Article

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Discovery of Indole- and Indazole-Acylsulfonamides as Potent and Selective $Na_V1.7$ Inhibitors for the Treatment of Pain

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ABSTRACT: 3-Aryl-indole and 3-aryl-indazole derivatives were identified as potent and selective $Na_v1.7$ inhibitors. Compound **29** was shown to be efficacious in the mouse formalin assay and also reduced complete Freund's adjuvant (CFA)-induced thermal hyperalgesia and chronic constriction injury (CCI) induced cold allodynia, models of inflammatory and neuropathic pain, respectively, following intraperitoneal (IP) doses of 30 mg/kg. The observed efficacy could be correlated with the mouse dorsal root ganglion exposure and $Na_V1.7$ potency associated with **29**.

INTRODUCTION

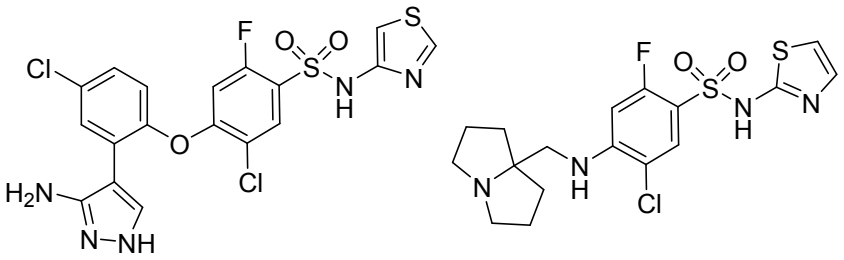
Chronic pain is an immense unmet medical need that affects about 20% of the adult population in the United States and incurs costs of approximately $600 billion annually.[1] Current pain therapeutics, including opioids and general analgesics, have many issues such as intolerable side effects, limited efficacy, and the potential for drug abuse and diversion.[2] New safe and efficacious analgesic agents are greatly needed and one attractive strategy is to develop drugs with novel mechanisms of action that would avoid some of the problems observed with existing drugs.[3] The voltage-gated sodium channel $Na_V1.7$ has emerged as a promising target for

a new class of analgesics based on genetic studies.[4-7] $Na_V1.7$, which is one of nine human Na_V channel subtypes ($Na_V1.1$-1.9), controls the passage of sodium ions into sensory neurons and plays a key role in the perception of pain in humans.[8] $Na_V1.7$ is highly expressed in nociceptive sensory neurons within the dorsal root ganglia (DRG) and mutations in *SCN9A*, the gene encoding for $Na_V1.7$, have been linked to a variety of pain disorders.[9,10] Loss-of-function mutations in SCN9A are associated with congenital insensitivity to pain,[11,12] while gain-of-function mutations result in painful conditions such as inherited erythromelalgia and paroxysmal extreme pain disorder.[13] Other than anosmia, patients with loss-of-function mutations in the $Na_V1.7$ gene appear to be normal.[14] In addition, knockout studies in mice have recapitulated the human phenotype and show the absence of pain-related behaviors following application of nociceptive stimuli.[15,16] These results suggest that the selective inhibition of $Na_V1.7$ will not incur on-target safety issues. However, one challenge with targeting $Na_V1.7$ for the treatment of pain is obtaining selectivity for this channel over other Na_V family members. Selectivity over $Na_V1.5$, which is expressed in atrial and ventricular myocytes, is particularly important in order to reduce the potential for adverse cardiovascular events such as arrhythmia.[17]

Given the high level of target validation, there has been significant documented effort to identify selective $Na_V1.7$ inhibitors for the treatment of pain, with representative $hNa_V1.7$ inhibitors shown in Figure 1.[18-25] One class of arylsulfonamide, represented by PF-05089711 (**1**), was advanced into phase II clinical trials, while **2** was reported to be orally efficacious in animal models of pain,[23] a result that was reproducible in our hands. Another major class of $hNa_V1.7$ inhibitors are based on acylsulfonamides, with **3** and **4** representative, although detailed structure-activity relationships (SARs) for these compound have not been described.[26,27] In previous work, we have disclosed a series of potent and selective sulfonamide-based $Na_V1.7$ blockers.[28-30] In other studies, we have been interested in retaining the acylsulfonamide functionality associated with $Na_V1.7$ inhibitors while replacing the middle linker region with saturated or unsaturated monocyclic or bicyclic scaffolds. While several prototype molecules were prepared, potent $hNa_V1.7$ inhibition was discovered in a series of 3-aryl indoles and 3-aryl indazoles related to **4** but which were specifically configured to provide an opportunity to more broadly study substitution patterns around the core heterocycle, notably at the 2-position where substituents would be anticipated to affect the conformation of the 3-aryl moiety (Figure 1). Herein we disclose SAR studies around

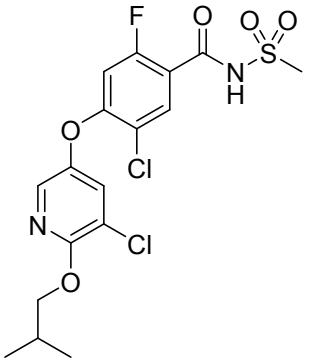
these cores and profile **29** as one of the more promising compounds that demonstrates activity in multiple models of pain.

Chart 1. Structures of representative $Na_V1.7$ inhibitors.

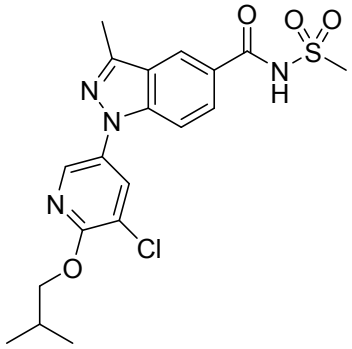


1 (PF-05089771)

2

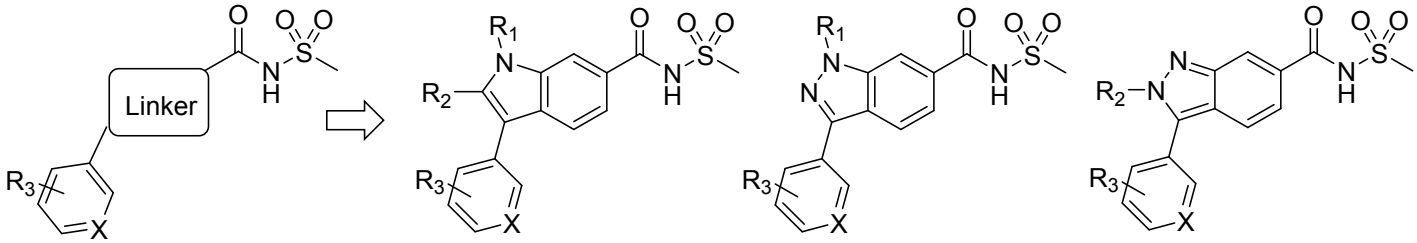


3



4 (PF-05241328)

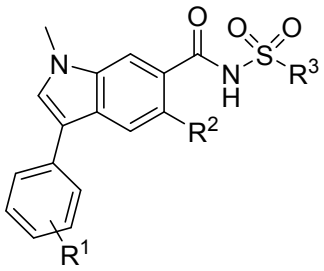
Figure 1. Design principles leading to 3-arylindole and 3-arylindazole acylsulfonamide-based $Na_V1.7$ inhibitors.



RESULTS AND DISCUSSION

The inhibitory activity of target compounds towards $hNa_V1.7$ and $hNa_V1.5$ channels was assessed using an automated 384-well IonWorks Barracuda® patch-clamp assay designed to measure the potency of test compounds on the inactivated channel. The data for compounds **5-27**, compiled in Table 1, reveals good inhibitory selectivity for $hNa_V1.7$ compared to $hNa_V1.5$. In the methyl sulfonamide series, the simple unsubstituted phenyl analog **5** inhibited $hNa_V1.7$ activity with an IC_{50} value of 740 nM with no significant activity towards $hNa_V1.5$ (>30 μM), data that meets targeted selectivity. Substitution of the pendent phenyl ring at the *meta*- or *para*-position with Me or Et groups (**6-9**) showed comparable or improved $hNa_V1.7$ potency. Interestingly, the introduction of a 4-CF_3 phenyl substituent (**10**) greatly increased $hNa_V1.7$ potency ($Na_V1.7$ IC_{50} = 88 nM), while 3-CF_3 substitution (**11**) was associated with significantly lower potency ($Na_V1.7$ IC_{50} = 1420 nM). Bis-substitution, especially at the *ortho*-position (**12** and **13**), generally led to a reduction in potency. Larger aliphatic substitutions at the *para*-position of the phenyl ring had only a modest effect on the potency, as exemplified by **14** and **15**. While a 4-OCF_3 substituent (**16**) showed inhibitory activity comparable to **10**, the removal of a single fluorine atom from **10** to afford **17** led to a 3-fold reduction in potency relative to prototype **10**. Further SARs around the methylsulfonamide group were explored in the context of **18**-**23**. Replacing the methyl group in **10** with a cyclopropane moiety retained potency but, interestingly, in this series the 4-CHF_2 analog **18** exhibited modestly more potent $Na_V1.7$ inhibition than the 4-CF_3 analog **19** that was accompanied by better selectivity over $hNa_V1.5$. Other groups in the R^3 position, compounds **20**-**23**, showed poorer potency relative to the methyl or cyclopropyl substituents. Fluorine substitution in the R^2 position next to the amide group was also explored in **24-27** with the result that this pattern generally improved the potency, particularly when combined with a cyclopropyl sulfonamide moiety.

Table 1. Structures and $hNa_V1.7$ and $hNa_V1.5$ inhibition IC_{50} data for compounds **5-27**.[a]



Compd	R^1	R^2	R^3	$hNa_V1.7$ IC_{50} (nM)[b]	$hNa_V1.5$ IC_{50} (μM)[c]
5	H	H	Me	740 ± 540	>30
6	4-Me	H	Me	740 ± 270	>30
7	3-Me	H	Me	380 ± 300	>30
8	4-Et	H	Me	170 ± 100	>30
9	3-Et	H	Me	220 ± 75	>30
10	4-CF_3	H	Me	88 ± 31	20
11	3-CF_3	H	Me	1420 ± 190	NT
12	2,3-diF	H	Me	2900 ± 1000	>30
13	2-Cl-4-CF_3	H	Me	600 ± 310	8.6
14	4-^{i}Bu	H	Me	363 ± 19	>30
15	4-O^{i}Bu	H	Me	530 ± 30	16
16	4-OCF_3	H	Me	80 ± 27	18
17	4-CHF_2	H	Me	262 ± 90	>30
18	4-CF_3	H		104 ± 51	8.4
19	4-CHF_2	H		69 ± 4	>30
20	4-CF_3	H	CF_3	810 ± 390	7.5

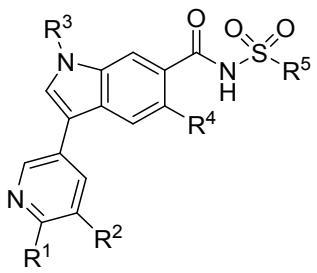
21	4-CF_3	H		1700 ± 320	19
22	4-CF_3	H		420 ± 83	3.9
23	4-CF_3	H		>3000	18
24	4-CF_3	F	Me	49 ± 34	NT
25	4-CF_3	F		16 ± 8	3.8
26	4-CHF_2	F	Me	91 ± 43	>30
27	4-CHF_2	F		38 ± 5	NT

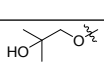
[a]Values are the means of at least two separate experiments. [b]The $hNa_V1.7$ inhibition data were collected using an IonWorks Barracuda automated electrophysiology platform using a protocol where cells were held at −60 mV. [c]The $hNa_V1.5$ data were collected on the same platform using a protocol where cells were held at −50 mV. NT = not tested.

The SARs surrounding the 3-pyridinyl analogs are documented in Table 2. While the unsubstituted pyridine analog **28** was inactive, substitution at the 5- and/or 6-positions of the pyridine generally led to improved activity. Introduction of the substituent groups found in **3** and **4** afforded analog **29** which exhibited potent $hNa_V1.7$ inhibition (IC_{50} = 108 nM) and good selectivity ($hNa_V1.5$ IC_{50} =19 μM). Removal of the Cl group modestly compromised potency (**30**) while replacement of the *iso*-butyl group with the cyclopropylmethyl group found in **31** had little effect on activity. However, replacement of the Cl group with CN gave **32**, which exhibited enhanced potency while maintaining selectivity, while substitution with a OMe group (**33**) substantially diminished the potency. Replacing the iso-butyl group in **29** with a difluoroethyl moiety (**34**) substantially decreased the potency but, interestingly, trifluoroethyl substitution provided an analog **35** with very good inhibitory potency. To improve the physicochemical properties of the series, a hydroxyl group was added to the iso-butyl substituent to give **36**; however, this change abrogated potency, indicating that hydrophilic polar groups are not tolerated in this region. SARs around the methyl sulfonamide group were explored in the context of **37-44** where, as observed in the phenyl series, the cyclopropyl derivatives **37-39** maintained or improved potency compared to the methyl homologue. The $hNa_V1.7$ inhibition potency gradually decreased as the substituent size increased, as exemplified

by **40-42**. In addition, replacing the methyl sulfonamide in this pyridinyl series with a sulfamoyl group, probed by **43** and **44**, also led to a decrease in inhibitory activity. 5-Fluoro-substituted indole analogs with a cyclopropyl in the R^5 position, compounds **45-48**, were more potent than the corresponding methyl analogs while analogs with a chlorine at R^2 were less potent than the des-Cl analogs. Compound **48** expressed potent hNa_V17 inhibition with an IC_{50} value of 59 nM. Finally, the larger N-substituents explored in the context of **49**-**51** substantially lowered the $hNa_V1.7$ inhibitory potency.

Table 2. Structures and $hNa_V1.7$ and $hNa_V1.5$ IC_{50} inhibition data for compounds **28-51**.[a]



Compd	R^1	R^2	R^3	R^4	R^5	$hNa_V1.7$ IC_{50} (nM)[b]	$hNa_V1.5$ IC_{50} (nM)[b]
28	H	H	Me	H	Me	>3000 [d]	NT
29		Cl	Me	H	Me	108 ± 71	19
30		H	Me	H	Me	164 ± 27	>30
31		Cl	Me	H	Me	123[d]	NT
32		CN	Me	H	Me	70 ± 32	21
33		OMe	Me	H	Me	510 ± 120	>30
34		Cl	Me	H	Me	850 ± 850	>30
35		Cl	Me	H	Me	63 ± 47	12
36		Cl	Me	H	Me	>30000 [d]	>30

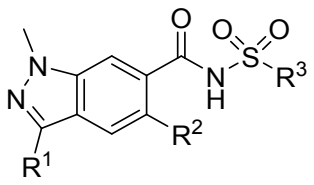
37		Cl	Me	H		290 ± 220	12
38		Cl	Me	H		82 ± 5	NT
39		OMe	Me	H		85 ± 18	>30
40		Cl	Me	H		154 ± 74	5.7
41		Cl	Me	H		460 ± 260	14
42		Cl	Me	H		1300 [d]	NT
43		Cl	Me	H		1300 [d]	6.3
44		Cl	Me	H		4200 [d]	NT
45		Cl	Me	F	Me	520 ± 440	7.2
46		Cl	Me	F		230 ± 170	5.1
47		H	Me	F	Me	89 ± 60	16
48		H	Me	F		59 ± 35	3.7
49		Cl	i-Pr	H	Me	700 ± 530	1.7
50		Cl	i-Butyl	H	Me	3330 ± 1200	24
51		Cl	i-Butyl	H		8100 ± 6700	11

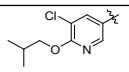
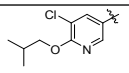
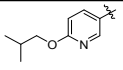
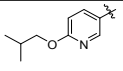
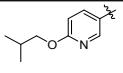
[a]Values are the means of at least two separate experiments. [b]The $hNa_V1.7$ inhibition data were collected using an IonWorks Barracuda automated electrophysiology platform using a protocol where cells were held at −60 mV. [c]The $hNa_V1.5$ data were collected on the same platform using a protocol where cells were held at −50 mV. [d]Tested only once. NT = not tested.

The SARs around the indazole core were also studied and the results of this phase of the survey are documented in Table 3. When compared to the indole core, the indazole derivatives were equally potent, with good levels of selectivity. In the trifluoromethylphenyl series **52-54** the potency was increased with addition of a

5-F on the indazole core incorporating a cyclopropyl sulfonamide moiety, leading to **54** with an IC_{50} value of 13 nM for $hNa_V1.7$ inhibition. In the substituted pyridine series **55-59**, methyl and cyclopropylsulfonamides were both well tolerated. Removal of the chlorine from the pyridyl led to improved selectivity over $Na_V1.5$ (compare **55** and **57**). The addition of fluorine in the R^2 position of the indazole (**58**) led to increased potency and further modification of the sulfonamide to a cyclopropyl further increased potency, with the $Na_V1.7$ IC_{50} value for **59** = 45 nM.

Table 3. Structures and $hNa_V1.7$ and $hNa_V1.5$ inhibition IC_{50} data for compounds **52-59**.[a]

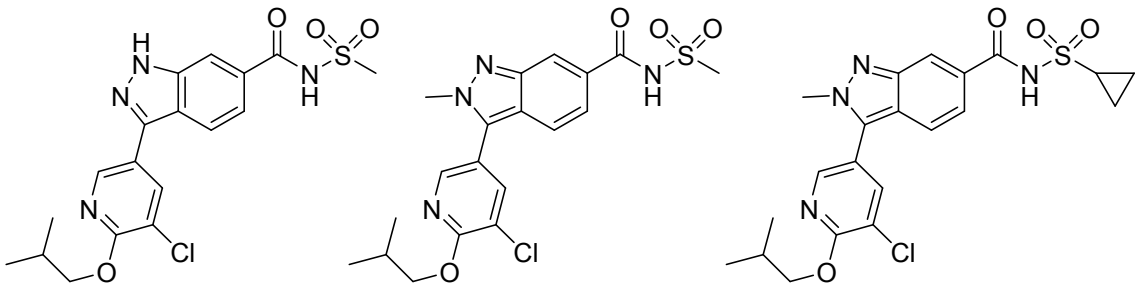


Compd	R^1	R^2	R^3	$hNa_V1.7$ IC_{50} (nM)[b]	$hNa_V1.5$ IC_{50} (μM)[c]
52		H	Me	194 ± 64	>30
53		F	Me	52 ± 20	>30
54		F		13 ± 2	6.4
55		H	Me	67 ± 48	6.5
56		H		104 ± 57	5.9
57		H	Me	314 ± 90	>30
58		F	Me	170 ± 25	>30
59		F		45 ± 30	11

[a]Values are the means of at least two separate experiments. [b]The $hNa_V1.7$ inhibition data were collected using an IonWorks Barracuda automated electrophysiology platform using a protocol where cells were held at −60 mV. [c]The $hNa_V1.5$ data were collected on the same platform using a protocol where cells were held at −50 mV.

