3.78 (3 H, s), 3.19–3.17 (4 H, m), 3.08–3.06 (4 H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.9, 154.2, 150.8, 144.9, 140.0, 139.1, 138.6, 135.9, 133.1, 129.1, 129.0, 127.6, 127.3, 126.9, 120.8, 116.4, 113.4, 111.2, 106.4, 55.5, 50.0, 45.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{28}H_{30}N_5O_3S$ 516.2064; found 516.2069; Purity (method A) 97%, t_R = 15.7 min.

***N*-(3-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-ethoxyphenyl)propane-2-sulfonamide (18j).** Prepared from **16r** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18j** (37%) as a yellow solid; ^{1}H NMR (CD_3OD, 600 MHz) 8.14 (1 H, d, *J* = 2.1 Hz), 7.59 (1 H, d, *J* = 2.1 Hz), 7.44 (2 H, d, *J* = 8.9 Hz), 7.02 (2 H, d, *J* = 8.9 Hz), 6.92 (1 H, s), 6.88 (1 H, t, *J* = 2.1 Hz), 6.76 (1 H, s), 4.05 (2 H, q, *J* = 6.9 Hz), 3.35–3.32 (1 H, m), 3.24–3.22 (4 H, m), 3.11–3.09 (4 H, m), 1.39 (3 H, t, *J* = 6.9 Hz), 1.34 (6 H, d, *J* = 6.9 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 161.8, 156.3, 151.8, 144.9, 141.7, 141.3, 137.4, 130.9,

128.3, 127.8, 123.2, 118.0, 112.9, 111.2, 106.4, 64.8, 53.4, 49.3, 45.9, 16.7, 15.1; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{34}N_5O_3S$ 496.2377; found 496.2381; Purity (method B) >99%, t_R = 16.5 min.

***N*-(3-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-5-isopropoxyphenyl)propane-2-sulfonamide (18k).** Prepared from **16s** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18k** (37%) as a yellow solid; ^1H NMR (CD_3OD, 400 MHz) 8.21 (1 H, d, *J* = 2.3 Hz), 7.50–7.47 (3 H, m), 6.97 (2 H, d, *J* = 9.2 Hz), 6.88 (1 H, s), 6.77 (1 H, s), 6.71 (1 H, s), 5.64 (2 H, br), 4.61 (1 H, sep, *J* = 6.3 Hz), 3.39–3.33 (1 H, m), 3.12–3.10 (4 H, m), 2.93–2.91 (4 H, m), 1.28–1.24 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 159.3, 150.2, 144.5, 139.9, 139.6, 136.1, 129.6, 127.4, 126.9, 121.3, 116.7, 111.7, 111.6, 106.5, 70.2, 52.6, 49.1, 45.0, 21.9, 16.4; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{27}H_{36}N_5O_3S$ 510.2533; found 510.2538; Purity (method B) >99%, t_R = 17.0 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-3-methoxy-2-methylphenyl)propane-1-sulfonamide (18l).** Prepared from **16l** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18l** (30%) as a yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.19 (1 H, d, *J* = 2.3 Hz), 7.54 (1 H, d, *J* = 2.3 Hz), 7.50 (2 H, d, *J* = 8.6 Hz), 7.08 (2 H, d, *J* = 9.2 Hz), 7.04 (1 H, d, *J* = 2.9 Hz), 6.73 (1 H, d, *J* = 2.9 Hz), 3.80 (3 H, s), 3.41–3.39 (4 H, m), 3.35–3.32 (4 H, m), 3.16–3.13 (2 H, m), 2.09 (3 H, s), 1.88 (2 H, sex, *J* = 8.0 Hz), 1.07 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 159.7, 156.6, 150.8, 145.0, 140.3, 138.4, 137.6, 131.8, 127.9, 127.6, 125.4, 123.4, 118.4, 114.5, 112.6, 55.9, 55.2, 48.1, 45.0, 18.4, 14.7, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{34}N_5O_3S$ 496.2377; found 496.2377; Purity (method B) 99%, t_R = 15.9 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (18m).** Prepared from **16j** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18m** (39%) as a yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.12 (1 H, s), 7.60 (1 H, d, *J* = 1.7 Hz), 7.56 (1 H, d, *J* = 1.7 Hz), 7.46 (2 H, d, *J* = 8.6 Hz), 7.32 (1 H, dd, *J* = 8.6, 1.7 Hz), 7.16 (1 H, d, *J* = 8.6 Hz), 7.03 (2 H, d, *J* = 8.6 Hz), 3.94 (3 H, s), 3.21–3.19 (4 H, m), 3.06–3.03 (6 H, m), 1.84 (2 H, sex, *J* = 8.0 Hz), 1.01 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.5, 152.7, 152.0, 144.4, 137.5, 131.6, 130.9, 128.6, 127.9, 127.8, 127.7, 125.7, 122.9, 118.0, 113.0, 56.5, 54.6, 50.4, 46.2, 18.3, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{32}N_5O_3S$ 482.2220; found 482.2223; Purity (method A) 98%, t_R = 14.1 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2-hydroxyphenyl)propane-1-sulfonamide (18n).** Prepared from **16w** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18n** (18%) as a yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.11 (1 H, s), 7.59 (1 H, d, *J* = 2.3 Hz), 7.50–7.48 (3 H, m), 7.20 (1 H, dd, *J* = 8.6, 2.3 Hz), 7.07 (2 H, d, *J* = 9.2 Hz), 7.00 (1 H ,d , *J* = 8.0 Hz), 3.39–3.37 (4 H, m), 3.30–3.29 (4 H, m), 3.08–3.05 (2 H, m), 1.91–1.84 (2 H, m), 1.02 (3 H, t, *J* = 7.4 Hz); HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{24}H_{29}N_5O_3S$ 468.2064; found 468.2071; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{24}H_{30}N_5O_3S$ 468.2064; found 468.2071; Purity (method A) >95%, t_R = 13.2 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2-methylphenyl)propane-1-sulfonamide (18o).** Prepared from **16k** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18o** (39%) as a pale yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.13 (1 H, d, *J* = 2.3 Hz), 7.60 (1 H, d, *J* = 2.3 Hz), 7.48 (1 H, d, *J* = 1.7 Hz), 7.44 (2 H, d, *J* = 8.6 Hz), 7.36 (1 H, d, *J* = 8.0 Hz), 7.27 (1 H, dd, *J* = 7.7, 1.7 Hz), 7.01 (2 H, d, *J* = 8.6 Hz),