The additional indazole derivatives shown in Figure 2 were prepared and tested in order to evaluate the effect of the *N*-methyl substituent and its site of deployment on inhibitory potency. The *N*-unsubstituted indazole **60** exhibited lowered potency compared to the methylated prototype **55** as did the isomeric *N*-2 methyl indazoles **61** and **62** when compared to their *N*-1 methyl matched pairs **55** and **56**. The latter SAR reflects observations made with the indole series where a bromo or chloro substituent attached to the 2-position of the indole heterocycle resulted in a 3-7-fold reduction potency (data not shown). However, indole 2-substitution was more readily tolerated in a related series of $Na_v1.7$ inhibitors that was spawned by observations made with this study and this aspect of the SARs was pursued in that chemotype.[32]

Figure 2. Structures and $Na_v1.7$ inhibition data for indazole derivatives **60**-**62**.



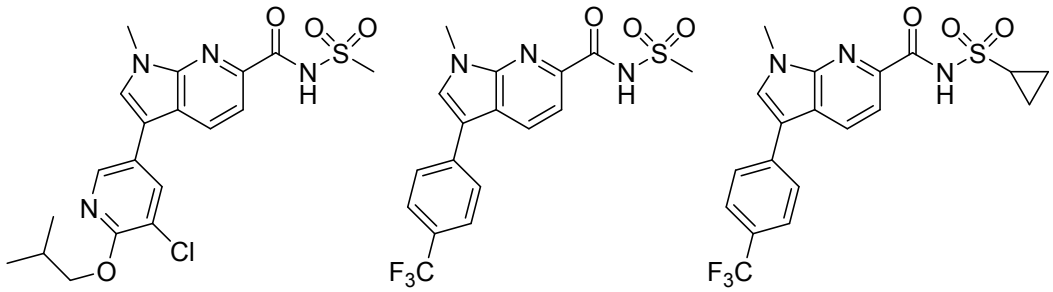
60
$Na_v1.7$ IC_{50} = 280 nM

61
$Na_v1.7$ IC_{50} = 790 nM

62
$Na_v1.7$ IC_{50} = 190 nM

The series of azaindole derivatives depicted in Figure 3 was prepared and evaluated in an effort to further probe aspects of electronic properties of the core heterocycle and its relationship with inhibitory activity. Both the 7-azaindole derivatives **63-65** and the 4-azaindole derivatives **66** and **67** exhibited lowered but measurable $hNa_V1.7$ inhibitory activity when compared to the corresponding indazole core derivatives while the activity of the 5-azaindole analog **66** was poor, with an IC_{50} value of >30 μM.

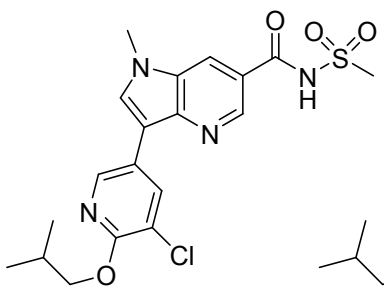
Figure 3. Structures and $Na_v1.7$ inhibition data for the series of azaindole derivatives **63-68**.



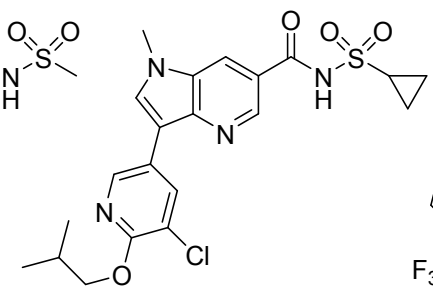
63
$Na_v1.7$ IC_{50} = 1400 nM

64
$Na_v1.7$ IC_{50} = 3020 nM

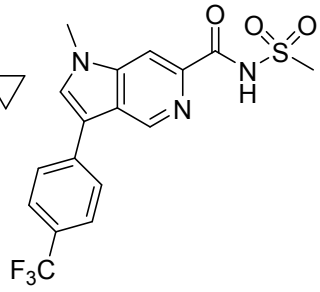
65
$Na_v1.7$ IC_{50} = 642 nM



66
$Na_v1.7$ IC_{50} = 7820 nM



67
$Na_v1.7$ IC_{50} = 2000 nM



68
$Na_v1.7$ IC_{50} > 30,000 nM

Those compounds demonstrating potent activity in the Barracuda assay were further profiled in a series of in vitro developability assays, with the results compiled in Table 4. These compounds were tested in a manual patch clamp electrophysiology (EP) assay, with the results confirming the potency measured in the Barracuda assay. In general, this set of compounds exhibited good metabolic stability in human, rat and mouse liver microsomes but was associated with high plasma protein binding, with free fractions of <1.5% in both human and mouse plasma. Unlike the aryl sulfonamides,[28] all of the acyl sulfonamide derivatives described here did not significantly inhibit CYP 3A4 and there was no evidence of time-dependent inhibition (data not shown). For example, both **29** and **47** exhibited acceptable CYP profiles (HLM-CYP IC_{50}s for compound **29** = 9.7 μM (2B6), 1.0 μM (2C8), 9.9 μM (2C9), 28 μM (2C19), >40 μM (2D6), >40 μM (3A4) and for **47** = >40 μM (2B6), 1.0 μM (2C8), 27 μM (2C9), 4.0 μM (2C19),

>40 μM (2D6), 15 μM (3A4) with no evidence of time-dependent inhibition. Moreover, both **29** and **47** showed PXR IC_{50} values of >50 μM. Although the permeability of many of these analogs in a Caco-2 cell assay appeared to be high, several compounds showed high efflux ratios. Notably, the addition of a 5-F substituent adjacent to the acylsulfonamide moiety, compounds **24**, **25**, **27**, **45**, **47**, and **48**, reduced the efflux ratios in Caco-2 cells and also plasma protein binding.[31] However, this effect did not extend to the 5-fluoro indazole analog **54** which exhibited a Caco-2 cell efflux ratio of >21.

Table 4. Further profiling of potent compounds.

Compd	$hNa_V1.7$ EP IC_{50} (nM)	Met. stab. In liver microsomes[b] (H/R/M)	F_u[c] H/M (%free)	PAMPA permeability pH = 5.5/7.4 (nm/sec)	Caco2 A-B/B-A (nm/sec)	Caco2 efflux ratio
10	96	100/74/54	<0.10/<0.10	972/171	<15/76	>5.1
14	23	100/94/100	0.10/0.30	NT	<15/78	>6.2
18	8	87/92/87	0.20/0.40	525/135	NT	NT
24	13	97/99/95	0.20/0.50	712/140	~20/125	6.1
25	5	100/100/-	0.25/0.35	1660/323	46/86	1.9
27	12	93/82/86	0.30/0.70	325/60	81/195	2.4
29	8	95/66/100	<0.10/0.20	443/216	<15/168	>5.5
38	27	97/77/93	<0.10/0.20	-/391	<15/114	>7.6
45	1.1	100/85/100	0.10/0.20	495/205	20/67	3.4
46	3.3	100/37/100	<0.10/0.20	335/310	34/102	3.0
47	25	98/98/99	0.80/1.40	802/164	61/186	3.1
48	19	100/78/98	2.4/0.60	851/254	120/189	1.6
54	21	100/100/100	NT/0.80	592/102	<15/312	>21
55	11	100/100/100	NT/0.20	1160/417	NT	NT
59	43	91/88/92	NT/1.1	762/100	NT	NT

[a]Data are from previous tables. [b]Values are percentage remaining after 10 minutes with 0.5 μM compounds incubated in liver microsomes. [c]Unbound percentage free fraction in human (H) and mouse (M) plasma. NT = not tested.

Selected compounds were next examined in the manual EP assay using the mouse $Na_V1.7$ channel isoform and the mouse PK profiles determined as a prelude to selecting compounds for evaluation in the mouse formalin model of pain. The results are compiled in Table 5 with the PK profiles of **29** and **47** following oral and IP dosing captured in Figure 4. The mouse formalin model of pain measures spontaneous, nociceptive-like paw flinching/licking responses after peripheral nociceptor activation and was chosen for in vivo efficacy screening since formalin-induced nociceptive behaviors were abolished in global $Na_V1.7$ knockout mice.[16] The injection of formalin elicits a biphasic behavioral flinching response; phase I occurs during the first 5 minutes post-injection and results from direct nociceptor activation, whereas phase II occurs 15-45 minutes after the injection and is thought to reflect a tonic state of pain similar to the relatively long-lasting stimuli in human disease, such as neuropathic pain.[33] Treatment of mice with compound **2** (30 mg/kg, PO), used as a positive control, 60 minutes prior to the injection of formalin had no effect on the phase I responses but abolished phase II nociceptive behaviors (Figure 5). When compound **29** was dosed IP at 3 or 10 mg/kg, there was no significant effect on either phase I or phase II responses in mice (Figure 5). However, phase II nociceptive behaviors were completely abolished when **29** was dosed at 30 mg/kg, IP but with no effect on the phase I symptoms. The percent reversal of nociceptive behaviors in the second phase is plotted in Figure 6. All other compounds shown in Table 5 were also tested at 30 mg/kg, PO, but failed to show significant efficacy in this model. Interestingly, when the indazole **55** was assessed in the mouse formalin model, dosing of the drug resulted in prostration, possibly due to sedation, as well as hypothermia (see note in Table 5). In contrast, none of the mice dosed with indole derivatives showed any detrimental side effects during the course of the in vivo pain model studies, indicating that small structural changes in this series can lead to significantly different profiles.[34] Compound **55** is structurally analogous to **4** but, unfortunately, details on the in vivo pharmacology of **4** that might place this observation in perspective have not been disclosed although this compound was advanced into clinical trials as part of a micro-dosing study.[35]

Table 5. Mouse data for potent compounds.

Compd.	$mNa_V1.7$ EP IC_{50} (nM)	$mNa_V1.7$ mDRG IC_{50} (nM)	F_u mDRG (%free)	Dose[a] PO/IP (mg/kg)	Plasma Conc.[b] (μM)	Free Plasma Conc. (nM)	DRG Conc. Total/Free (nM)[b]	Active in Formalin Test
5	3.9	1.8	100	30	1.4	340	340/340	Yes
25	27	5	-	30	140 ± 7.8	490	-	No
27	231	12		30	173 ± 3.5	1211	-	No
29	35	11	3.5	30	59 ± 5	118	2720/95	Yes
46	10	-	-	30	58 ± 20	116	11000/-	No
47	115	14	8.5	30	44 ± 11	616	990/84	No
48	37	24	-	30	132 ± 15	792	-	No
55	-	12	-	3[c]	0.28 ± 0.18	0.56	-	No

[a]Compound dosed PO to male mice in 0.5% Methocel/0.1% Tween/99.4% water (10 mL/kg) and measured at 75 minutes, with the exception of **29** which was dosed IP. [b]Results are presented as the mean, n = 3–9 per group. [c]Compound **55** at 30 mg/kg caused prostration or sedation and hypothermia in three mice and was tested at a lower 3 mg/kg dose.

Figure 4. Mouse PK profiles of compounds **29** and **47** dosed at 30 mg/kg IP and PO.

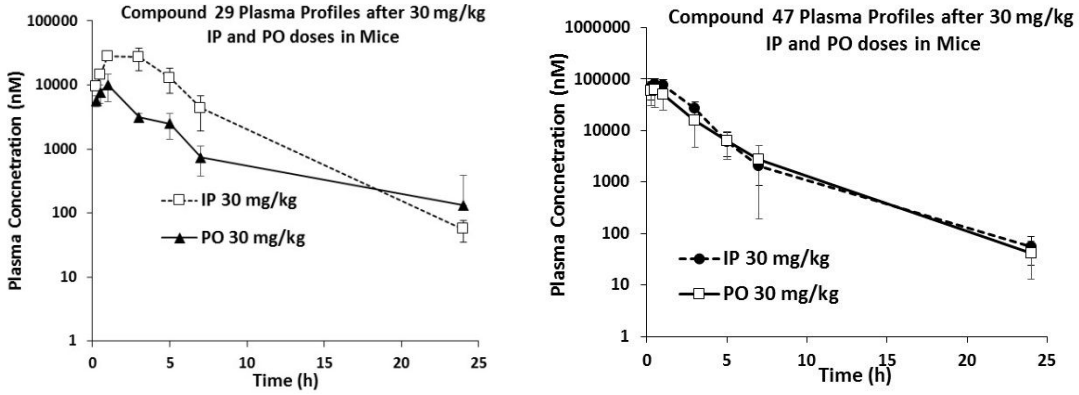


Figure 5. Effect of **2** (30 mg/kg, PO) or **29** (3, 10, 30 mg/kg, IP) on phase I/II formalin-induced nociceptive behaviors. Results are presented as the mean ± SEM response (n = 12-15 per group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; ***P<0.001 compared to vehicle/formalin group.

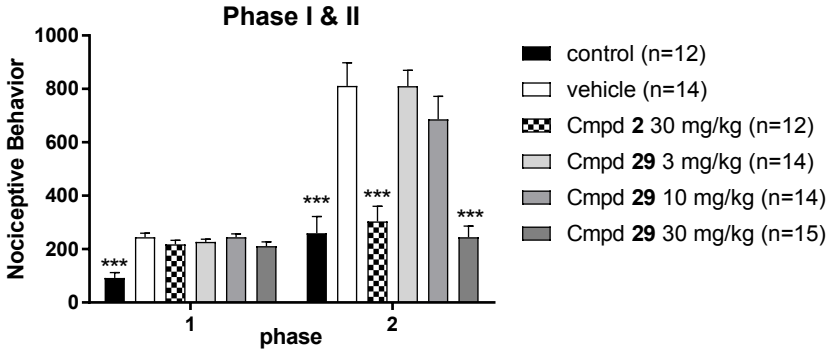
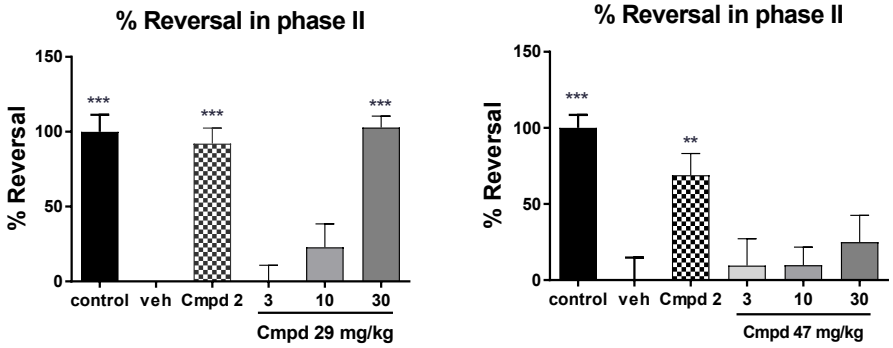


Figure 6. Effect of **2** (30 mg/kg, PO) or **29** (3, 10, 30 mg/kg, IP), or **47** (3, 10, 30 mg/kg, PO) on percentage reversal of phase II formalin-induced nociceptive behaviors. Results are presented as the mean ± SEM response (n = 12-15 per group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; ***P<0.001 compared to vehicle/formalin group.



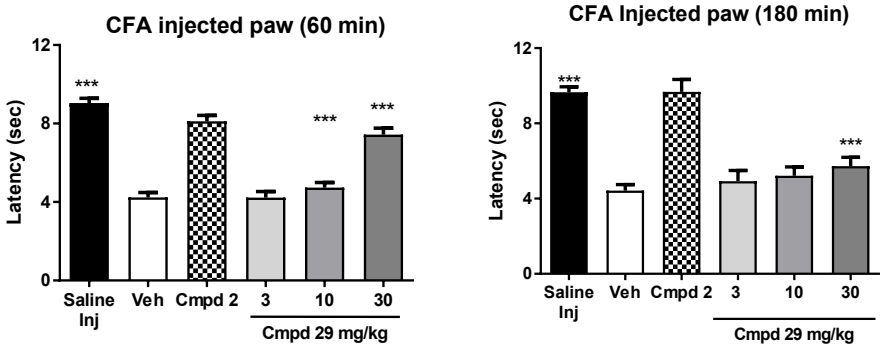
Why compound **29** demonstrated complete reversal of nociceptive behavior while **47**, a close analog with similar in vitro properties, was not efficacious is enigmatic. Analogous discrepancies between PK and efficacy the formalin test model have been reported with aminotriazine-based $Na_V1.7$ inhibitors[36] and arylsulfonamide-based $Na_V1.7$ inhibitors.[28] In an effort to further investigate this anomaly, we studied additional aspects of the biochemical pharmacology of the compounds. Kinetic studies with **29** and **47** on $hNa_V1.7$ also showed that both compounds exhibited similar on- and off-rates (onset at -70 mV: tau on for **29** and **47** were 9.6 and 12.1 seconds, respectively; recovery times at -120 mV: tau off for **29** and **47** were 45 and 99 seconds, respectively. The tissue binding of both **29** and **47** in dorsal root ganglia (DRG) and trigeminal ganglia (TGG) tissue from both mouse and rat were examined since these are believed to be key sites of action of $Na_V1.7$ inhibitors. It was found that **29** had similar unbound free fractions in the DRG and TGG tissues of mouse (3.5%) and rat (3.4%). The unbound free fractions for **47** were more variable; in the mouse these were 8.4% (DRG) and 6.9% (TGG), whereas lower free

fractions were seen in the rat DRG (3.9%) and TGG (4.5%). It was our belief that compounds able to achieve free tissue concentrations in the DRG above the $Na_V1.7$ manual EP IC_{50} would show efficacy in the formalin-induced pain model. As can be seen from Table 5, using the total mouse DRG exposure at 30 mg/kg (2724 nM for **29** and 910 nM for **47**), mouse DRG binding (3.5% free for **29** and 8.5% free for **47**), and mouse DRG $Na_V1.7$ manual EP IC_{50} (11 nM for **29** and 14 nM for **47**), we can calculate the free[DRG]/IC_{50} values for **29** and **47** as 8.7 and 5.5, respectively. This small difference in values fails to adequately explain why **29** is efficacious in the formalin-induced pain model but **47** is not. However, the ability to accurately measure the in vitro properties of very lipophilic compounds can be challenging and precise determination of the free fraction in plasma is often less accurate for compounds that are highly protein bound. Determining the free fraction in DRG tissue is also technically challenging. Assuming the free drug concentration in the DRG needs to cover the mNaV1.7 IC_{50} by 10-fold, a 2-fold decrease in the calculated DRG free fraction may be enough to predict that compound **47** would be inactive. With regard to activity at other Na_V subtypes, both compounds exhibit similarly advantageous selectivity (for **29**: Barracuda assay results were IC_{50} values of 16, >30, 4.8, 18.5 μM for $hNa_V1.2/1.3/1.4/1.5$, respectively). PK studies with **47** showed that plasma exposures in CD1 mice were similar following either oral or IP administration at 30 mg/kg, so the route of administration does not appear to explain the cause of the lack of efficacy with this analog (see Figure 4). No off-target activities were seen in an in-house, CEREP-like, safety panel assay for either **29** or **47** that could explain their different profiles (data not shown). It is worth noting that in some of the efficacy models, including the formalin mouse model, there is a steep dose response curve which may suggest that a somewhat modest increase or decrease in the dose may have a dramatic effect on the behavioral response based on tissue exposure. The doses tested in the formalin mouse model were limited to 30 mg/kg in an effort to avoid potential off-target activities, particularly since the plasma exposures at this dose were high (Figure 4).

Compounds **29** and **47** were also tested in the mouse complete Freund's adjuvant (CFA) model of inflammatory pain.[37] It has been shown that $Na_V1.7$ knockout mice do not develop CFA-induced thermal hyperalgesia.[16] Treatment with compound **29** (30 mg/kg, IP) significantly reduced CFA-induced thermal hyperalgesia without affecting thermal response latency of the untreated, contralateral (left) paw. Compound **29**

was efficacious in reversing thermal hyperalgesia at 60 minutes post-treatment but not at 180 minutes after treatment (Figure 7). Similar to previous results, **47** (30 mg/kg, PO) was not effective in the CFA thermal hyperalgesia model. Plasma exposures at these doses/routes, determined in satellite groups of mice, were 63 ± 4.8 μM and 38 ± 10 μM for **29** and **47**, respectively. This corresponded to a mouse free plasma concentration of 126 nM for **29** (0.2% plasma free fraction) and 532 nM for **47** (1.4% plasma free fraction), corresponding to ~4-5-fold coverage of the mouse cellular IC_{50} values that were determined by electrophysiology ($mNa_v1.7$ IC_{50} = 35 nM for **29**, $mNa_v1.7$ IC_{50} = 115 nM for **47**).

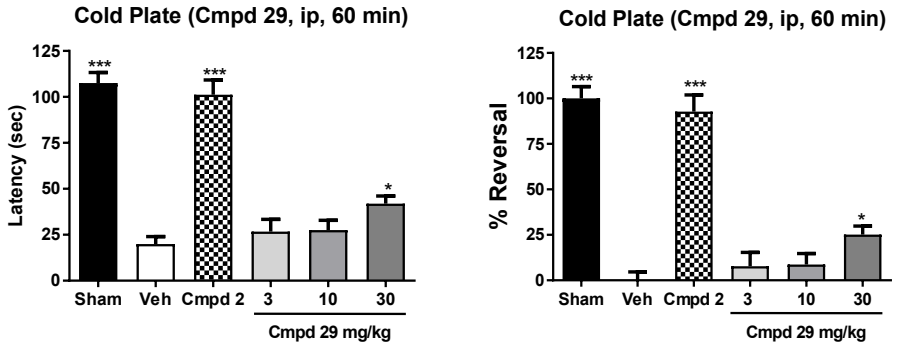
Figure 7. Effect of compound **2** (60 mg/kg, PO) or **29** (3, 10, 30 mg/kg, IP) on latency of thermal hyperalgesia in CFA mice. Results are presented as the mean ± SEM response (n = 12-14/group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; ***P<0.001 compared to vehicle/control group.



Next, **29** was tested in the mouse chronic constriction injury (CCI) model in which three ligatures are loosely tied around the left sciatic nerve to simulate the conditions associated with nerve compression injury.[38] In contrast to mice receiving sham surgery, CCI mice showed increased sensitivity to cold and a faster latency to exhibit nociceptive-like behaviors when placed on a cold plate maintained at 5 ^{0}C. CD1 mice receiving CCI or sham surgery were tested 5 weeks later and were treated IP with either vehicle or **29** 30 minutes prior to testing. As can be seen from Figure 8 (left), an IP dose of 30 mpk **29** produced a significant increase in the latency in the response to cold in CCI mice. Figure 8 (right) shows that the cold allodynia response in CCI mice was reversed by a modest 25% following treatment with a dose of 30 mpk of **29**. The total plasma exposures at 60 minutes post-

dose were 3.3 ± 1.0, 27 ± 6.8, and 68 ± 31 μM following administration of 3, 10, and 30 mg/kg, respectively, which corresponds to a free plasma concentrations of 6.6, 54, and 136 nM, respectively.

Figure 8. Effect of compound **2** (60 mg/kg, PO) or **29** (3, 10, 30 mg/kg, IP) on latency of cold allodynia in CCI mice. Results are presented as the mean ± SEM response (n = 12-14 per group) and were analyzed by ANOVA followed by Dunnett's post-hoc tests; ***P<0.001, *p<0.05 compared to vehicle/control group.



To further explore the differences between **29** and **47**, sural fascicle recording studies were performed in order to determine if the compounds would differentially affect mechanoreceptor-mediated afferent transmission in wild-type mice, a modified form of the model described by Koltzenburg et al.[39] The assay was validated with systemic mexiletine (IP; 10 mg/kg) and local tetrodotoxin (300 nM applied to the nerve) applications (data not shown). Systemic IP dosing of either **29** or **47** at doses of 30 mg/kg was followed by recording of the sural nerve mechano-sensitivity at 5, 30, 60, 90, and 120 minutes post-dose. While brush and low-threshold pressure (1.6 mN) did not show any difference between treated and non-treated animals, differences were noted at the higher pressures of 98 mN and 980 mN, as shown in Figure 9. At the longer time points of 90–120 minutes, both **29** and **47** showed significant reductions in mechanically-elicited afferent firing, with the systemic exposures measured 2 hours after IP dosing determined to be 89 μM and 57 μM, respectively. In a second study, **29** or **47** were applied directly onto the nerve fascicle, with the effects summarized in Figure 10. Intriguingly, in this study, only compound **29** and not compound **47** showed a significant effect.

Figure 9. Effects of **29** and **47** (30 mg/kg) on mechano-sensitivity of the mouse sural nerve when dosed IP. *indicates significant difference from vehicle (2-way ANOVA followed by Dunnett's test).

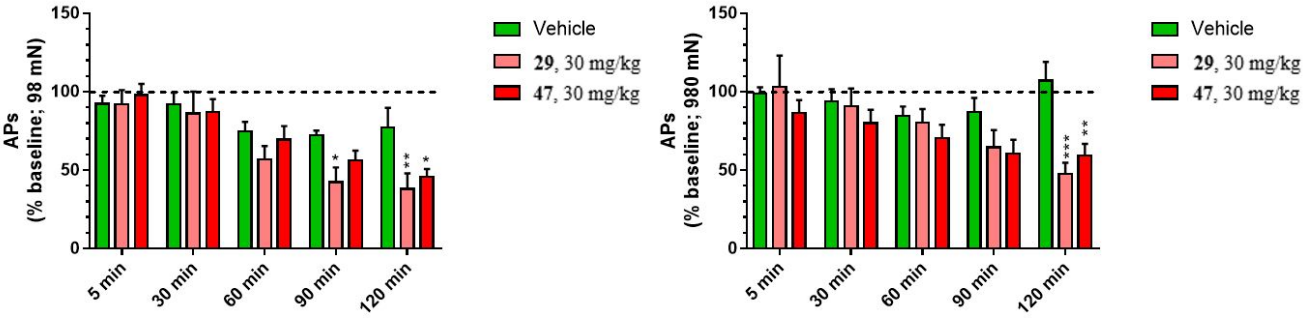
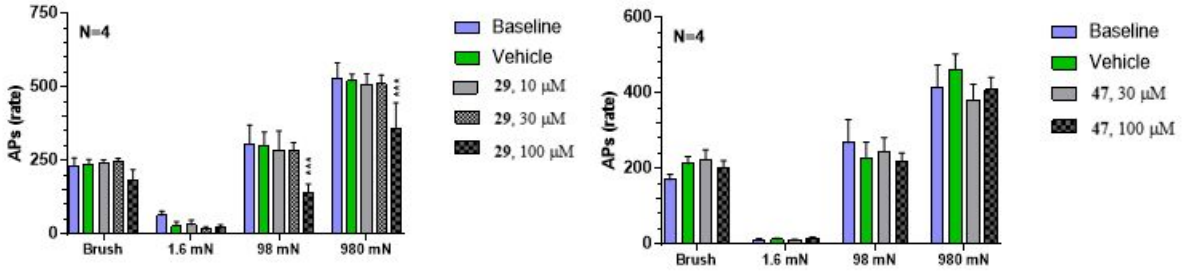


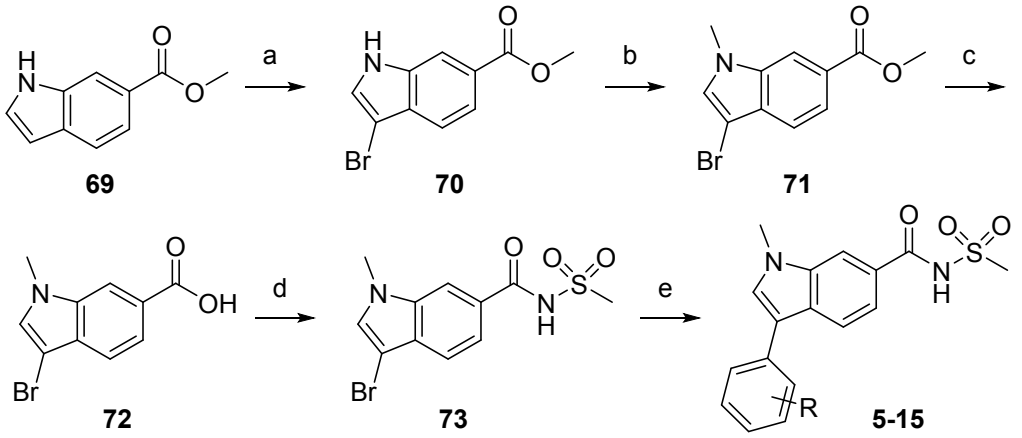
Figure 10. Effects of **29** and **47** on mechano-sensitivity of the mouse sural nerve when applied directly to the nerve. *indicates significant difference from vehicle (2-way ANOVA followed by Dunnett's test).



CHEMISTRY

Scheme 1 describes the general synthesis of compounds **5-15**. Bromination of methyl indole-6-carboxylate (**69**) using NBS afforded bromide **70** which, after methylation of the indole nitrogen atom, provided **71**. Following hydrolysis of **71**, the resultant acid **72** was converted to the acylsulfonamide **73** using the Mukaiyama reagent for the acid activation.[40] Finally, a Suzuki coupling of bromide **73** with a phenylboronic acid derivative afforded the aryl indoles **5-15**.

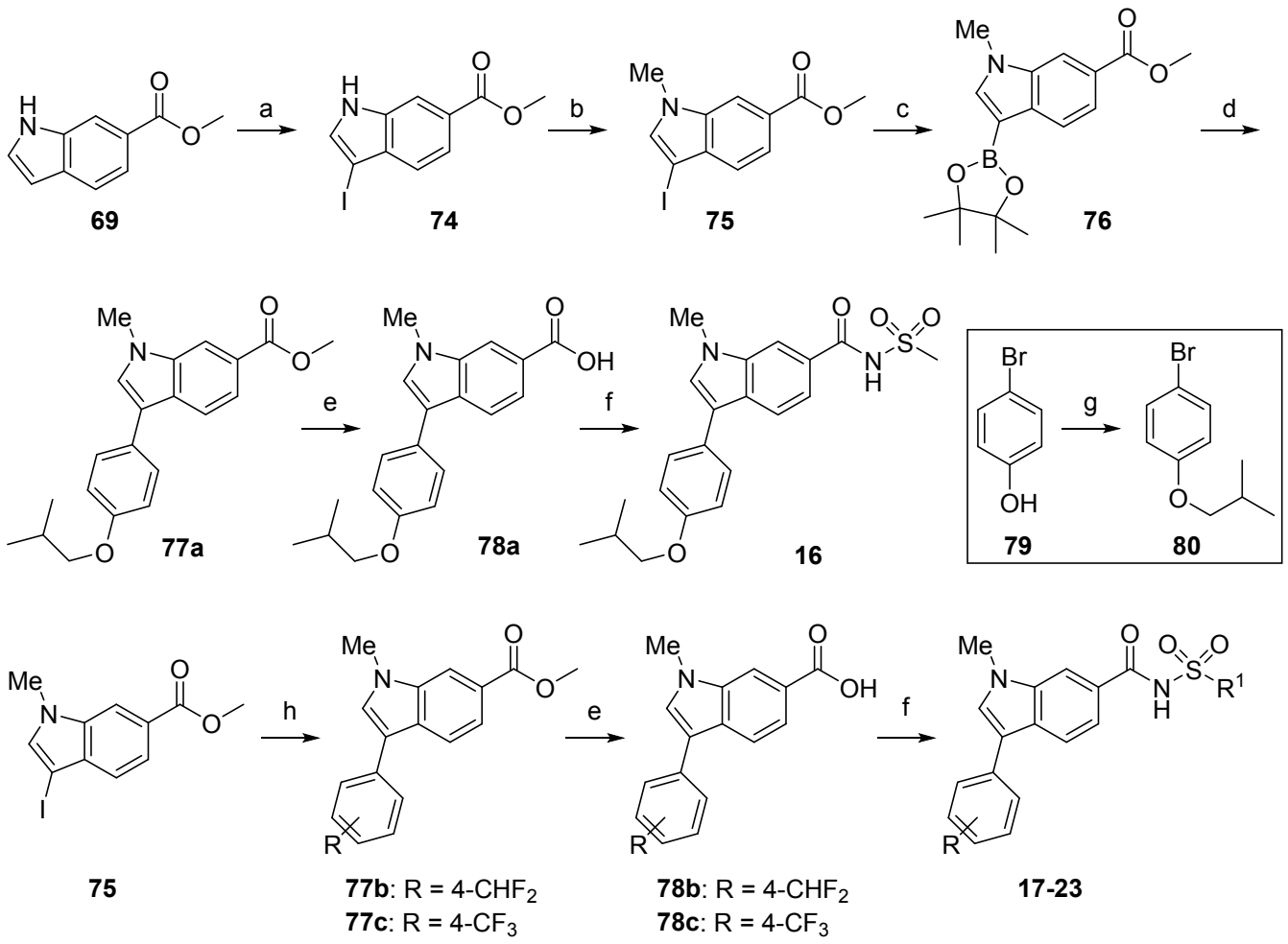
Scheme 1. Synthetic approaches to indoles **5**-**15**.



[a]Reagents and conditions: (a) NBS, DMF, rt, 2 h, 93%; (b) MeI, K_2CO_3, DMF, rt, 18 h, 90%; (c) LiOH, THF-MeOH, H_2O, rt, 18 h, 92%; (d) Methansulfonamide, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, DMAP, CH_2Cl_2, rt, 1.5 h, 93%; (e) R-ArB$(OH)_2$, $PdCl_2$(dppf), Na_2CO_3, dioxane, 100 ºC, 2 h.

Scheme 2 describes the synthesis routes employed to prepare **16-23**. Indole **69** was converted to the N-methylated iodoindole **75** through the intermediacy of **74**.[41] The stable boronate **76**, prepared from iodide **75**, was purified and characterized.[42] Boronate **76** reacted with bromide **80**, which was prepared from **79** under standard Mitsunobu conditions, to generate **77a**. After hydrolysis, the acid **78a** was converted to **16** as described above. Alternatively, the boronate formation and Suzuki coupling from **75** could be carried out in a single pot[42] to afford intermediates **77b/c**, which led to compounds **17-23**.

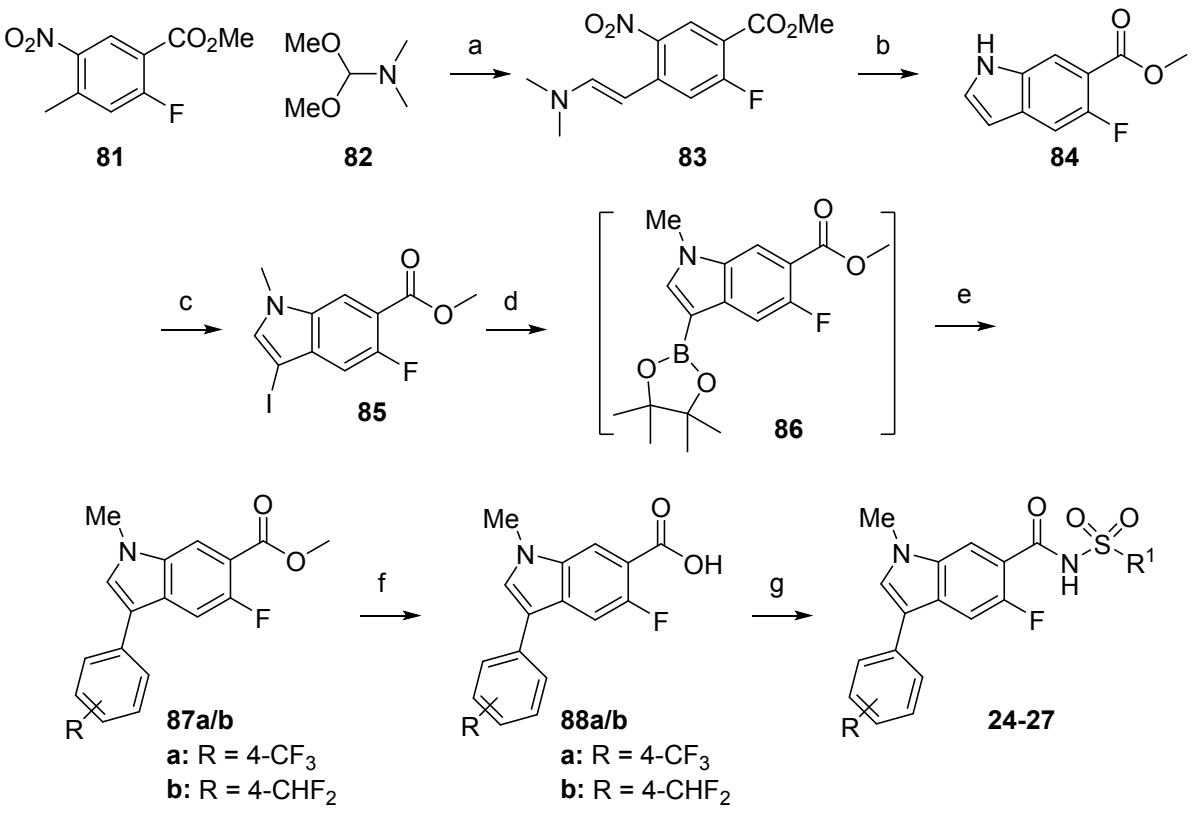
Scheme 2. Synthetic approaches to the preparation of **16**-**23**.