3.19–3.17 (4 H, m), 3.13–3.10 (2 H, m), 3.21–3.18 (4 H, m), 3.04–3.02 (4 H, m), 2.40 (3 H, s), 1.89–1.81 (2 H, m), 1.03 (3 H, t, J = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.4, 152.0, 144.7, 137.6, 137.5, 137.3, 134.5, 133.0, 128.5, 127.7, 126.9, 122.8, 117.9, 55.4, 50.4, 46.2, 18.4, 18.3, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{32}N_5O_2S$ 466.2271; found 466.2275; Purity (method A) 99%, t_R = 14.2 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2,3-dimethoxyphenyl)propane-1-sulfonamide (18p).** Prepared from **16u** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18p** (49%) as a yellow solid; ^{1}H NMR (CD_3OD, 600 MHz) 8.14 (1 H, d, J = 2.1 Hz), 7.62 (1 H, d, J = 2.8 Hz), 7.47 (2 H, d, J = 8.9 Hz), 7.20 (1 H, d, J = 1.4 Hz), 7.04 (2 H, d, J = 8.9 Hz), 6.94 (1 H, d, J = 2.1 Hz), 3.01 (3 H, s), 3.90 (3 H, s), 3.26–3.24 (4 H, m), 3.13–3.10 (6 H, m), 1.84 (2 H, sex, J = 7.6 Hz), 1.02 (3 H, t, J = 7.6 Hz); ^{13}C NMR (CD_3OD, 150 MHz) 156.4, 154.6, 151.7, 144.7, 141.2, 137.5, 134.8, 132.8, 131.1, 128.4, 127.8, 123.1, 118.1, 115.8, 110.6, 61.4, 56.6, 54.8, 49.7, 45.8, 18.4, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{34}N_5O_4S$ 512.2326; found 512.2332; Purity (method A) 98%, t_R = 14.9 min.

N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-3-ethoxy-2-methoxyphenyl)propane-1-sulfonamide (18q).** Prepared from **16v** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18q** (52%) as a yellow solid; ^{1}H NMR (CD_3OD, 600 MHz) 8.24 (1 H, s), 7.70 (1 H, d, J = 2.1 Hz), 7.52 (2 H, d, J = 8.9 Hz), 7.10 (1 H, s), 7.06 (2 H, d, J = 8.9 Hz), 6.91 (1 H, s), 4.08 (2 H, q, J = 6.9 Hz), 3.88 (3 H, s), 3.30–3.29 (4 H, m), 3.18–3.17 (4 H, m), 2.74–2.69 (1 H, m), 2.67–2.62 (1 H, m), 1.46–1.42 (1 H, m), 1.41–1.36 (4 H, m), 0.77 (3 H, t, J = 7.6 Hz); ^{13}C NMR** (CD_3OD, 150 MHz) 156.7, 151.6, 151.0, 149.2, 145.2, 139.2, 131.0, 128.7, 128.6, 127.9, 127.8, 121.3, 118.1, 116.0, 113.7, 65.9,