[a]Reagents and conditions: (a) I_2, KOH, DMF, rt, 18 h, 91%; (b) MeI, K_2CO_3, DMF, rt, 18 h, 89%; (c) $Pd(PPh_3)_4$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dioxane, 80 ºC, 2 h, 81%; (d) 4-isobutoxyphenyl bromide, $PdCl_2$(dppf), Na_2CO_3, dioxane, 80 ºC, 12 h; (e) LiOH, THF-MeOH, H_2O, rt, 18 h, 88%; (f) DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, $R^1SO_2NH_2$, CH_2Cl_2, rt, 1 h, 28%; (g) PPh_3, DIAD, THF, rt, 2 h, 40%; (h) $Pd(PPh_3)_4$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dioxane, 80 ºC, 2 h; then MeOH, R-Ar-Br, Cs_2CO_3, 80 ºC, 4 h, 60-63%.

Scheme 3 describes the synthesis of the 5-fluoroindole derivatives **24-27**. The 5-fluoro-6-indole ester **84** was prepared from intermediate **83** which, in turn, was generated by using the Leimgruber-Batcho reaction in which **81** is exposed to **82**.[43] Iodination and methylation of **84** took place in one pot to generate intermediate **85**, which could be converted into **24-27** as described previously.

Scheme 3. Synthetic approaches to the preparation of **24**-**27.**

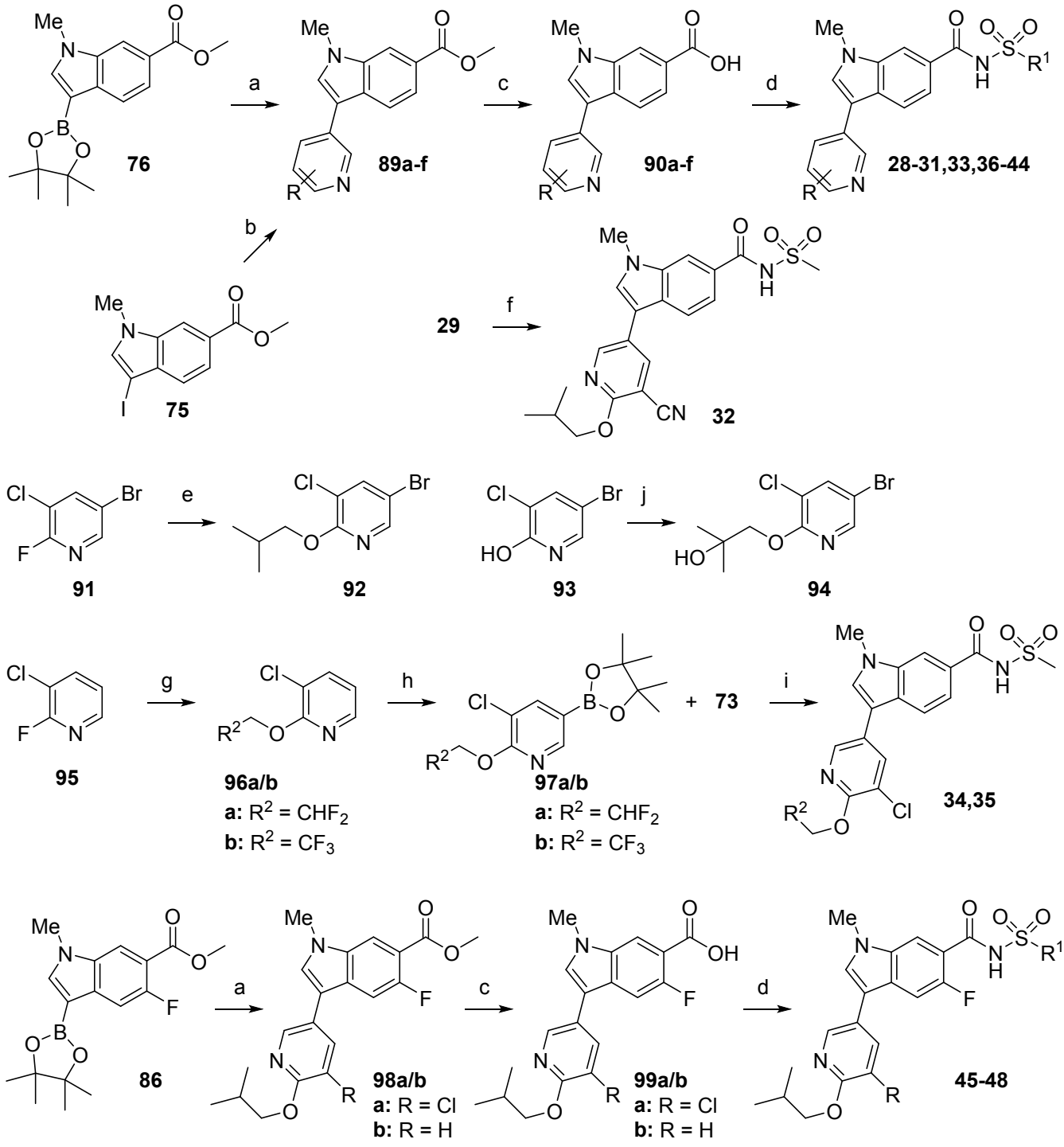


[a]Reagents and conditions: (a) DMF, 100 ºC, 1 h, 86%; (b) Pd/C, H_2, EtOAc, rt, 2 h, 70%; (c) I_2, KOH, DMF, rt, 16 h; then MeI, rt, 5 h, 85%; (d) $Pd(PPh_3)_4$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dioxane, 80 ºC, 2 h; (e) MeOH, R-Ar-Br, Cs_2CO_3, dioxane, 80 ºC, 4 h; (f) LiOH, THF, H_2O, rt, 18 h; (g) DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, $R^1SO_2NH_2$, CH_2Cl_2, rt, 1 h.

Scheme 4 describes the synthetic approaches to 3-(3-pyrindinyl)indole derivatives **28**-**48**. Boronate **76** or iodide **75** were converted into **28-31**, **33**, and **36-44** as described above. Intermediate bromide **92** was conveniently prepared from the 2-fluoropyridine **91**, while bromide **94** was prepared by the reaction of hydroxypyridine **93** with 2,2-dimethyloxirane. All other bromides used were commercially available. Cyano derivative **32** was directly prepared from the chloride **29**,[44] while **34** and **35** were prepared from bromide **73** and boronates **97a/b**, respectively, which, in turn, were prepared from the pyridine intermediates **96a/b** following a literature procedure.[27,45] Intermediates **96a/b** were prepared from 2-fluoro-3-chloro-pyridine (**95**) while the 5-

fluoro-indole derivatives **45**-**48** were prepared from the boronate **86** and the corresponding bromides following the established conditions.

Scheme 4. Synthetic approaches to the preparation of **28**-**48**.

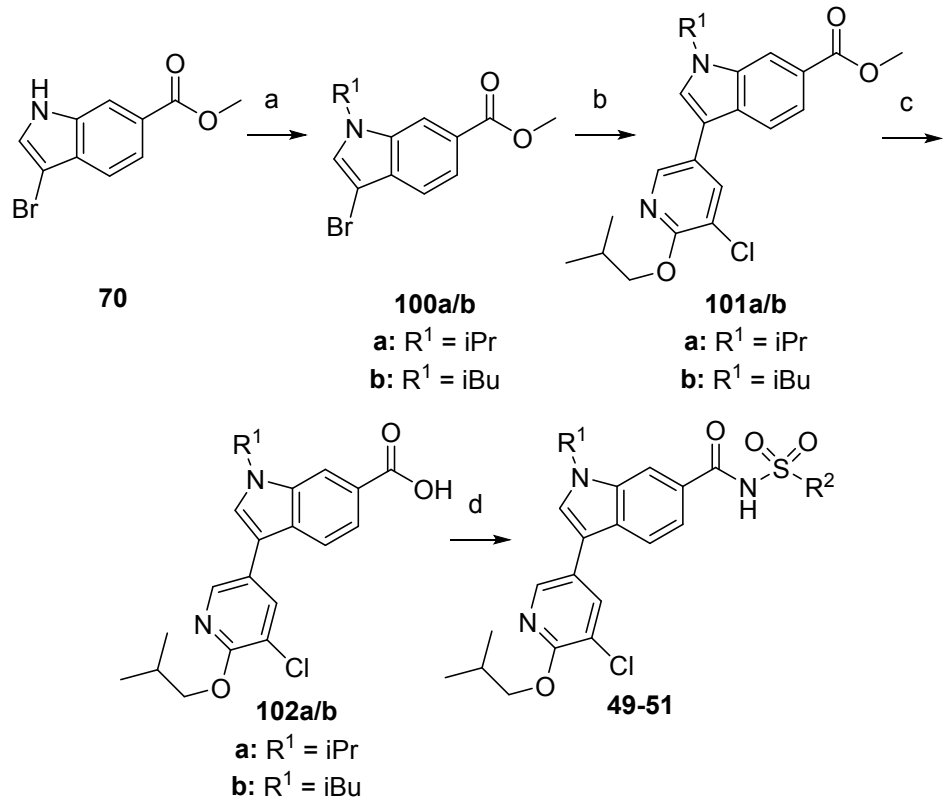


[a]Reagents and conditions: (a) R-pyridyl bromide, $PdCl_2$(dppf), Na_2CO_3, dioxane, 80 ºC, 12 h; (b) $Pd(PPh_3)_4$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dioxane, 80 ºC, 2 h, then MeOH, R-pyridyl bromide, Cs_2CO_3, 80 ºC, 4 h;

(c) LiOH, THF-MeOH, H_2O, rt, 18 h; (d) $R^1SO_2NH_2$, DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, CH_2Cl_2, rt, 1 h; (e) Cs_2CO_3, 2-methylpropanol, DMSO, 90 ºC, 10 h, 91%; (f) (1,1'-binaphthalen)-2-yl di-tert-butylphosphine, Zn, $Pd(O_2CCF_3)_2$, $Zn(CN)_2$, DMAC, 95 ºC, 3 h, 56%; (g) R^2CH_2OH, Cs_2CO_3, DMSO, 80 ºC, 18 h; (h) (1,5-Cyclooctadiene)(methoxy)iridium(i) dimer, bis(pinacolato)diboron, 4,4'-di-tert-butyl-2,2'-bipyridine, tBuOMe, 80 ºC, 30 min; (i) $PdCl_2$(dppf), Na_2CO_3, dioxane, 100 ºC, 2 h; (j) K_2CO_3, 2,2-dimethyloxirane, 2-butanone, 80 ºC, 18 h, 19%.

Scheme 5 describes the synthesis of the N-alkylated indole derivatives **49**-**51**. Alkylation of the 3-bromoindole **70** with either 2-iodoprapane or 1-iodo-2-methylpropane led to formation of intermediates **100a/b**, respectively. Suzuki coupling to install the pyridyl side chain followed by hydrolysis of the acid and coupling with a sulfonamide led to acylsulfonamides **49-51**.

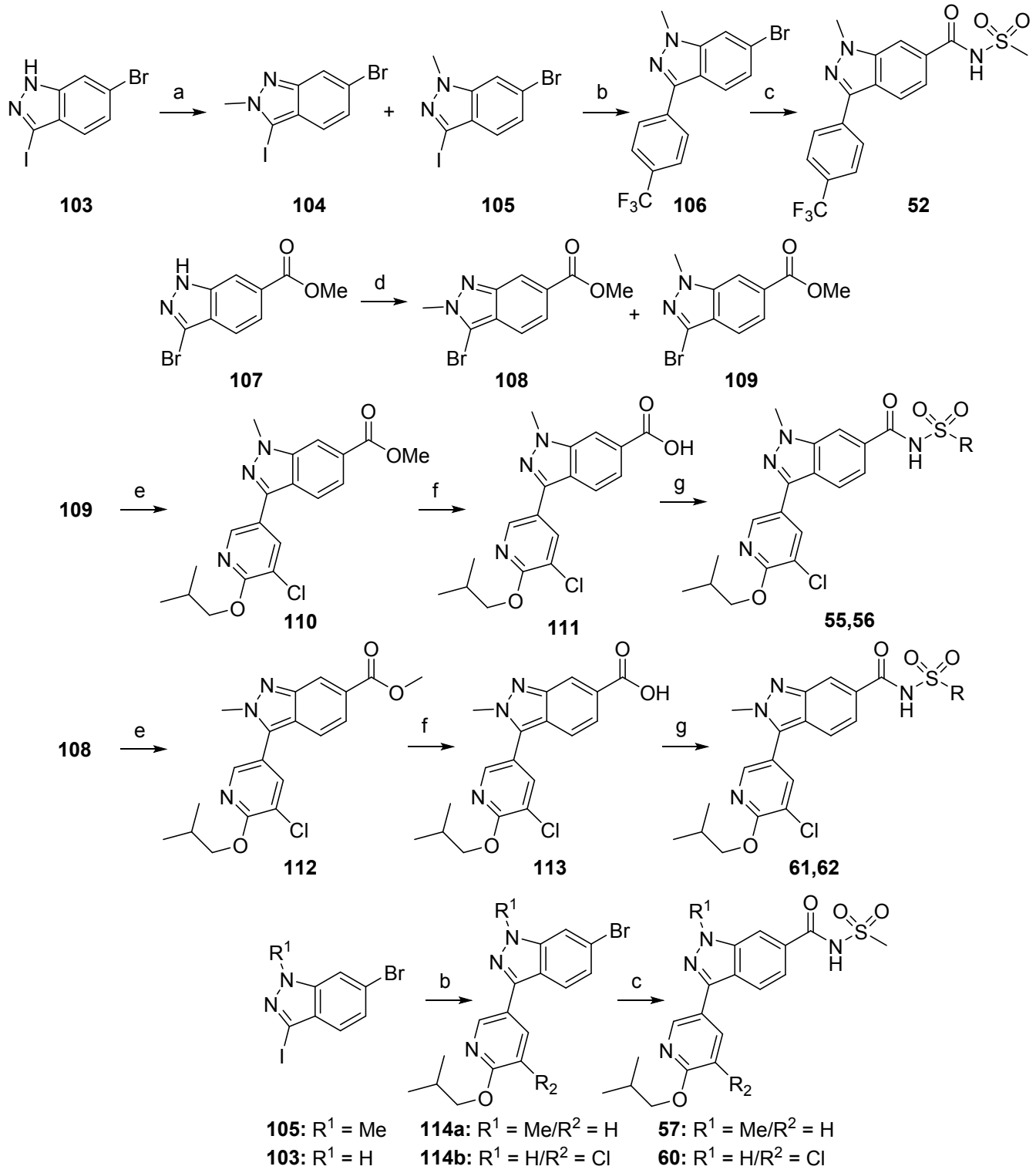
Scheme 5. Synthetic approaches to the N-alkylated indole derivatives **49**-**51**.



[a]Reagents and conditions: (a) R^1-I, K_2CO_3, DMF, rt, 18 h, 44-46%; (b) 5-bromo-3-chloro-2-isobutoxypyridine, $PdCl_2$(dppf), Na_2CO_3, dioxane, 80 ºC, 12 h; (c) LiOH, THF-MeOH, H_2O, rt, 18 h; (d) $R^2SO_2NH_2$, DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, CH_2Cl_2, rt, 1 h.

Scheme 6 describes the synthetic routes used to procure the indazole derivatives **52**, **55**-**57**, and **60**-**62**. Methylation of indazole **103**[46] led to two separable isomers **104** and **105**, with the major isomer **105** subjected to a selective Suzuki coupling at the iodo substituent to afford bromide **106** which, in turn, was transformed into **52** following literature conditions.[47] Methylation of the indazole **107** led to the formation of the two separable isomers **108** and **109**, whose structures were identified by NOE studies. Isomer **109** was converted to the N-1 methyl indazole analogs **55** and **56**, while isomer **108** was converted to the N-2 methyl indazole derivatives **61** and **62** following the established conditions. Derivatives **57** and **60** were prepared from the bromides **114a/b** which were obtained from iodides **105** and **103**, respectively, following the previously outlined conditions.

Scheme 6. Synthetic approaches to the preparation of indazole derivatives **52**, **55**-**57**, and **60**-**62**.

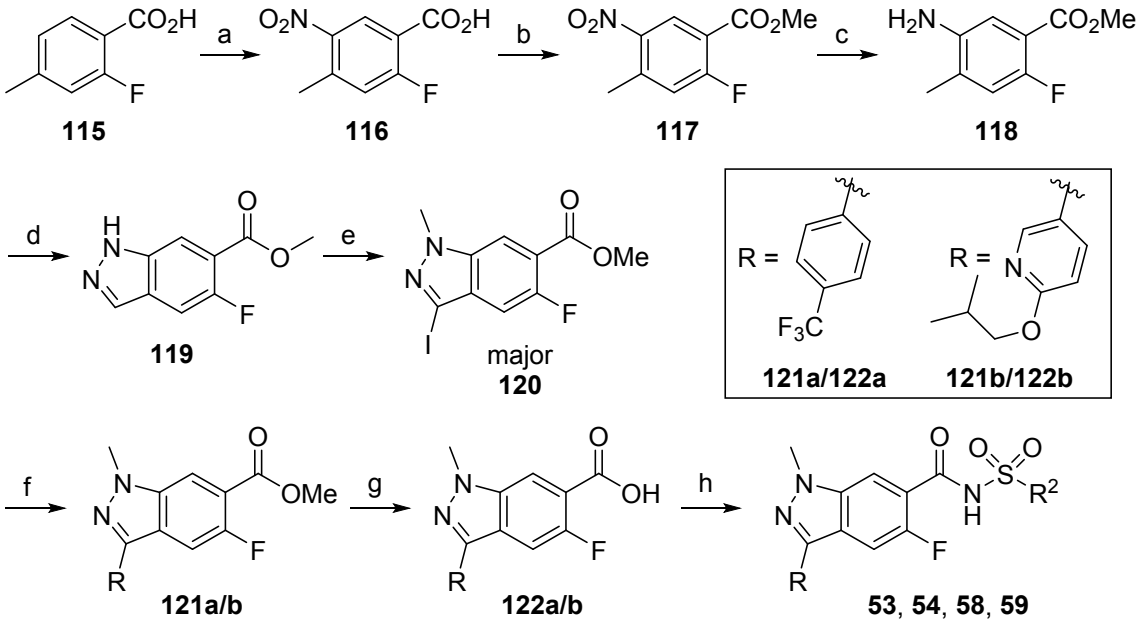


[a]Reagents and conditions: (a) K_2CO_3, DMF, MeI, rt, 72 h, **104** (14%), **105** (48%); (b) 4-trifluoromethylphenyl bromide, $PdCl_2$(dppf), Na_2CO_3, dioxane, 80 ºC, 1 h; (c) Methanesulfonamide, $Mo(CO)_6$, DBU, tri-tert-butylphosphonium tetrafluoroborate, trans-di-mu-acetatobis[2-[bis(2-methylphenyl)phosphino]benzyl]dipalladium, dioxane, 140 ºC, 10 min, 61%; (d) NaH, THF, MeI, rt, 18 h, **108** (18%),

109 (34%); (e) 5-bromo-3-chloro-2-isobutoxypyridine, $PdCl_2$(dppf), Na_2CO_3, dioxane, 100 ºC, 2 h; (f) LiOH, THF-MeOH, H_2O, rt, 18 h; (g) RSO_2N_2, DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, CH_2Cl_2, rt, 1 h.