56.6, 55.4, 45.6, 18.2, 15.1, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{27}H_{36}N_5O_4S$ 526.2483; found 526.2493; Purity (method A) 95%, t_R = 14.5 min. *One of ^{13}C NMR peak was hidden in CD_3OD peaks due to low sample concentration.

***N*-(7-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)propane-1-sulfonamide (18r).** Prepared from 5-bromo-3-(8-((propylsulfonyl)methyl)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyridin-2-amine (**16** where R_1–R_2 = OCH_2CH_2O, R_3 = $NHSO_2{}^nPr$ and R_4 = NH_2), which was generated from **14s**, but was not characterized. The product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18r** (37% over three steps) as a light brown solid; ^1H NMR (CD_3OD, 600 MHz) 8.12 (1 H, s), 7.58 (1 H, d, *J* = 1.4 Hz), 7.48 (2 H, d, *J* = 8.9 Hz), 7.12 (1 H, s), 7.06 (2 H, d, *J* = 8.2 Hz), 6.85 (1 H, s), 4.38–4.37 (2 H, m), 4.32–4.31 (2 H, m), 3.36–3.34 (4 H, m), 3.27–3.25 (4 H, m), 3.09 (2 H, t, *J* = 7.6 Hz), 1.86 (2 H, sex, *J* = 7.6 Hz), 1.03 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, 150 MHz) 156.5, 151.1, 145.8, 144.6, 137.4, 137.3, 131.6, 131.5, 128.2, 128.0, 127.9, 122.8, 118.3, 117.7, 115.5, 66.0, 65.6, 54.7, 45.3, 30.7, 18.4, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{32}N_5O_4S$ 510.2170; found 510.2173; Purity (method A) 98%, t_R = 14.2 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2-methoxy-3-methylphenyl)propane-1-sulfonamide (18s).** Prepared from **16n** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 10:90 to 15:85) to give **18s** (53%) as a yellow solid; ^1H NMR (CD_3OD, 600 MHz) 8.13 (1 H, d, *J* = 2.1 Hz), 7.59 (1 H, d, *J* = 2.1 Hz), 7.46 (1 H, d, *J* = 8.9 Hz), 7.43 (1 H, d, *J* = 1.4 Hz), 7.11 (1 H, s), 7.03 (2 H, d, *J* = 8.9 Hz), 3.82 (3 H, s), 3.24–3.23 (4 H, m), 3.18–3.16 (2 H, m), 3.11–3.09 (4 H, m), 2.36 (3 H, s), 1.86 (2 H, sex, *J* = 7.6 Hz), 1.03 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR (CD_3OD, 150 MHz) 156.4, 151.8, 150.8, 144.6, 137.5,

135.1, 133.9, 132.7, 131.0, 128.7, 128.4, 127.8, 123.0, 121.2, 118.0, 61.2, 55.2, 49.9, 45.9, 18.4, 16.4, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{34}N_5O_3S$ 496.2377; found 496.2383; Purity (method A) 97%, t_R = 15.1 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (18t).** Prepared from **16m** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18t** (52%) as a yellow solid; m.p. 142 – 144 °C; ^{1}H NMR (CD_3OD, 500 MHz) 8.13 (1 H, d, *J* = 2.3 Hz), 7.58 (1 H, d, *J* = 2.3 Hz), 7.44–7.40 (3 H, m), 7.10 (1 H, dd, *J* = 12.0, 2.3 Hz), 7.00 (2 H, d, *J* = 8.6 Hz), 4.01 (3 H, d, *J* = 1.7 Hz), 3.19–3.17 (4 H, m), 3.14–3.11 (2 H, m), 3.04–3.02 (4 H, m), 1.88–1.81 (2 H, m), 1.02 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.8 (d, J_{CF} = 246.1 Hz), 156.2, 152.0, 145.1, 140.1 (d, J_{CF} = 13.5 Hz), 137.5, 134.6 (d, J_{CF} = 9.8 Hz), 133.6 (d, J_{CF} = 4.9 Hz), 130.6, 128.4, 127.7, 121.8, 119.6, 117.9, 114.4, 62.1 (d, J_{CF} = 7.4 Hz), 55.0, 50.3, 46.1, 18.4, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{31}FN_5O_3S$ 500.2126; found 500.2137; Purity (method B) 98%, t_R = 15.9 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-3-chloro-2-methoxyphenyl)propane-1-sulfonamide (18u).** Prepared from **16t** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18u** (62%) as a yellow solid; ^{1}H NMR (CD_3OD, 500 MHz) 8.16 (1 H, d, *J* = 2.3 Hz), 7.60 (1 H, d, *J* = 2.3 Hz), 7.57 (1 H, d, *J* = 1.7 Hz), 7.46 (2 H, d, *J* = 9.2 Hz), 7.31 (1 H, d, *J* = 1.7 Hz), 7.03 (2 H, d, *J* = 8.6 Hz), 3.93 (3 H, s), 3.27–3.25 (4 H, m), 3.20–3.12 (6 H, m), 1.86 (2 H, sex, *J* = 8.0 Hz), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.4, 151.6, 148.2, 145.3, 137.6, 136.2, 134.7, 130.9, 129.7, 128.4, 127.8, 127.2, 122.0, 121.6, 118.1, 61.7, 55.4, 49.6, 45.8, 18.4, 13.2; HRMS (ESI-

QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{31}ClN_5O_3S$ 516.1831; found 516.1836; Purity (method B) 96%, t_R = 16.4 min.

3-(3-Fluoro-4,5-dimethoxyphenyl)-5-(4-(piperazin-1-yl)phenyl)pyridin-2-amine (18v). Prepared from **16x** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18v** (47%) as a pale yellow solid; ^1H NMR ($CDCl_3$, 400 MHz) 8.273 (1 H, d, *J* = 1.8 Hz), 7.55 (1 H, d, *J* = 2.3 Hz), 7.46 (2 H, d, *J* = 8.2 Hz), 6.99 (2 H, d, *J* = 8.7 Hz), 6.88 (1 H, dd, *J* = 11.0, 1.8 Hz), 6.81 (1 H, s), 4.72 (2 H, br), 3.98 (3 H, s), 3.90 (3 H, s), 3.42 (4 H, br), 3.29 (4 H, br); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.1 (d, J_{CF} = 246.5 Hz), 154.4, 154.1 (d, J_{CF} = 5.9 Hz), 149.6, 144.9, 136.1, 132.9, 130.5, 127.6 (d, J_{CF} = 35.2 Hz), 127.1, 120.7, 117.3, 113.8, 109.5, (d, J_{CF} = 20.5 Hz), 108.2, 61.6 (d, J_{CF} = 3.9 Hz), 56.4, 47.9, 44.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{23}H_{26}FN_4O_2$ 409.2034; found 409.2038; Purity (method A) 99%, t_R = 14.6 min.

***N*-(5-(2-Amino-5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)-2-methoxybenzyl)propane-1-sulfonamide (18w).** Prepared from **16o** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18w** (39%) as a yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.10 (1 H, d, *J* = 2.3 Hz), 7.57 (1 H, d, *J* = 2.3 Hz), 7.48 (1 H, d, *J* = 2.3 Hz), 7.45–7.40 (3 H, m), 7.10 (1 H, d, *J* = 8.6 Hz), 7.02 (2 H, d, *J* = 9.2 Hz), 4.28 (2 H, s), 3.91 (3 H, s), 3.22–3.20 (4 H, m), 3.08–3.06 (4 H, m), 2.94–2.90 (2 H, m), 1.77–1.69 (2 H, m), 0.97 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 158.4, 156.6, 151.8, 144.2, 137.5, 131.1, 131.0, 130.8, 130.5, 128.5, 128.0, 127.7, 123.3, 118.0, 112.2, 56.1, 55.2, 50.1, 46.0, 42.8, 18.4, 13.3; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{34}N_5O_3S$ 496.2377; found 496.2386; Purity (method B) 98%, t_R = 15.8 min.

5-(4-(Piperazin-1-yl)phenyl)-3-(1-(propylsulfonyl)indolin-6-yl)pyridin-2-amine (18x). Prepared from **16p** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 10:90) to give **18x** (38%) as a yellow solid; ^1H NMR ($CDCl_3$, 500 MHz) 8.27 (1 H, d, *J* = 2.3 Hz), 7.55 (1 H, d, *J* = 2.3 Hz), 7.47–7.43 (3 H, m), 7.29 (1 H, d, *J* = 8.0 Hz), 7.13 (1 H, dd, *J* = 7.7, 1.2 Hz), 6.98 (2 H, d, *J* = 8.6 Hz), 4.66 (2 H, br), 4.09 (2 H, t, *J* = 8.6 Hz), 3.22–3.18 (6 H, m), 3.09–3.04 (6 H, m), 1.94–1.86 (2 H, m), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.4, 150.7, 144.9, 143.0, 138.0, 136.1, 130.7, 129.4, 127.7, 127.0, 125.9, 123.6, 121.4, 116.5, 113.5, 51.3, 50.5, 49.9, 45.8, 27.8, 16.7, 13.1; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{32}N_5O_2S$ 478.2271; found 478.2277; Purity (method A) 98%, t_R = 15.4 min.

5-(4-(Piperazin-1-yl)phenyl)-3-(4-(propylsulfonyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)pyridin-2-amine (18y). Prepared from **16q** and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18y** (56%) as a pale yellow solid; ^1H NMR (CD_3OD, 500 MHz) 8.13 (1 H, d, *J* = 2.3 Hz), 7.71 (1 H, d, *J* = 2.3 Hz), 7.60 (1 H, d, *J* = 2.3 Hz), 7.48 (2 H, d, *J* = 9.2 Hz), 7.19 (1 H, dd, *J* = 8.3, 2.3 Hz), 7.07–7.03 (3 H, m), 4.34 (2 H, t, *J* = 4.6 Hz), 3.88 (2 H, t, *J* = 4.6 Hz), 3.30–3.24 (6 H, m), 3.17–3.15 (4 H, m), 1.85 (2 H, sex, *J* = 8.0 Hz), 1.04 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) 156.5, 152.0, 147.6, 144.4, 137.4, 131.4, 130.8, 128.5, 127.7, 126.9, 126.0, 124.1, 123.0, 119.5, 117.9, 66.2, 54.9, 50.4, 46.2, 45.2, 18.2, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{26}H_{32}N_5O_3S$ 494.2220; found 494.2226; Purity (method A) >99%, t_R = 15.5 min.

***N*-(3-Fluoro-2-methoxy-5-(5-(4-(piperazin-1-yl)phenyl)pyridin-3-yl)phenyl)propane-1-sulfonamide (18z).** Prepared from **16y** and purified by column chromatography on silica gel (EtOAc/hexane, 0:100 to 30:70) to give **18z** (30%) as a pale yellow solid; ^1H NMR ($CDCl_3$, 600 MHz) 8.80 (1 H, s), 8.68 (1 H, s), 7.93 (1 H, s), 7.61 (1 H, s), 7.55 (2 H, d, *J* = 7.8 Hz), 7.14 (1

H, d, J = 12.6 Hz), 7.05 (2 H, d, J = 9.0 Hz), 4.08 (1 H, s), 3.24 (4 H, t, J = 4.8 Hz), 3.12 (2 H, t, J = 8.1 Hz), 3.07 (4 H, t, J = 4.2 Hz), 1.91–1.84 (2 H, sex, J = 7.8 Hz), 1.04 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) 153.8 (d, J_{CF} = 245.7 Hz), 151.8, 147.1, 145.70, 136.6 (d, J_{CF} = 11.6 Hz), 136.4, 134.6, 133.9 (d, J_{CF} = 9.0 Hz), 131.8, 131.6 (d, J_{CF} = 23.4 Hz), 127.9, 116.1, 112.9, 111.2 (d, J_{CF} = 21.6 Hz), 61.6, 53.6, 49.8, 46.0, 17.3, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calculated for $C_{25}H_{29}FN_4O_3S$ 507.1837; found 507.1848; Purity (method A) 100%, t_R = 16.9 min.

Preparation of 3-phenyl-5-(methylsulfonyl)phenyl)pyridin-2-amines. Intermediate **16j** was coupled to either 2-, 3-, or 4-(methanesulfonyl)phenylboronic acid using the conditions described for the general procedure for the preparation of 3-bromo-5-phenylpyridines.