Scheme 7 describes the synthesis route leading to 5-fluoroindazole derivatives **53**, **54**, **58**, and **59**. Nitration of **115** in concentrated H_2SO_4/HNO_3 afforded nitro derivative **116**. After ester formation and nitro reduction, the indazole intermediate **119** was formed from 2-methylaniline precursor **118**. Iodination and methylation of **119** in one pot led to intermediate **120** along with small amounts of the minor isomer. The isomers were separable and identified by NOE studies. Iodide **120** was transformed into the final products, **53**, **54**, **58**, and **59**, through the established routes and conditions.

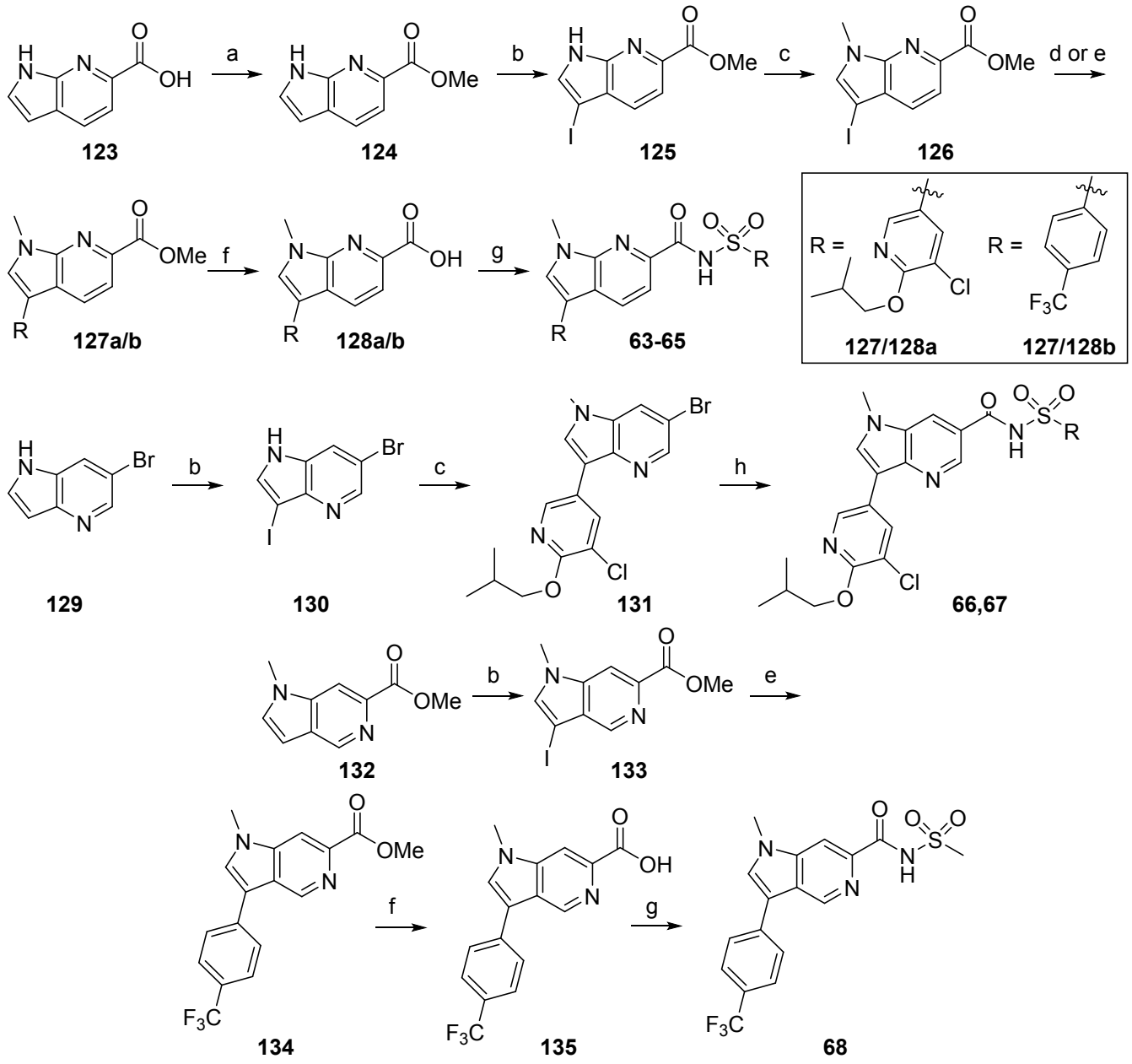
Scheme 7. Synthetic approaches to the 5-fluoroindazole derivatives **53**, **54**, **58**, and **59**.



[a]Reagents and conditions: (a) H_2SO_4, HNO_3, 0 ºC, 3 h; (b) H_2SO_4, MeOH, 65 ºC, 20 h, 92% for 2 steps; (c) Pd/C, H_2, EtOAc, rt, 2 h, 95%; (d) KOAc, AcOH, isoamyl nitrite, CHCl3, rt, 3 h, 13%; (e) I_2, KOH, DMF, rt, 18 h, then MeI, 20 h, 59%; (f) $PdCl_2$(dppf), Na_2CO_3, dioxane, 80 ºC, 18 h; (g) LiOH, THF-MeOH, H_2O, rt, 18 h; (h) Sulfonamides, DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, CH_2Cl_2, rt, 1 h.

Scheme 8 describes routes to access the azaindole derivatives **63**-**68**. The synthesis of the 7-azaindole derivatives **63-65** originated with **123**. Ester formation, iodination, and indole methylation led to intermediate **126** which was converted into analogs **63-65** following previously outlined conditions. The 4-azaindole derivatives **66** and **67** were prepared from bromide **131** which, in turn, was generated from **129** after iodination and methylation, following the established conditions. Finally the 5-azaindazole **68** originated from **132**, which was prepared using literature conditions.[48] Iodination of **132** provided iodide **133** which reacted with 4-trifluoromethylphenyl boronic acid to afford **134**. After hydrolysis of **134** to acid intermediate **135**, analog **68** was obtained after acylsulfonamide formation.

Scheme 8. Synthetic approaches to the azaindole derivatives **63**-**68**.



[a]Reagents and conditions: (a) H_2SO_4, MeOH, 70 ºC, 4 h; (b) I_2, KOH, DMF, rt, 18 h; (c) MeI, K_2CO_3, DMF, rt, 18 h; (d) **127a**: $Pd(PPh_3)_4$, Et_3N, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, dioxane, 80 ºC, 2 h, then MeOH, R-Ar-Br, Cs_2CO_3, 80 ºC, 4 h; (e) **127b**: AR-$B(OH)_2$, $PdCl_2(dppf)$, Na_2CO_3, dioxane, 80 ºC, 18 h; (f) LiOH, THF-MeOH, H_2O, rt, 18 h; (g) Sulfonamides, DMAP, 2-chloro-1-methylpyridin-1-ium iodide, Et_3N, CH_2Cl_2, rt, 1 h; (h) RSO_2NH_2, $Mo(CO)_6$, DBU, tri-tert-butylphosphonium tetrafluoroborate, trans-di-mu-acetatobis[2-[bis(2-methylphenyl)phosphino]benzyl]dipalladium, dioxane, 140 ºC, 10 min.

CONCLUSION

In summary, we have described the discovery and profiling of a series of 3-arylindole-derived acylsulfonamides that are potent and selective $hNa_V1.7$ inhibitors. Extensive structure-activity relationship studies were conducted in an effort to understand aspects of the core heterocycle as well as the side chains and led to the identification of several analogs that demonstrated potent channel inhibitory activity for both $hNa_V1.7$ and $mNa_V1.7$. Within this series, **29** was efficacious in several mouse models of neuropathic pain following doses of 30 mg/kg. It is noteworthy that the closely related analog **47**, which was also orally bioavailable, did not demonstrate any efficacy in two of these models. However, application of these two compounds directly to the mouse fascial sural nerve did suggest a modest difference between the efficacies of these two closely-related analogs. However, additional work would need to be carried out to more fully understand all of the parameters that drive the efficacy of these $Na_V1.7$ inhibitors in vivo.

EXPERIMENTAL PROCEDURES

Patch Clamp Electrophysiology. $Na_V1.7$ currents were recorded using whole-cell patch clamp of HEK293 cells stably expressing recombinant human or mouse $Na_V1.7$. Glass microelectrodes filled with internal solution containing (in mM) 50 CsCl, 90 CsF, 10 NaF, 2 $MgCl_2$, 10 EGTA, 10 HEPES, pH 7.2 with CsOH had resistances of 1-4 MΩ The external solution was (in mM): 150 NaCl, 4 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$, 10 HEPES, 10 glucose, pH 7.4 with NaOH. Series resistance was kept below 10 MΩ and electronically compensated at least 50%. Currents were acquired at 50 kHz via an EPC-10 amplifier with Patchmaster software (HEKA Instruments Inc., Bellmore, NY). Leakage subtraction was performed with the P/N method. Solution exchange was performed with a 16-well Dynaflow Resolve glass chip (Cellectricon, Sweden). The holding potential was -70 mV unless otherwise indicated. Following a 100 msec prepulse to -130 mV, $Na_V1.7$ current was elicited by a 10 msec step to +10 mV. Peak inward current was measured with PatchMaster software and percent inhibition calculated. IC_{50} values were obtained by fits of the Hill equation to the average percent inhibition data.

Automated Electrophysiology Methods: Ion Works Barracuda Population Patch Clamp (PPC). PPC measurements from HEK293 cells expressing $Na_V1.7$ and $Na_V1.5$ channels were performed using an IonWorks

Barracuda instrument (Molecular Devices Corporation, Union City, CA) using a proprietary PPC PatchPlate™ substrate (Molecular Devices Corporation) with 64 patch clamp apertures per well. The ability to average $Na_V1.x$ currents from 64 recordings from each well greatly improves data consistency and recording success rates in the measurement of $Na_V1.x$ mediated ionic currents. Calculated leak current was digitally subtracted from the total cell $Na_V1.x$ current for each sample data point acquired.

$Na_V1.7$ currents were elicited by a voltage clamp protocol designed to strongly bias the $Na_V1.7$ channels toward their inactivated state as follows. From a holding potential of -60 mV, cells were briefly hyperpolarized to -100 mV for 1.25 sec, then stepped to -20 mV for 20 sec to inactivate the channels. This was followed by a relatively brief hyperpolarization to -100 mv for 300 ms, then a 20 msec test pulse to -20 mV to elicit the $Na_V1.7$ current used to measure the pharmacology of all test compounds. Compounds were incubated for 600 sec between the pre- and post-compound reads. The external recording solution used was (in mM) 137 NaCl, 4 KCl, 1 $MgCl_2$, 1.8 $CaCl_2$, 10 Hepes, 10 glucose, pH to 7.4 with NaOH, and the internal solution used was (in mM) 100 K-gluconate, 40 KCl, 3.2 $MgCl_2$, 5 EGTA, 10 HEPES pH to 7.2 with KOH. The same solutions were used to record $Na_V1.5$ currents following a voltage clamp protocol in which $Na_V1.5$ currents were elicited by a voltage clamp protocol designed to bias the $Na_V1.5$ channels to their inactivated state as follows. From a holding potential of -40 mV cells, were briefly hyperpolarized to -100mV for 300 ms and then stepped to -10 mV for 20 seconds to inactivate the channels. This was followed by a relatively brief hyperpolarization to -100mv for 30 ms, then a 20 msec test pulse to -10mV to elicit the $Na_V1.5$ current used to measure the pharmacology of all test compounds.

HEK293 cells expressing $Na_V1.7$ and $Na_V1.5$ channels were used (Essen Biosciences, Ann Arbor, Michigan). Cells were cultured in T-175 flasks and passaged every 2 to 3 days at 1:3 to 1:6 seeding density dilutions. Cells were grown to 70% to 90% confluence in a flask and removed from the incubator (37 °C, 5% CO_2) 1 to 3 days after plating. Growth medium was aspirated from the culture flasks. Cells were gently rinsed with 10 mL of phosphate-buffered saline (PBS) to remove residual media. Next, a total of 2 mL TrypLE (Gibco) solution was added and the flasks containing cells sat for 3 minutes at rt after which the cells became visibly rounded and were easily dislodged from the bottom of the flask with a few brief taps on a solid surface. A total of 8 mL of media was added to the flask to inactivate the TrypLE and the mixture was centrifuged at 910 rpm for 4 minutes. The cell

supernatant was decanted and the cell pellets were resuspended in 5-6 mL of external solution followed by gentle trituration using a 10 mL pipette, and transferred to a 15 mL conical tube and immediately brought to the IW Barracuda instrument. The cell suspension had a final concentration of ~2 to 3 million cells per mL; this corresponds to 10,000 cells added per well.

Peak membrane currents were analyzed with IW Barracuda software and exported to MicroSoft Excel for further analysis. Concentration response curve fitting was performed with BMS in-house software. IC_{50} values were obtained by fits of the Hill equation to the average percent inhibition data plotted versus compound concentration. Concentration-response curves for all test compounds were fitted to a 4-parameter equation: % of control = 100 (1 + ([drug]/IC_{50})p)–1, where IC_{50} is the concentration of drug required to inhibit current by 50% and p is the Hill slope. Data for $Na_V1.7$ are presented as mean ± S.E.M.

Formalin Test: Studies were conducted in male CD1 mice. Persistent pain was induced with an injection of formalin in the dorsum of one hind paw as previously described.[24] Formalin-induced flinching was quantified with an automated system (Automated Nociception Analyzer, UCSD, La Jolla, CA, USA). A metal band was placed on the right hind paw and the mouse was then acclimated for 60 minutes in an individual Plexiglas test chamber. Each mouse was dosed with test compound (10 mL/kg, IP or PO) or vehicle 30 minutes before formalin injection. The right hind paw was injected with 20 µL of saline or 5% w/v formalin and the animal was immediately placed back into the chamber. Each time the band breaks the electromagnetic field located under the mouse a signal was generated and a nociceptive response and behavior was recorded for 45 minutes.

Sural Fascicle Recording Studies: In isoflurane-anesthetized mouse, the sural branch that runs from the lateral foot region was identified and exposed and a fine bared silver wire (0.005" diameter; A-M systems, Sequim, WA) was wrapped around the nerve. A reference wire electrode was placed in the nearby connective tissue. The other ends of the wires were fused to gold plated male pins and plugged into the head stage (10x amplification) of an ExoAmp KB AC-coupled extracellular amplifier (200x-20,000x amplification; Kation Scientific, Minneapolis, MN) for monopolar recording. A viscous mixture of petroleum jelly and paraffin oil was used to cover and stabilize the nerve. Baseline mechano-sensitivity was characterized by application of graded stimuli (brush and von Frey filaments) within the field of innervation. Sural nerve preparation was used to investigate the effect of $Na_V1.7$

inhibitors **29** and **47** or vehicle after IP dosing over a 2 hour period and terminal blood was collected for determination of drug exposure. For direct application on the nerve, the petroleum jelly-paraffin oil mixture was sucked out and the drug or vehicle were applied in a 50 µL volume of 1% DMSO in PBS and after 20 minutes of incubation time, the applied fluid was sucked back and replaced by the oil and mechanical testings were performed. This process was repeated for additional applications as needed.

Complete Freund's adjuvant (CFA) thermal hyperalgesia model: Studies were conducted in 7-8 week old male CD1 mice and thermal responses were assessed using the Hargreave's test. Mice were acclimated to the equipment (IITC Plantar) for at least 60 minutes each day for up to 3 days prior to testing. On the last day of acclimation, the baseline of thermal response latency was taken by applying a radiant heat stimulus to the plantar surface of each hind paw. Upon lifting of the paw, the light beam was shut off and the timer stopped. The average of 3 tests was recorded. Each mouse was then injected with either saline or 20 µL CFA (Sigma F5881) subcutaneously into the intra-plantar region of the right paw. 72 Hours later, mice were dosed with test compound or vehicle (10 mL/kg) and the average thermal response latency to 3 applications recorded 60 minutes after dosing.

Chronic constriction injury (CCI) cold allodynia model: Male CD1 mice (8-9 weeks of age) were anesthetized with isoflurane and three ligatures of 5–0 chromic gut loosely tied around the sciatic nerve 1 mm apart and proximal to the trifurcation using aseptic surgical techniques. All mice received 1 mL of a warmed lactated Ringer's solution, administered subcutaneously, for fluid replacement at the end of surgery. 5 Weeks following surgery, mice were dosed with compound or vehicle (10 mL/kg) and tested 60 minutes post-treatment on a 5 °C cold plate (IITC model # 400, Series 8). Upon lifting of the left hind paw, the timer was stopped and the mouse removed from the plate.

Chemistry. Proton magnetic resonance (^{1}H NMR) spectra were recorded on either a Bruker Avance 400 or a JEOL Eclipse 500 spectrometer and are reported in ppm relative to the reference solvent of the sample in which they were run. HPLC and LC−MS analyses were conducted using a Shimadzu SCL-10A liquid chromatograph and a SPD UV−vis detector at 220 nm with the MS detection performed with either a Micromass Platform LC

spectrometer or a Waters Micromass ZQ spectrometer. All flash column chromatography was performed on EM Science silica gel 60 (particle size of 40−60 μm). All reagents were purchased from commercial sources and used without further purification unless otherwise noted. All reactions were performed under an inert atmosphere. HPLC analyses were performed using the following conditions. All final compounds had an HPLC purity of ≥ 95% unless specifically mentioned.