***N*-(5-(2-Amino-5-(2-(methylsulfonyl)phenyl)pyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (18ab).** Purified by column chromatography on silica gel (EtOAc/hexane, 50:50 to 80:20) to give **18ab** (22%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.24 (1 H, dd, J = 7.7, 1.7 Hz), 8.05 (1 H, d, J = 2.3 Hz), 7.69–7.66 (3 H, m), 7.57 (1 H, td, J = 7.4, 1.2 Hz), 7.42 (1 H, dd, J = 7.4, 1.2 Hz), 7.29 (1 H, dd, J = 8.2, 2.3 Hz), 6.99 (1 H, d, J = 8.6 Hz), 6.83 (1 H, s), 4.84 (2 H, br), 3.93 (3 H, s), 3.11–3.08 (2 H, m), 2.79 (3 H, s), 1.87 (2 H, sex, J = 8.0 Hz), 1.03 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 155.7, 148.6, 146.8, 140.4, 139.6, 138.3, 133.4, 133.2, 130.3, 129.0, 128.1, 126.8, 125.5, 125.0, 119.9, 119.3, 111.4, 56.0, 53.9, 43.5, 17.2, 12.8; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{22}H_{26}N_3O_5S_2$ 476.1308; found 476.1313; Purity (method B) 95%, t_R = 18.0 min.

***N*-(5-(2-Amino-5-(3-(methylsulfonyl)phenyl)pyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (18ac).** Purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 2.5:97.5 to 5:95) to give **18ac** (60%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.32 (1 H, s), 8.08 (1

H, s), 7.88 (1 H, d, *J* = 7.4 Hz), 7.82 (1 H, d, *J* = 8.0 Hz), 7.66–7.60 (3 H, m), 7.24 (1 H, dd, *J* = 8.3, 2.9 Hz), 7.03 (1 H, d, *J* = 8.6 Hz), 6.95 (1 H, s), 4.83 (2 H, br), 3.95 (3 H, s), 3.10–3.06 (5 H, m), 1.91–1.84 (2 H, m), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 155.9, 148.8, 145.6, 141.2, 139.8, 136.4, 131.2, 130.4, 130.0, 126.9, 125.6, 125.4, 124.8, 121.0, 120.3, 120.3, 111.4, 50.0, 53.7, 44.5, 17.2, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + Na]^+$ calculated for $C_{22}H_{25}N_3NaO_5S_2$ 498.1128; found 498.1132; Purity (method B) 96%, t_R = 17.7 min.

***N*-(5-(2-Amino-5-(4-(methylsulfonyl)phenyl)pyridin-3-yl)-2-methoxyphenyl)propane-1-sulfonamide (18ad).** Purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 2.5:97.5 to 5:95) to give **18ad** (83%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 500 MHz) 8.35 (1 H, d, *J* = 1.7 Hz), 7.98 (2 H, d, *J* = 8.6 Hz), 7.72 (2 H, d, *J* = 8.0 Hz), 7.66 (1 H, d, *J* = 1.7 Hz), 7.60 (1 H, d, *J* = 2.3 Hz), 7.20–7.24 (1 H, m), 7.03 (1 H, d, *J* = 8.6 Hz), 6.90 (1 H, s), 4.84 (2 H, br), 3.95 (3 H, s), 3.09–3.06 (5 H, m), 1.88 (2 H, sex, *J* = 8.0 Hz), 1.03 (3 H, t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 156.1, 148.8, 145.9, 143.7, 138.5, 136.4, 130.4, 128.1, 127.0, 126.8, 125.6, 125.3, 120.9, 120.2, 111.3, 56.0, 53.8, 44.6, 17.2, 12.9; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{22}H_{26}N_3O_5S_2$ 476.1308; found 476.1318; Purity (method B) 97%, t_R = 17.5 min.

Preparation of *N*-(5-(2-Amino-5-(3-(piperazin-1-yl)phenyl)pyridin-3-yl)-3-fluoro-2-methoxyphenyl)propane-1-sulfonamide (18ae). Prepared from **16m** and 3-(4-tert-butoxycarbonylpiperazinyl)phenylboronic acid pinacol ester using the conditions described for the general procedure for the preparation of 3-bromo-5-phenylpyridines. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 70:30) to afford the coupling product then anhydrous CH_2Cl_2 (3 mL), and trifluoroacetic acid (0.3 mL) were added. The mixture was stirred at room temperature for 16 h. After being quenched with saturated aqueous $NaHCO_3$ (5 mL), CH_2Cl_2 were added, and the layers were separated. The combined

organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95 to 15:85) to give **18ae** (48%) as a pale yellow solid; ^{1}H NMR (CD_3OD, 500 MHz) 8.18 (1 H, d, J = 2.1 Hz), 7.64 (1 H, d, J = 2.1 Hz), 7.42 (1 H, d, J = 1.4 Hz), 7.30 (1 H, t, J = 7.6 Hz), 7.15–7.13 (2 H, m), 7.07 (1 H, d, J = 7.7 Hz), 6.94 (1 H, dd, J = 8.2, 2.1 Hz), 4.01 (3 H, d, J = 2.1 Hz), 3.28–3.27 (4 H, m), 3.15–3.11 (6 H, m), 1.89–1.82 (2 H, m), 1.04 (3 H, t, J = 7.6 Hz); ^{13}C NMR (CD_3OD, 150 MHz) 156.9, 156.8 (d, J_{CF} = 246.9 Hz), 153.3, 145.8, 140.2 (d, J_{CF} = 11.8 Hz), 140.0, 138.1, 134.5 (d, J_{CF} = 8.9 Hz), 133.6 (d, J_{CF} = 5.9 Hz), 130.8, 128.9, 121.7, 119.6, 119.5, 116.5, 115.6, 114.5 (d, J_{CF} = 19.2 Hz), 62.1 (d, J_{CF} = 7.4 Hz), 55.0, 50.1, 46.0, 18.4, 13.2; HRMS (ESI-QTOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{31}FN_5O_3S$ 500.2126; found 500.2132; Purity (method B) >99%, t_R = 16.5 min.

RIPK2 enzyme assay. Recombinant RIPK2 protein (20 ng per reaction) is diluted in the reaction buffer consisting of 40 mM Tris (pH 7.5); 20 mM $MgCl_2$; 0.1 mg/ml BSA; 50 μM DTT. Diluted protein is added to low volume white 384 well plates (2 μL/well). Inhibitors are diluted in reaction buffer (final 25% DMSO), 1 μL is added to each well and incubated 5 min at room temperature. Reactions are initiated by the addition of 2 μL of 100 μM ATP and 1 mg/ml RS repeat peptide (SignalChem) in the reaction buffer. Plates are sealed with plastic coverslips and incubated at room temperature for 2 h. Reactions are stopped by the addition of 5 μL of ADP-Glo reagent (Promega) and ADP generation reaction is performed for 40 min at room temperature. Luminescence signal is generated by the addition of 10 μL of Kinase detection reagent (Promega) for 30 min at room temperature. Luminescence signals are determined using appropriate luminescence plate-reader (typical integration time 0.3-1 sec). To calculate percent inhibition, average background signal is subtracted from test well and maximal signal wells.

Inhibition, % = (1- (test signal/maximal signal))*100. The percent inhibition at a specified concentration is determined or IC_{50} values are calculated based on a dose range of inhibitor concentrations using non-linear regression in GraphPad Prism software.

ALK2 enzyme assay. Enzyme inhibitory activity was evaluated in a standard kinase enzyme assay by incubating human ALK2 with the protein substrate casein (1 mg/mL) and γ-^{33}ATP (10 μM) in the presence of various concentrations of test compounds (10 nM – 100 μM). After 30 min the amount of ^{33}P-casein was determined. A plot of inhibitor concentration versus % activity was constructed and from this plot an IC_{50} value was determined.

Human NOD2 signaling using a HEKBlue reporter assay. HEK293 cell line expressing hNOD2 and NFκB-SEAP reporter cassette was obtained from Invivogen. Cells were maintained in Dulbecco's Modified Eagle Medium /10% fetal bovine serum media supplemented with zeocin, blasticidin and normocin as suggested by Invivogen. For the experiments, cells were seeded at 7.5-15x10^3 cells/well in clear 96-well plates. After 24–48 h, cells were changed into HEKBlue detection media (Invivogen) and treated with 11-point dose ranges for each inhibitor along with 1 ng/mL L18-MDP (Invivogen). After 7–9 h, absorbance at 620 nm was measured using a Victor3V plate reader (Perkin Elmer, Waltham, MA). Values of media-only wells were subtracted and %inhibition for each compound concentration relative to the DMSO/L18-MDP-treated controls was calculated. Inhibition values were fitted by non- linear regression using Prism software (GraphPad Software, La Jolla, CA) to calculate IC_{50} values.

Data collection and Structure determination. The kinase domain of human RIPK2 (Uniprot: O43353, residues 3-317) was recombinantly expressed in Sf9 insect cells and purified by nickel-affinity and size exclusion chromatography as previously described [7]. Mass spectrometry