HPLC Methods. Analytical HPLC analyses were carried out following methods A and B, and preparatory reverse-phase scale purifications were performed using methods C.

Method A. A linear gradient using 5% CH_3CN, 95% H_2O, and 0.05% CF_3CO_2H (solvent A) and 95% acetonitrile, 5% H_2O, and 0.05% CF_3CO_2H (solvent B) (t = 0 min, 10% B; t = 15 min, 100% B) was employed on a SunFire C18 3.5 μm 3.5 mm × 150 mm column. Flow rate was 0.5 mL/min, and UV detection was set to 220 nm. The LC column was maintained at ambient temperature.

Method B. A linear gradient using 5% CH_3CN, 95% H_2O, and 0.05% CF_3CO_2H (solvent A) and 95% CH_3CN, 5% H_2O, and 0.05% CF_3CO_2H (solvent B) (t = 0 min, 10% B; t = 15 min, 100% B (20 min)) was employed on a XBridge Ph 3.5 μm 3.0 mm × 150 mm column. Flow rate was 0.5 mL/min, and UV detection was set to 220 nm. The LC column was maintained at ambient temperature.

Method C. Column: XBridge C18, 19 x 200 mm, 5-μm particles; Mobile Phase A: 5:95 CH_3CN: H_2O with 10-mM NH_4OAc; Mobile Phase B: 95:5 CH_3CN:$H_2O$with 10-mM NH_4OAc; Gradient: 10-50% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation.

General Chemistry Details. All commercially-available reagents and solvents were used without further purification unless otherwise stated. All reactions were carried out under an inert atmosphere of dry N_2 gas in oven- or flame-dried glassware unless otherwise stated. Flash column chromatography was performed using 40-60 μm Silica Gel 60 (EMD Chemicals, Inc.) as the stationary phase, or pre-packed columns from ISCO Inco., Biotage, or Thomson Instrument Co. ^{1}H-NMR spectra were recorded on a Bruker 400 or 500 MHz machine with tetramethylsilane or residual protiated solvent used as a reference. ^{13}C-NMR were recorded on a Bruker DRX-500

instrument operating at 125 MHz with residual ^{12}C solvent used as a reference. Low resolution mass spectra were recorded using a Waters Micromass ZQ with electrospray ionization. High resolution mass spectra were recorded using a Waters Micromass LCT time of flight mass spectrometer with electrospray ionization. The purity of all compounds was determined by either Liquid chromatography–mass spectrometry (LCMS) or analytical HPLC and was confirmed to be greater than 95% purity.

1-Methyl-N-(methylsulfonyl)-3-phenyl-1H-indole-6-carboxamide (5). A mixture of Na_2CO_3 (0.19 mL, 0.37 mmol), $PdCl_2$(dppf) (3.4 mg, 4.7 μmol), $PhB(OH)_2$ (0.011 g, 0.093 mmol) and 3-bromo-1-methyl-N-(methylsulfonyl)-1*H*-indole-6-carboxamide (**73**) (0.031 g, 0.093 mmol) in dioxane (0.5 mL) was heated at 100 °C for 2 h. The desired product was purified by prep-HPLC (Method C) to afford the desired product (5.6 mg, 17%): MS (ESI) *(m/z)*: 329.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.26 (s, 1H), 7.96 - 7.92 (m, 2H), 7.74 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.27 (t, J = 7.5 Hz, 1H), 3.93 (s, 3H), 3.34 (s, 3H).

2-Chloro-N-(4-methoxypyridin-3-yl)isonicotinamide (6): Prepared using the procedures described for **5**. (4.9 mg, 13%). MS (ESI) *(m/z)*: 343.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.26 (s, 1H), 7.91 (d, J = 1.0 Hz, 1H), 7.89 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 3.92 (s, 3H), 3.35 (br. s., 3H), 2.35 (s, 3H).

1-Methyl-N-(methylsulfonyl)-3-(m-tolyl)-1H-indole-6-carboxamide (**7**): Prepared using the procedures described for **5**. (6.0 mg, 17%). MS (ESI) *(m/z)*: 343.0 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.25 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.91 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 3.92 (s, 3H), 3.31 - 3.30 (m, 3H), 2.39 (s, 3H).

3-(4-Ethylphenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (8): Prepared using the procedures described for **5** (3.8 mg, 11%). MS (ESI) *(m/z)*: 357.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.28 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 3.93 (s, 3H), 3.39 (s, 3H), 2.69 - 2.62 (m, 2H), 1.23 (t, J = 7.5 Hz, 3H).

3-(3-Ethylphenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (9): Prepared using the procedures described for **5** (4.5 mg, 13%). MS (ESI) *(m/z)*: 357.0 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.29 (s, 1H), 7.98 -

7.94 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.15 - 7.10 (m, 1H), 3.93 (s, 3H), 3.41 (s, 3H), 2.69 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H).

1-Methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (10): Prepared using the procedures described for **5** (7.0 mg, 18%). MS (ESI) *(m/z)*: 397.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.31 (s, 1H), 8.14 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 3H), 3.95 (s, 3H), 2.55 (s, 3H).

1-Methyl-N-(methylsulfonyl)-3-(3-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (11): Prepared using the procedures described for **5** (8.4 mg, 16%). MS (ESI) *(m/z)*: 397.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.15 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.98 - 7.93 (m, 2H), 7.79 (dd, J = 8.4, 1.1 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.61 (d, *J*=8.1 Hz, 1H), 3.95 (s, 3H) (3H of methyl sulfonamide was buried in solvent peak); ^{19}F NMR (471 MHz, DMSO-d_6) δ -61.09 (s, 3F).

3-(2,3-Difluorophenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (12): Prepared using the procedures described for **5** (4.7 mg, 15%). MS (ESI) *(m/z)*: 365.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.29 (s, 1H), 7.96 (s, 1H), 7.78 - 7.76 (m, 2H), 7.56 - 7.51 (m, 1H), 7.37 - 7.29 (m, 2H), 3.96 (s, 3H), 3.35 - 3.34 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -138.59 (s, 1F), -141.82 (s, 1F).

3-(2-Chloro-4-(trifluoromethyl)phenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (13): Prepared using the procedures described for **5** (8.4 mg, 16%). MS (ESI) *(m/z)*: 431.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.33 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.81 (s, 2H), 7.76 - 7.72 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.40 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.97 (s, 3F).

3-(4-Isobutylphenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (14): Prepared using the procedures described for **5** (7.7 mg, 20%). MS (ESI) *(m/z)*: 385.1.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.73 (dd, J = 8.1, 0.7 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.7 Hz, 2H), 3.93 (s, 3H), 2.48 (d, J = 6.2 Hz, 2H), 1.92 - 1.83 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). (3H of methyl sulfonamide was buried in solvent peak).

1-Methyl-N-(methylsulfonyl)-3-(4-(trifluoromethoxy)phenyl)-1H-indole-6-carboxamide (15): Prepared from **73** using the procedures described for **5** (2.2 mg, 5.5%). MS (ESI) *(m/z)*: 365.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-

d6) δ 8.27 (s, 1H), 7.99 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 3.93 (s, 3H), 3.33 - 3.32 (m, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -56.76 (s, 3F).

3-(4-Isobutoxyphenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (16): 2-Chloro-1-methylpyridin-1-ium iodide (0.021 g, 0.081 mmol), methanesulfonamide (0.019 g, 0.201 mmol) and TEA (0.028 mL, 0.201 mmol) was added to the CH_2Cl_2 (0.2 mL) suspension of 3-(4-isobutoxyphenyl)-1-methyl-1H-indole-6-carboxylic acid (**78a**, 0.022 g, 0.067 mmol) and DMAP (0.4 mg, 3.4 µmol) at rt. The reaction was stirred at rt for 1.5 h. The solvent was removed via vacuum and the crude was purified by prep-HPLC (Method C) (7.6 mg, 28%). MS (ESI) *(m/z)*: 401.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 11.98 (br. s., 1H), 8.26 (s, 1H), 7.89 (d, J=8.5 Hz, 1H), 7.84 (s, 1H), 7.74 - 7.71 (m, 1H), 7.58 (d, J=8.5 Hz, 2H), 7.03 (d, J=8.5 Hz, 2H), 3.91 (s, 3H), 3.79 (d, J=6.7 Hz, 2H), 3.36 (s, 3H), 2.05 (dt, J=13.5, 6.8 Hz, 1H), 1.01 (d, J=6.7 Hz, 6H).

3-(2,3-Difluorophenyl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (17): Prepared from **78b** using the procedures described for **16** (6.1 mg, 39%). MS (ESI) *(m/z)*: 379.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.30 (s, 1H), 8.08 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.77 (dd, J = 8.7, 1.4 Hz, 1H), 7.65 (d, J = 7.9 Hz, 2H), 7.06 (t, J = 56.0 Hz, 1H), 3.95 (s, 3H), 3.40 (br. s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -108.62 (s, 2F).

N-(Cyclopropylsulfonyl)-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (18): Prepared from **78c** using the procedures described for **16** (6.9 mg, 44%). MS (ESI) *(m/z)*: 423.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 12.00 (br. s., 1H), 8.31 (s, 1H), 8.16 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.81 - 7.75 (m, 3H), 3.96 (s, 3H), 3.22 - 3.15 (m, 1H), 1.21 - 1.10 (m, 4H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.63 (s, 3F).

N-(Cyclopropylsulfonyl)-3-(4-(difluoromethyl)phenyl)-1-methyl-1H-indole-6-carboxamide (19): Prepared from **78b** using the procedures described for **16** (10.5 mg, 75%). MS (ESI) *(m/z)*: 405.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 11.99 (br. s., 1H), 8.29 (s, 1H), 8.08 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.77 (dd, J = 8.5, 1.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.06 (t, J = 56.0 Hz, 1H), 3.95 (s, 3H), 3.22 - 3.14 (m, 1H), 1.20 - 1.09 (m, 4H); ^{19}F NMR (471MHz, DMSO-d6) δ -108.64 (s, 2F).

1-Methyl-3-(4-(trifluoromethyl)phenyl)-N-((trifluoromethyl)sulfonyl)-1H-indole-6-carboxamide (20): Prepared from **78c** using the procedures described for **16** (9.1 mg, 61%). MS (ESI) *(m/z)*: 449.0 $(M-H)^+$; ^{1}H NMR

(500MHz, DMSO-d6) δ 8.11 (s, 1H), 8.01 (s, 1H), 7.94 - 7.89 (m, 3H), 7.83 (dd, J = 8.4, 1.5 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 3.92 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.57 (s, 3F), -76.66 (s, 3F).

N-(N,N-Dimethylsulfamoyl)-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (21): Prepared from **78c** using the procedures described for **16** (9.8 mg, 74%). MS (ESI) *(m/z)*: 426.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.04 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.75 (br d, *J* = 8.2 Hz, 3H), 3.94 (s, 3H), 2.92 (s, 6H); ^{19}F NMR (471 MHz, DMSO-d_6) δ -61.25 (s, 3F).

1-Methyl-N-(thiophen-2-ylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (22): Prepared from **78c** using the procedures described for **16** (9.5 mg, 59%). MS (ESI) *(m/z)*: 465.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.98 - 7.89 (m, 3H), 7.85 - 7.69 (m, 4H), 7.23 - 6.96 (m, 3H), 3.93 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.60 (s, 3F).

N-((3,4-Difluorophenyl)sulfonyl)-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (23): Prepared from **78c** using the procedures described for **16** (7.7 mg, 49%). MS (ESI) *(m/z)*: 495.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.27 (s, 1H), 8.15 (s, 1H), 8.10 - 8.04 (m, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.96 - 7.88 (m, 3H), 7.80 - 7.68 (m, 4H), 3.95 (s, 3H).

5-Fluoro-1-methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (24): Prepared from **88a** using the procedures described for **16** (8.0 mg, 55%). MS (ESI) *(m/z)*: 415.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.14 (s, 1H), 7.92 (dd, J = 15.1, 7.2 Hz, 3H), 7.80 - 7.72 (m, 3H), 3.93 (s, 3H), 3.26 (s, 3H); ^{19}F NMR (471 MHz, DMSO-d6) δ -60.64 , -123.71.

N-(Cyclopropylsulfonyl)-5-fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxamide (25): Prepared from **88a** using the procedures described for **16** (6.3 mg, 44%). MS (ESI) *(m/z)*: 441.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.17 (s, 1H), 7.93 (dd, J = 17.8, 7.0 Hz, 3H), 7.81 - 7.75 (m, 3H), 3.94 (s, 3H), 3.12 (ddd, J = 12.9, 7.8, 4.8 Hz, 1H), 1.23 - 1.07 (m, 4H); ^{19}F NMR (471 MHz, DMSO-d6) δ -60.66 , -123.65.

3-(4-(Difluoromethyl)phenyl)-5-fluoro-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (26): Prepared from **88b** using the procedures described for **16** (4.4 mg, 32%). MS (ESI) *(m/z)*: 397.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.12 (s, 1H), 7.96 (d, J = 5.9 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 12.0 Hz, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 56.1 Hz, 1H), 3.94 (s, 3H), 3.38 (s, 3H); ^{19}F NMR (471 MHz, DMSO-d6) δ -108.71 , -124.14.

N-(Cyclopropylsulfonyl)-3-(4-(difluoromethyl)phenyl)-5-fluoro-1-methyl-1H-indole-6-carboxamide (27): Prepared from **88b** using the procedures described for **16** (6.1 mg, 47%). MS (ESI) *(m/z)*: 423.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.12 (s, 1H), 7.94 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 12.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 56.1 Hz, 1H), 3.94 (s, 3H), 3.14 (tt, J = 7.9, 4.9 Hz, 1H), 1.23 - 1.10 (m, 4H); ^{19}F NMR (471 MHz, DMSO-d6) δ -108.70 , -123.94.

1-Methyl-N-(methylsulfonyl)-3-(pyridin-3-yl)-1H-indole-6-carboxamide (28): Prepared from **90a** using the procedures described for **16** (8.4 mg, 38%). MS (ESI) *(m/z)*: 330.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.92 (s, 1H), 8.47 (d, J = 4.6 Hz, 1H), 8.26 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 8.01 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.47 (dd, J = 7.8, 4.7 Hz, 1H), 3.95 (s, 3H), 3.28 (s, 3H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (29): Prepared from **90b** using the procedures described for **16** (300 mg, 63%). MS (ESI) *(m/z)*: 434.2 $(M-H)^+$; ^{1}H NMR (400MHz, DMSO-d6) δ 12.00 (br. s., 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 1.3 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 8.4, 1.6 Hz, 1H), 4.17 (d, J = 6.5 Hz, 2H), 3.92 (s, 3H), 3.40 (s, 3H), 2.09 (dt, J = 13.4, 6.7 Hz, 1H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101MHz, DMSO-d6) δ 166.8, 156.8, 142.2, 136.7, 136.3, 132.0, 128.4, 125.5, 124.7, 120.2, 119.1, 117.4, 111.9, 110.6, 72.6, 41.6, 33.1, 27.6, 19.1.

3-(6-Isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (30): Prepared from **90c** using the procedures described for **16** (12.3 mg, 54%). MS (ESI) *(m/z)*: 402.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 12.01 (br. s., 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.28 (s, 1H), 7.99 (dd, J = 8.5, 2.7 Hz, 1H), 7.93 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 8.5, 1.5 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 4.09 (d, J = 6.4 Hz, 2H), 3.93 (s, 3H), 3.37 (s, 3H), 2.07 (dt, J = 13.4, 6.7 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-(cyclopropylmethoxy)pyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (31): Prepared from **90d** using the procedures described for **16** (20.7 mg, 75%). MS (ESI) *(m/z)*: 434.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.43 (d, J = 1.8 Hz, 1H), 8.28 (s, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 4.28 (d, J = 7.0 Hz, 2H), 3.94 (s, 3H), 3.37 (s, 3H), 1.37 - 1.27 (m, 1H), 0.63 - 0.57 (m, 2H), 0.43 - 0.38 (m, 2H).

3-(5-Cyano-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (32): The mixture of [1,1'-binaphthalen]-2-yldi-tert-butylphosphine (2.0 mg, 5.1 µmol), zinc (0.66 mg, 10 µmol), palladium(II) trifluoroacetate (0.84 mg, 2.5 µmol), 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (**29**, 0.022 g, 0.051 mmol) and zinc cyanide (3.6 mg, 0.030 mmol) in dimethylacetamide (0.5 mL) underwent vacuum/N_2 fill cycle three times. The reaction was heated at 95 °C for 3 h. The reaction mixture was diluted with DMF, filtered and purified by prep-HPLC (Method C) (12.7 mg, 56%). MS (ESI) *(m/z)*: 427.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 11.87 (br. s., 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 2.4 Hz, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 8.5, 1.5 Hz, 1H), 4.27 (d, J = 6.4 Hz, 2H), 3.95 (s, 3H), 3.39 (s, 3H), 2.13 (dt, J = 13.3, 6.8 Hz, 1H), 1.04 (d, J = 6.7 Hz, 6H).

3-(6-Isobutoxy-5-methoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (33): Prepared from **90e** using the procedures described for **16** (9.1 mg, 56%). MS (ESI) *(m/z)*: 432.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.23 (s, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.89 - 7.86 (m, 2H), 7.77 (d, J = 9.5 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 4.12 (d, J = 6.7 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.25 (s, 3H), 2.10 (dt, J = 13.4, 6.6 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-(2,2-difluoroethoxy)pyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (34): The mixture of sodium carbonate (0.14 mL, 0.275 mmol), $PdCl_2$(dppf) (5.0 mg, 6.9 µmol), 3-chloro-2-(2,2-difluoroethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**95a**, 0.044 g, 0.137 mmol) and 3-bromo-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (0.045 g, 0.137 mmol) in dioxane (1 mL) was heated at 80 °C for 4 h. The reaction mixture was diluted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated. The product was purified by prep-HPLC (Method C) (6.0 mg, 9.8%). MS (ESI) *(m/z)*: 444.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.47 (d, J = 2.1 Hz, 1H), 8.26 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.00 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 8.5, 1.2 Hz, 1H), 6.44 (tt, J = 54.6, 3.5 Hz, 1H), 4.72 (td, J = 14.9, 3.5 Hz, 2H), 3.93 (s, 3H), 3.32 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -125.62 (s, 2F).

3-(5-Chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (35): Prepared from **95b** using the procedures described for **34** (19.9 mg, 23%). MS (ESI) *(m/z)*: 462.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.49 (d, J = 1.8 Hz, 1H), 8.26 - 8.22 (m, 2H), 8.01 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.79

(d, J = 7.9 Hz, 1H), 5.12 (q, J = 8.9 Hz, 2H), 3.93 (s, 3H), 3.27 (br. s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -72.35 (s, 3F).

3-(5-Chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (36): Prepared from **90f** using the procedures described for **16** (20.6 mg, 56%). MS (ESI) *(m/z)*: 452.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.18 (s, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.83 - 7.77 (m, 2H), 7.77 - 7.73 (m, 1H), 4.88 (s, 1H), 4.11 (s, 2H), 3.88 (s, 3H), 3.17 (s, 3H), 1.16 (s, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-1-methyl-1H-indole-6-carboxamide (37): Prepared from **90b** using the procedures described for **16** (17.0 mg, 87%). MS (ESI) *(m/z)*: 462.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.44 (d, J = 2.1 Hz, 1H), 8.24 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.99 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.76 (dd, J = 8.5, 1.5 Hz, 1H), 4.18 (d, J = 6.4 Hz, 2H), 3.92 (s, 3H), 3.18 - 3.11 (m, 1H), 2.10 (dt, J = 13.4, 6.6 Hz, 1H), 1.10 (br. s., 2H), 1.02 (m, 8H).

3-(5-Chloro-6-(cyclopropylmethoxy)pyridin-3-yl)-N-(cyclopropylsulfonyl)-1-methyl-1H-indole-6-carboxamide (38): Prepared from **90d** using the procedures described for **16** (13.4 mg, 60%). MS (ESI) *(m/z)*: 460.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.43 (d, J = 2.1 Hz, 1H), 8.27 (s, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 4.28 (d, J = 7.0 Hz, 2H), 3.94 (s, 3H), 1.38 - 1.28 (m, 1H), 1.23 - 1.18 (m, 2H), 1.15 - 1.09 (m, 2H), 0.63 - 0.58 (m, 2H), 0.40 (q, J = 4.8 Hz, 2H) (1H was buried under the water signal).

N-(Cyclopropylsulfonyl)-3-(6-isobutoxy-5-methoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxamide (39): Prepared from **90e** using the procedures described for **16** (9.1 mg, 64%). MS (ESI) *(m/z)*: 458.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.25 (s, 1H), 8.00 (d, J = 1.2 Hz, 1H), 7.92 (t, J = 4.3 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 4.12 (d, J = 6.4 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.42 - 3.34 (m, 1H), 2.09 (dt, J = 13.4, 6.6 Hz, 1H), 1.22 - 1.17 (m, 2H), 1.15 - 1.10 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(ethylsulfonyl)-1-methyl-1H-indole-6-carboxamide (40): Prepared from **90b** using the procedures described for **16** (7.6 mg, 46%). MS (ESI) *(m/z)*: 450.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.44 (d, J = 1.8 Hz, 1H), 8.29 (s, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.98 (s, 1H), 7.90 (d, J = 8.9 Hz, 1H), 7.78 - 7.75 (m, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.94 (s, 3H), 3.51 (q, J = 7.4 Hz, 2H), 2.12 (dt, J = 13.4, 6.7 Hz, 1H), 1.30 (t, J = 7.3 Hz, 3H), 1.03 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(isopropylsulfonyl)-1-methyl-1H-indole-6-carboxamide (41): Prepared from **90b** using the procedures described for **16** (13.7 mg, 85%). MS (ESI) *(m/z)*: 464.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.43 (d, J = 2.1 Hz, 1H), 8.28 (s, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.99 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.78 - 7.74 (m, 1H), 4.21 (d, J = 6.7 Hz, 2H), 3.94 (s, 3H), 3.89 (dt, J = 13.7, 6.8 Hz, 1H), 2.12 (dt, J = 13.4, 6.6 Hz, 1H), 1.36 (d, J = 6.7 Hz, 6H), 1.03 (d, J = 6.7 Hz, 6H).

N-(tert-Butylsulfonyl)-3-(5-chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxamide (42): Prepared from **90b** using the procedures described for **16** (11.9 mg, 70%). MS (ESI) *(m/z)*: 478.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.44 (d, J = 1.8 Hz, 1H), 8.23 (s, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.97 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.94 (s, 3H), 2.12 (dt, J = 13.2, 6.7 Hz, 1H), 1.46 (s, 9H), 1.04 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(N,N-dimethylsulfamoyl)-1-methyl-1H-indole-6-carboxamide (43): Prepared from **90b** using the procedures described for **16** (14.0 mg, 78%). MS (ESI) *(m/z)*: 465.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 11.72 (s, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.30 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 8.5, 1.2 Hz, 1H), 4.18 (d, J = 6.4 Hz, 2H), 3.93 (s, 3H), 2.93 (s, 6H), 2.10 (dt, J = 13.4, 6.6 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(piperidin-1-ylsulfonyl)-1H-indole-6-carboxamide (44): Prepared from **90b** using the procedures described for **16** (13.5 mg, 65%). MS (ESI) *(m/z)*: 505.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.44 (d, *J* = 2.1 Hz, 1H), 8.29 (s, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.73 (dd, *J* = 8.4, 1.4 Hz, 1H), 4.18 (d, *J* = 6.7 Hz, 2H), 3.93 (s, 3H), 2.14 - 2.06 (m, 1H), 1.62 - 1.55 (m, 4H), 1.54 - 1.48 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 6H) (4H of sulfonamide piperidine was buried in the solvent peak).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-5-fluoro-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (45): Prepared from **99a** using the procedures described for **16** (10.7 mg, 74%). MS (ESI) *(m/z)*: 454.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.40 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.97 (s, 1H), 7.88 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 11.8 Hz, 1H), 4.17 (d, J = 6.6 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.10 (dt, J = 13.5, 6.8 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H); ^{19}F NMR (471 MHz, DMSO-d6) δ -123.94.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-5-fluoro-1-methyl-1H-indole-6-carboxamide (46): Prepared from **99a** using the procedures described for **16** (8.8 mg, 59%). MS (ESI) *(m/z)*: 480.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.41 (d, J = 2.2 Hz, 1H), 8.14 (d, J = 2.2 Hz, 1H), 8.05 (s, 1H), 7.92 (d, J = 5.9 Hz, 1H), 7.72 (d, J = 11.9 Hz, 1H), 4.17 (d, J = 6.6 Hz, 2H), 3.91 (s, 3H), 3.19 - 3.09 (m, 1H), 2.11 (dq, J = 13.4, 6.7 Hz, 1H), 1.21 - 1.12 (m, 4H), 1.01 (d, J = 6.7 Hz, 6H); ^{19}F NMR (471 MHz, DMSO-d6) δ -124.04.

5-Fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (47): Prepared from **99b** using the procedures described for **16** (7.9 mg, 49%). MS (ESI) *(m/z)*: 420.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.42 (d, J = 2.7 Hz, 1H), 7.98 (dd, J = 8.5, 2.5 Hz, 1H), 7.96 (s, 1H), 7.92 (d, J = 5.9 Hz, 1H), 7.64 (d, J = 11.9 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.07 (d, J = 6.6 Hz, 2H), 3.91 (s, 3H), 3.38 (s, 3H), 2.06 (dp, J = 13.5, 6.8 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); ^{19}F NMR (471 MHz, DMSO-d6) δ -124.53.

N-(Cyclopropylsulfonyl)-5-fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxamide (48): Prepared from **99b** using the procedures described for **16** (7.9 mg, 57%). MS (ESI) *(m/z)*: 446.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.43 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 8.5, 2.5 Hz, 1H), 7.95 (s, 1H), 7.91 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 11.9 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 4.08 (d, J = 6.7 Hz, 2H), 3.91 (s, 3H), 3.12 (ddd, J = 12.8, 8.1, 4.8 Hz, 1H), 2.07 (dp, J = 13.4, 6.8 Hz, 1H), 1.20 - 1.07 (m, 4H), 1.00 (d, J = 6.7 Hz, 6H); ^{19}F NMR (471 MHz, DMSO-d6) δ -124.27.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-isopropyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (49): Prepared from **102a** using the procedures described for **16** (9.7 mg, 45%). MS (ESI) *(m/z)*: 464.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.47 (d, J = 2.1 Hz, 1H), 8.34 (s, 1H), 8.20 - 8.17 (m, 2H), 7.91 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 4.91 (dt, J = 13.4, 6.7 Hz, 1H), 4.21 (d, J = 6.4 Hz, 2H), 3.37 (s, 3H), 2.12 (dt, J = 13.4, 6.6 Hz, 1H), 1.58 (d, J = 6.7 Hz, 6H), 1.03 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-isobutyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (50): Prepared from **102b** using the procedures described for **16** (12.0 mg, 96%). MS (ESI) *(m/z)*: 478.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.46 (d, J = 2.1 Hz, 1H), 8.28 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.08 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.75 (dd, J = 8.7, 1.4 Hz, 1H), 4.18 (d, J = 6.7 Hz, 2H), 4.10 (d, J = 7.3 Hz, 2H), 3.37 (s, 3H), 2.32 - 2.24 (m, 1H), 2.11 (dt, J = 13.2, 6.7 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H), 0.92 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-1-isobutyl-1H-indole-6-carboxamide (51): Prepared from **102b** using the procedures described for **16** (15.0 mg, 90%). MS (ESI) *(m/z)*: 504.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.46 (d, J = 2.1 Hz, 1H), 8.26 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.08 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.77 - 7.73 (m, 1H), 4.18 (d, J = 6.7 Hz, 2H), 4.11 (d, J = 7.3 Hz, 2H), 3.22 - 3.15 (m, 1H), 2.33 - 2.24 (m, 1H), 2.11 (dt, J = 13.4, 6.7 Hz, 1H), 1.19 - 1.14 (m, 2H), 1.14 - 1.07 (m, J = 6.4 Hz, 2H), 1.02 (d, J = 6.7 Hz, 6H), 0.92 (d, J = 6.7 Hz, 6H).

1-Methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-indazole-6-carboxamide (52): The mixture of 6-bromo-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole (**106**, 0.011 g, 0.032 mmol), molybdenum hexacarbonyl (14 mg, 0.053 mmol), DBU (0.014 mL, 0.095 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.9 mg, 3.2 µmol), methanesulfonamide (15 mg, 0.158 mmol), trans-di-mu-acetatobis[2-[bis(2-methylphenyl)phosphino]benzyl]dipalladium (1.5 mg, 1.6 µmol) in dioxane (0.3 mL) in a sealed tube was heated at 140 °C for 10 min. The reaction mixture was filtered and purified by prep-HPLC (Method A) (8.0 mg, 61%). MS (ESI) *(m/z)*: 398.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.38 (s, 1H), 8.24 (d, J = 8.2 Hz, 2H), 8.17 (d, J = 8.9 Hz, 1H), 7.90 - 7.85 (m, 3H), 4.21 (s, 3H), 3.22 (br. s., 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -61.03 (s, 3F).

5-Fluoro-1-methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-indazole-6-carboxamide (53): Prepared from **123a** using the procedures described for **16** (8.3 mg, 51%). MS (ESI) *(m/z)*: 414.1 $(M-H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.23 (d, J = 7.6 Hz, 2H), 8.19 - 8.14 (m, 1H), 8.05 (d, J = 14.3 Hz, 1H), 7.86 (d, J = 7.0 Hz, 2H), 4.22 (s, 3H), 3.40 (s, 3H); ^{19}F NMR (471 MHz, DMSO-d6) δ -61.08, -123.50.

N-(Cyclopropylsulfonyl)-5-fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole-6-carboxamide (54): Prepared from **123a** using the procedures described for **16** (8.8 mg, 59%). MS (ESI) *(m/z)*: 442.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.23 (d, J = 8.2 Hz, 2H), 8.16 (d, J = 5.6 Hz, 1H), 8.06 (d, J = 10.8 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 4.23 (s, 3H), 3.13 (dt, J = 8.2, 4.6 Hz, 1H), 1.27 - 1.14 (m, 4H); ^{19}F NMR (471 MHz, DMSO-d6) δ -61.09, -123.44.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indazole-6-carboxamide (55): Prepared from **111a** using the procedures described for **16** (6.9 mg, 15%). MS (ESI) *(m/z)*: 437.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.72 (d, J = 2.1 Hz, 1H), 8.41 (s, 1H), 8.35 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.80 -

7.76 (m, 1H), 4.25 (d, J = 6.7 Hz, 2H), 4.20 (s, 3H), 3.38 (s, 3H), 2.14 (dt, J = 13.2, 6.7 Hz, 1H), 1.04 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-1-methyl-1H-indazole-6-carboxamide (56): Prepared from **111a** using the procedures described for **16** (18.9 mg, 82%). MS (ESI) *(m/z)*: 463.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.72 (d, J = 2.1 Hz, 1H), 8.38 - 8.34 (m, 2H), 8.14 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 4.25 (d, J = 6.4 Hz, 2H), 4.19 (s, 3H), 3.13 - 3.09 (m, 1H), 2.14 (dt, J = 13.4, 6.7 Hz, 1H), 1.17 - 1.11 (m, 2H), 1.07 - 1.01 (m, J = 6.7 Hz, 8H).

3-(6-Isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indazole-6-carboxamide (57): Prepared from **114a** using the procedures described for **52** (21.0 mg, 70%). MS (ESI) *(m/z)*: 403.1 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.75 (d, J = 2.1 Hz, 1H), 8.31 (s, 1H), 8.26 (dd, J = 8.5, 2.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 4.18 - 4.13 (m, 5H), 3.17 (s, 3H), 2.10 (dt, J = 13.1, 6.6 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H).

5-Fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-indazole-6-carboxamide (58): Prepared from **123b** using the procedures described for **16** (12.5 mg, 79%). MS (ESI) *(m/z)*: 421.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.72 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 8.5, 2.5 Hz, 1H), 7.99 (d, J = 5.7 Hz, 1H), 7.83 (d, J = 10.8 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.15 (s, 3H), 4.14 (s, 2H), 3.16 (s, 3H), 2.10 (dt, J = 13.3, 6.6 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H); ^{19}F NMR (471 MHz, DMSO-d6) δ -123.57.

N-(Cyclopropylsulfonyl)-5-fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole-6-carboxamide (59): Prepared from **123b** using the procedures described for **16** (3.6 mg, 27%). MS (ESI) *(m/z)*: 447.0 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.72 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 8.6, 2.5 Hz, 1H), 7.98 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 10.7 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.14 (d, J = 6.4 Hz, 5H), 3.02 (ddd, J = 13.1, 8.4, 4.9 Hz, 1H), 2.10 (dt, J = 13.5, 6.7 Hz, 1H), 1.10 - 1.04 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H), 0.96 (dd, J = 8.1, 2.9 Hz, 2H); ^{19}F NMR (471 MHz, DMSO-d6) δ -123.36.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(methylsulfonyl)-1H-indazole-6-carboxamide (60): Prepared from **114b** using the procedures described for **52** (28.4 mg, 51%). MS (ESI) *(m/z)*: 423.0 $(M+H)^+$; ^{1}H NMR (500MHz,

DMSO-d6) δ 8.74 (d, J = 1.8 Hz, 1H), 8.38 (d, J = 1.8 Hz, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 4.25 (d, J = 6.7 Hz, 2H), 3.12 (br. s., 3H), 2.14 (dt, J = 13.5, 6.5 Hz, 1H), 1.04 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-2-methyl-N-(methylsulfonyl)-2H-indazole-6-carboxamide (61): Prepared from **113** using the procedures described for **16** (4.2 mg, 46%). MS (ESI) *(m/z)*: 437.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.40 (d, J = 2.1 Hz, 1H), 8.34 (s, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.67 - 7.59 (m, 2H), 4.27 (d, J = 6.4 Hz, 2H), 4.19 (s, 3H), 3.21 (s, 3H), 2.15 (dt, J = 13.6, 6.6 Hz, 1H), 1.05 (d, J = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-2-methyl-2H-indazole-6-carboxamide (62): Prepared from **113** using the procedures described for **16** (8.6 mg, 55%). MS (ESI) *(m/z)*: 463.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.41 (d, J = 1.8 Hz, 1H), 8.35 (s, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.65 - 7.62 (m, 2H), 4.28 (d, J = 6.7 Hz, 2H), 4.20 (s, 3H), 3.12 (dt, J = 8.4, 4.0 Hz, 1H), 2.16 (dt, J = 13.3, 6.5 Hz, 1H), 1.16 - 1.12 (m, 2H), 1.07 - 1.02 (m, 8H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamide (63): Prepared from **128a** using the procedures described for **16** (5.6 mg, 16%). MS (ESI) *(m/z)*: 437.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 9.41 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.68 - 7.64 (m, 1H), 7.60 - 7.57 (m, 1H), 7.14 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 9.2 Hz, 1H), 2.28 (s, 3H).

1-Methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamide (64): Prepared from **128b** using the procedures described for **16** (4.8 mg, 27%). MS (ESI) *(m/z)*: 398.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.56 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H), 8.00 - 7.95 (m, 3H), 7.80 (d, J = 8.2 Hz, 2H), 4.07 (s, 3H), 3.40 (s, 3H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.79 (s, 3F).

N-(Cyclopropylsulfonyl)-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxamide (65): Prepared from **128b** using the procedures described for **16** (4.4 mg, 30%). MS (ESI) *(m/z)*: 424.0 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.57 (d, J = 8.2 Hz, 1H), 8.39 (s, 1H), 7.98 (d, J = 7.9 Hz, 3H), 7.80 (d, J = 8.2 Hz, 2H), 4.07 (s, 3H), 3.16 - 3.14 (m, 1H), 1.25 (d, J = 3.7 Hz, 2H), 1.14 (d, J = 5.2 Hz, 2H); ^{19}F NMR (471MHz, DMSO-d6) δ -60.80 (s, 3F).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-N-(methylsulfonyl)-1H-pyrrolo[3,2-b]pyridine-6-carboxamide (66): Prepared from **131** using the procedures described for **52** (3.7 mg, 16%). MS (ESI) *(m/z)*: 436.9 $(M+H)^+$; ^{1}H

NMR (500MHz, DMSO-d6) d 9.03 (d, *J* = 1.5 Hz, 1H), 8.92 (d, *J* = 1.8 Hz, 1H), 8.69 (d, *J* = 2.1 Hz, 1H), 8.52 (d, *J* = 1.5 Hz, 1H), 8.36 (s, 1H), 4.20 (d, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 2.16 - 2.05 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-N-(cyclopropylsulfonyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-6-carboxamide (67): Prepared from **131** using the procedures described for **52** (5.6 mg, 15%). MS (ESI) *(m/z)*: 462.9 $(M+H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 9.02 (d, J = 1.5 Hz, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.55 (s, 1H), 8.40 (s, 1H), 4.20 (d, J = 6.4 Hz, 2H), 3.95 (s, 3H), 3.15 - 3.09 (m, 1H), 2.11 (dt, J = 13.4, 6.6 Hz, 1H), 1.13 (br. s., 2H), 1.06 - 1.04 (m, 2H), 1.03 (d, J = 6.7 Hz, 6H).