revealed the phosphorylation state to be a mixture of between 2 to 5 phosphorylations. Protein buffered in 50 mM HEPES pH 7.5, 300 mM NaCl, 5% glycerol, and 1 mM tris(2-carboxyethyl)phosphine was concentrated to 10 mg/mL and 2 mM **18f** added. This sample was then incubated for 10 minutes, spun down, and filtered to 0.22 µm. Crystals were grown using the vapor-diffusion technique at 4 ºC in 150 nL sitting drops containing 100 nL protein and 50 nL of a reservoir solution containing 20% High PEG Smear, 0.1M citrate pH 5.5 [36]. Crystals were cryo-protected by addition of 25% ethylene glycol before being vitrified in liquid nitrogen. Diffraction data were collected at 100 K on Diamond Light Source beamline I24 using 0.9785 Å light. Data were indexed and integrated using XDS [37-38] and scaled using AIMLESS [39]. Phases were identified using molecular replacement in PHASER [40] and the PDB 6FU5 as a search model. The structure was refined and modified using PHENIX.REFINE [41] and COOT [42]. The refined structure was validated with MolProbity [43] and the atomic coordinate files deposited in the Protein Data Bank with Autodep [44].

***In Vivo* Pharmacokinetics.** The pharmacokinetic study was performed in accordance with an approved protocol by the Institutional Care and Use Committee (IACUC) at the University of Houston (PROTO201800072: PK and Perfusion in Mice). For *in vivo* pharmacokinetic experiments, **18t** was administered to 8 week old female C57BL/6 mice (N = 5) intraperitoneally at a dose of 10 mg/kg with vehicle (6% Captisol® in water). Blood samples were collected per mouse under light anesthesia at 0.25, 0.5, 1, 2, 4, 6, and 24 h after dosing. An LC−MS/MS bioanalysis method was developed. A plasma concentration-time profile was obtained and the data subjected to non-compartmental analysis using Phoenix WinNonlin (version 8.1) to assess pharmacokinetic parameters.

Conflicts of interest

C.S., A.D. and G.D.C. declare the following financial interests/personal relationships that may be considered as potential competing interests: PCT patent application (Publication Number 20200030303) assigned to the University of Houston System and Trustees of Tufts College. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Accession codes

Atomic coordinates for the x-ray structures of **18f•**RIPK2 (PDB 6S1F), **18m•**RIPK2 (PDB 6FU5) and **9b•**ALK2 (PDB 4BGG) are available from the RCSB Protein Data Bank (www.rscb.org).

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Appendix A. Supporting data

Synthesis scheme and procedures of starting materials **11i**–**o**, **12b**, **13v** and intermediate **19**, the pharmacokinetic procedure, copies of NMR spectra, and data collection and refinement statistics for the RIPK2•**18f** crystal structure are provided. The supporting data to this article can be found online at

Abbreviations used

ADME: adsorption, distribution, metabolism and excretion, ALK2: activin receptor-like kinase 2, ADP: adenosine diphosphate, ATP: adenosine triphosphate, AUC: area under the curve, BRET: bioluminescence resonance energy transfer, CARD: caspase-activated recruitment domain, CL: clearance, C_{max}: concentration maximum, CXCL8: C-X-C motif chemokine ligand 8, DAP: diaminopimelic acid, DFG: aspartic acid-phenyl alanine-glycine, DTT: dithiothreitol, HEPES: (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), HPLC: high-performance liquid chromatography, HRMS: high resolution mass spectra, IL: interleukin, ip: intraperitoneal, LUBAC: linear ubiquitin chain assembly complex, MAPK: mitogen-activated protein kinase, NBD: nucleotide-binding oligomerization domains, NLR: NOD-like receptor, NOD: nucleotide-binding oligomerization domain, PAMPA: parallel artificial membrane permeability assay, PBS: phosphate-buffered saline, PDB: protein data bank, PG: peptidoglycan, PPI: protein-protein interaction, RIPK2: receptor-interacting protein kinase 2, SAR: structure-activity relationship,

SEAP: secreted embryonic alkaline phosphatase, TNF: tumor necrosis factor, Tris: tris(hydroxymethyl)aminomethane, Ub: ubiquitin, XIAP: X-linked inhibitor of apoptosis

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Highlights

- Demonstration of 3,5-diphenyl-2-aminopyridines as potent inhibitors of receptor-interacting protein kinase 2 (RIPK2).
- SAR insights into achieving RIPK2 dependent nucleotide-binding oligomerization domain (NOD) cell signaling inhibition.
- SAR insights into selectivity versus structurally related activin receptor-like kinase 2 (ALK2).
- *In vitro* ADME and *in vivo* pharmacokinetic characterization of a representative RIPK2 kinase/NOD cell signaling inhibitor illustated.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

C.S., A.D. and G.D.C. declare the following financial interests/personal relationships which may be considered as potential competing interests: PCT patent application (Publication Number 20200030303) assigned to the University of Houston System and Trustees of Tufts College. All other authors declare no conflict of interest about this article. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.