1-Methyl-N-(methylsulfonyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxamide (68): Prepared from **135** using the procedures described for **16** (0.9 mg, 14%). MS (ESI) *(m/z)*: 398.0 $(M+H)^+$.

Methyl 3-bromo-1-methyl-1H-indole-6-carboxylate (70). To the DMF solution (60 mL) of methyl 1H-indole-6-carboxylate (**69**, 5.1 g, 29.1 mmol) was added dropwise a solution of NBS (5.70 g, 32.0 mmol) in 40 mL DMF at -60 °C. The reaction was stirred for 2 h while it was warmed up to rt. The reaction mixture was poured into iced water (1 L) and the precipitate was collected through filtration. The solid was dissolved in EtOAc and washed twice with brine. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated to give the crude product (6.86 g, 93%): MS (ESI) *(m/z)*: 254.1 $(M+H)^+$.

Methyl 3-bromo-1-methyl-1H-indole-6-carboxylate (71). Potassium carbonate (1.68 g, 12.16 mmol) was added to the DMF (10 mL) solution of methyl 3-bromo-1H-indole-6-carboxylate (**70**, 1.03 g, 4.05 mmol) at rt. The mixture was stirred at rt for 30 min. The reaction was cooled to 0 °C and methyl iodide (0.30 mL, 4.86 mmol) was added to the reaction mixture. The reaction was stirred overnight while it was warmed up to rt. The reaction was diluted with water and extracted three times with diethyl ether. The diethyl ether layer was combined, dried (Na_2SO_4), filtered and concentrated. The product was purified via flash column eluted with EtOAc in hexane from 0 to 25% as a white solid (0.98 g, 90%). MS (ESI) *(m/z)*: 267.0 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.12 - 8.09 (m, 1H), 7.88 (dd, J = 8.4, 1.4 Hz, 1H), 7.59 (dd, J = 8.4, 0.6 Hz, 1H), 7.24 (s, 1H), 3.97 (s, 3H), 3.87 (s, 3H).

3-Bromo-1-methyl-1H-indole-6-carboxylic acid (72). The mixture of LiOH (0.172 g, 7.20 mmol) and methyl 3-bromo-1-methyl-1H-indole-6-carboxylate (**71**, 0.965 g, 3.60 mmol) in THF (4 mL), water (0.8 mL) and MeOH (1

mL) at room temperature for 36 hours. The volatile was removed via vacuum and the crude was added 1N HCl (6 mL). The slurry was filtered and the solid was collected, washed with water. The solid was taken up in EtOAc and dried with anhydrous Na_2SO_4. The EtOAc layer was filtered and concentrated to give the crude product (0.84 g, 92%) as a white solid. MS (ESI) *(m/z)*: 254.1 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.93 (dd, J = 8.3, 1.3 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.28 (s, 1H), 3.89 (s, 3H).

3-Bromo-1-methyl-N-(methylsulfonyl)-1H-indole-6-carboxamide (73). 2-chloro-1-methylpyridin-1-ium iodide (1.01 g, 3.95 mmol), methanesulfonamide (0.94 g, 9.88 mmol) and TEA (1.4 mL, 9.88 mmol) was added to the CH_2Cl_2 (10 mL) solution of 3-bromo-1-methyl-1H-indole-6-carboxylic acid (**72**, 0.837 g, 3.29 mmol) and DMAP (0.020 g, 0.165 mmol) at rt. The reaction was stirred at rt for 1.5. The solvent was removed via vacuum and the crude was added 1H HCl (3 mL) and water (20 mL). The aqueous layer was extracted three times with EtOAc. The EtOAc layer was combined, dried (Na_2SO_4), filtered and concentrated. The crude was added methanol and a white suspension formed. The solid was filtered, discarded and the filtrate was concentrated to afford the desired product (1.02 g, 93%). MS (ESI) *(m/z)*: 329.0 $(M-H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.81 (s, 1H), 7.75 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H) (3H of methyl sulfonamide was buried in solvent peak).

Methyl 3-iodo-1H-indole-6-carboxylate (74). The mixture of KOH (1.79 g, 31.9 mmol) and methyl 1H-indole-6-carboxylate (2.31 g, 13.17 mmol) in DMF (30 mL) was stirred at rt for 1 h. Iodine (3.34 g, 13.17 mmol) in DMF (7 mL) was added to the reaction mixture at rt. The reaction was continue to stir for 18 h. The reaction was poured into 400 mL ice water and the solid was filtered, washed with water. The solid was dissolved in EtOAc and dried with Na_2SO_4. The EtOAc layer was filtered and concentrated to give the crude product (3.61 g, 91%) as a brown solid. MS (ESI) *(m/z)*: 301.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.67 - 8.53 (s, 1H), 8.15 (d, *J* = 0.8 Hz, 1H), 7.90 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 1H), 3.96 (s, 3H).

Methyl 3-iodo-1-methyl-1H-indole-6-carboxylate (75). Potassium carbonate (2.085 g, 15.09 mmol) was added to the DMF (10 mL) solution of methyl 3-iodo-1H-indole-6-carboxylate (**74**, 1.514 g, 5.03 mmol) at rt. The mixture was stirred at rt for 30 min. Methyl iodide (0.38 mL, 6.03 mmol) was added to the reaction mixture and the reaction was stirred for 2 h at rt. The reaction mixture was diluted with water and extracted three times with diethyl ether. The diethyl ether layer was combined, washed with brine, dried (Na_2SO_4), filtered and concentrated

to the desired product (1.410 g, 89%): MS (ESI) *(m/z)*: 300.0 $(M-H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.06 (d, *J* = 0.8 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H).

Methyl 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (76). Tetrakis(triphenylphosphine)palladium (0) (0.076 g, 0.065 mmol) and methyl 3-iodo-1-methyl-1H-indole-6-carboxylate (**75**, 0.688 g, 2.18 mmol) in dioxane (7.5 ml) in a pressure vial underwent vacuum/N_2 fill for three times. TEA (3.04 ml, 21.83 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.475 ml, 3.27 mmol) was added to the reaction mixture slowly (bubbling generation observed) and the reaction was heated at 80 °C for 2 h. The reaction was cooled to room temperature. Methanol (0.5 mL) was added to the reaction mixture (violent gas evolution observed). The volatile was removed via vacuum and the crude was purified by flash column eluted with EtOAc in hexane from 0 to 25% to give the desired product (0.555 g, 81%) as a white solid. ^1H NMR (400MHz, $CDCl_3$) δ 8.10 (d, J = 0.8 Hz, 1H), 8.03 (dd, J = 8.3, 0.5 Hz, 1H), 7.87 (dd, J = 8.5, 1.5 Hz, 1H), 7.66 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 1.38 (s, 12H).

Methyl 3-(4-isobutoxyphenyl)-1-methyl-1H-indole-6-carboxylate (77a). The mixture of sodium carbonate (2.0 M, 0.104 mL, 0.208 mmol), $PdCl_2$(dppf) (6.3 mg, 8.7 μmol), 1-bromo-4-isobutoxybenzene (0.083 g, 0.362 mmol) and methyl 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (**76**, 0.055 g, 0.173 mmol) in dioxane (1 mL) was heated at 80 °C for 12 h. The reaction was diluted with EtOAc and washed with water three times. The EtOAc layer was separated, dried (Na_2SO_4), filtered and concentrated to the crude product (25.8 mg, 31%): MS (ESI) *(m/z)*: 338.2 $(M+H)^+$.

Methyl 3-(4-(difluoromethyl)phenyl)-1-methyl-1H-indole-6-carboxylate (77b). Tetrakis(triphenylphosphine)palladium (0) (0.013 g, 10.97 μmol) and methyl 3-iodo-1-methyl-1H-indole-6-carboxylate (**75**, 0.115 g, 0.366 mmol) in dioxane (2.5 ml) in a pressure vial underwent vacuum/N_2 fill for three times. TEA (0.510 ml, 3.66 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.080 ml, 0.548 mmol) was added to the reaction mixture slowly (bubbling observed). The reaction was heated at 80 °C for 2 h. The reaction was cooled to rt. Methanol (1.5 mL) was added to the reaction mixture (violate gas evolution observed). 1-Bromo-4-(difluoromethyl)benzene (0.123 g, 0.595 mmol) and cesium carbonate (0.298 g, 0.914 mmol) was added to the

reaction mixture. The reaction was heated at 80 °C for 4 h. The reaction mixture was filtered and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash column eluted with EtOAc in hexane from 0 to 25% to 40% to give the desired product (72.8 mg, 63%). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.95 - 7.87 (m, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.40 (s, 1H), 6.71 (t, J = 56.0 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H); ^{19}F NMR (376MHz, $CDCl_3$) δ -109.86 (s, 2F).

Methyl 1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxylate (77c). Prepared from **75** using the procedures described for **77b** (67.0 mg, 60%): MS (ESI) *(m/z)*: 334.0 $(M-H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.95 - 7.88 (m, 2H), 7.78 - 7.68 (m, 4H), 7.46 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H); ^{19}F NMR (376MHz, $CDCl_3$) δ -62.31 (s, 3F).

3-(4-Isobutoxyphenyl)-1-methyl-1H-indole-6-carboxylic acid (78a). The mixture of LiOH (9.2 mg, 0.384 mmol) and methyl 3-(4-isobutoxyphenyl)-1-methyl-1H-indole-6-carboxylate (**77a**, 0.026 g, 0.076 mmol) in THF (0.5 mL), water (0.2 mL) and MeOH (0.2 mL) was stirred at rt for 40 h. The volatile was removed via vacuum. The crude was added 1N HCl (0.5 mL), and extracted with EtOAc twice. The EtOAc layer was combined, dried with Na_2SO_4, filtered and concentrated to give the crude product as a brown solid (21.7 mg, 88%). MS (ESI) *(m/z)*: 324.1 $(M+H)^+$.

3-(4-(Difluoromethyl)phenyl)-1-methyl-1H-indole-6-carboxylic acid (78b). Prepared from **77b** using the procedures described for **78a** (62.0 mg, 90%): MS (ESI) *(m/z)*: 300.1 $(M-H)^+$.

1-Methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxylic acid (78c). Prepared from **77c** using the procedures described for **78a** (64.2 mg, 100%): MS (ESI) *(m/z)*: 318.1 $(M-H)^+$; ^{1}H NMR (500MHz, DMSO-d6) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.81 - 7.77 (m, 3H), 3.94 (s, 3H).

1-Bromo-4-isobutoxybenzene (80). DIAD (1.911 mL, 9.83 mmol) was added dropwise to the THF (30 mL) solution of triphenylphosphine (2.58 g, 9.83 mmol), 4-bromophenol (**79**, 1.546 g, 8.93 mmol) and 2-methylpropan-1-ol (0.795 g, 10.72 mmol) at 0 °C. The reaction was stirred for 2 h and the volatile was removed via vacuum. The crude was purified by flash column eluted with EtOAc in hexane from 0 to 25%. The product was eluted out at solvent front as a clear oil (810 mg, 40%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40 - 7.34 (m, 2H), 6.81 - 6.76 (m, 2H), 3.69 (d, J = 6.5 Hz, 2H), 2.14 - 2.02 (m, 1H), 1.03 (d, J = 6.8 Hz, 6H).

(E)-Methyl 4-(2-(dimethylamino)vinyl)-2-fluoro-5-nitrobenzoate (83). In a 250 mL round-bottomed flask was methyl 2-fluoro-4-methyl-5-nitrobenzoate (**81**, 2.57 g, 12.06 mmol) in DMF (10 mL) to give a colorless solution. 1,1-dimethoxy-N,N-dimethylmethanamine (**82**, 1.94 mL, 14.47 mmol) was added. The mixture was stirred under nitrogen at 100°C for 1 h. After heating for another hour, the mixture was diluted with water. The solids were filtered and dried to obtain the desired product (2.77 g, 86%) as a red solid. MS (ESI) *(m/z)*: 269.0 $(M+H)^+$.

Methyl 5-fluoro-1H-indole-6-carboxylate (84). In a 500 mL round-bottomed flask was (E)-methyl 4-(2-(dimethylamino)vinyl)-2-fluoro-5-nitrobenzoate (**83**, 2.77 g, 10.33 mmol) in EtOAc (100 mL) to give a red solution. Pd/C (0.110 g, 0.103 mmol) was added. After vacuum and refill, the mixture was stirred under hydrogen (balloon) for 2 h (with deep red color fainted). After vacuum and refilled with nitrogen, the mixture was filtered and rinsed with EtOAc. The combined organic solution was concentrated. The residue was purified by FCC up to 50% EtOAc/hexane to afford the desired product (1.40 g, 70%) as a yellow solid. MS (ESI) *(m/z)*: 192.1 $(M-H)^+$.

Methyl 5-fluoro-3-iodo-1-methyl-1H-indole-6-carboxylate (85). The mixture of KOH (0.651 g, 11.60 mmol) and methyl 5-fluoro-1H-indole-6-carboxylate (**84**, 0.896 g, 4.64 mmol) in DMF (10 mL) was stirred at rt for 30 min. Iodine (1.177 g, 4.64 mmol) in DMF (5 mL) was added to the reaction mixture at rt. The reaction was continue to stir overnight for 16 h. LCMS showed the desired intermediate as the major peak: MS (ESI) *(m/z)*: 318.0 $(M-H)^+$. MeI (0.348 mL, 5.57 mmol) was added. The mixture was stirred at rt for 5 h. Excess water was added and the solids were filtered and further rinsed with water. The solids were further dried overnight to afford the desired product (1.32 g, 85%) as a yellow solid. MS (ESI) *(m/z)*: 334.0 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 5.7 Hz, 1H), 7.32 (s, 1H), 7.18 (d, J = 11.3 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.09.

Methyl 5-fluoro-1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (86). Prepared from **85** using the procedures described for **76**. The crude material was divided and used as is.

Methyl 5-fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxylate (87a). In a 5 mL vial was 1-bromo-4-(trifluoromethyl)benzene (68.5 mg, 0.305 mmol) and cesium carbonate (248 mg, 0.761 mmol) under nitrogen. Methyl 5-fluoro-1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-6-carboxylate (**86**, 101 mg, 0.305 mmol) in dioxane (2 mL) was added. The vial was sealed and heated at 80 °C for 5 h. Volatiles were

stripped off and the residue was directly loaded onto a 24 g flash column. FCC purification up to 50% EtOAc/hexane afforded the desired product (72.9 mg, 68% for two steps) as a white solid. MS (ESI) *(m/z)*: 351.9 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 5.8 Hz, 1H), 7.71 (s, 4H), 7.61 (d, J = 12.0 Hz, 1H), 7.49 (s, 1H), 4.01 (s, 3H), 3.93 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.35, -121.02.

Methyl 3-(4-(difluoromethyl)phenyl)-5-fluoro-1-methyl-1H-indole-6-carboxylate (87b). Prepared from **86** using the procedures described for **87a** as a white solid (70.0 mg, 69% for two steps): MS (ESI) *(m/z)*: 334.0 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 6.0 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.65 - 7.58 (m, 3H), 7.47 (s, 1H), 6.71 (t, J = 56.6 Hz, 1H), 4.00 (s, 3H), 3.92 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.06 , -121.29.

5-Fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indole-6-carboxylic acid (88a). Prepared from **87a** using the procedures described for **78a** as a light tan solid (70.0 mg, 100%): MS (ESI) *(m/z)*: 337.2 $(M-H)^+$.

3-(4-(Difluoromethyl)phenyl)-5-fluoro-1-methyl-1H-indole-6-carboxylic acid (88b). Prepared from **87b** using the procedures described for **78a** as a light tan solid (67.1 mg, 100%): MS (ESI) *(m/z)*: 320.2 $(M+H)^+$.

Methyl 1-methyl-3-(pyridin-3-yl)-1H-indole-6-carboxylate (89a). Prepared from **76** using the procedures described for **77a** as a light tan solid (33.4 mg, 22%): MS (ESI) *(m/z)*: 267.2 $(M+H)^+$.

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (89b). Prepared from **75** using the procedures described for **77b** as a light tan solid (356.2 mg, 51%): MS (ESI) *(m/z)*: 373.0 $(M+H)^+$.

Methyl 3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (89c). Prepared from **76** using the procedures described for **77a** as a light tan solid (22.8 mg, 40%): MS (ESI) *(m/z)*: 339.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.42 (dd, J = 2.5, 0.5 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.90 - 7.80 (m, 3H), 7.33 (s, 1H), 6.85 (dd, J = 8.5, 0.8 Hz, 1H), 4.13 (d, J = 6.8 Hz, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 2.14 (dt, J = 13.5, 6.7 Hz, 1H), 1.06 (d, J = 6.8 Hz, 6H).

Methyl 3-(5-chloro-6-(cyclopropylmethoxy)pyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (89d). Prepared from **75** using the procedures described for **77b** as a light tan solid (159.0 mg, 36%): MS (ESI) *(m/z)*: 371.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.29 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.90 - 7.79 (m, 3H), 7.33 (s, 1H), 4.29 (d, J = 7.0 Hz, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 1.45 - 1.34 (m, 1H), 0.69 - 0.62 (m, 2H), 0.46 - 0.40 (m, 2H).

Methyl 3-(6-isobutoxy-5-methoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (89e). Prepared from **75** using the procedures described for **77b** as a light tan solid (24.6 mg, 38%): MS (ESI) *(m/z)*: 369.2 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.90 - 7.83 (m, 2H), 7.35 (s, 1H), 7.30 (d, J = 2.0 Hz, 1H), 4.22 (d, J = 7.0 Hz, 2H), 3.98 (s, 3H), 3.94 (d, J = 6.5 Hz, 6H), 2.24 (dt, J = 13.6, 6.8 Hz, 1H), 1.07 (d, J = 6.5 Hz, 6H).

Methyl 3-(5-chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (89f). Prepared from **75** and **97** using the procedures described for **77b** (64.8 mg, 34%): MS (ESI) *(m/z)*: 389.0 $(M+H)^+$.

1-Methyl-3-(pyridin-3-yl)-1H-indole-6-carboxylic acid (90a). Prepared from **89a** using the procedures described for **78a** as a light tan solid (16.8 mg, 34%): MS (ESI) *(m/z)*: 253.2 $(M+H)^+$.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (90b). Prepared from **89b** using the procedures described for **78a** as an off-white solid (582 mg, 89%): MS (ESI) *(m/z)*: 359.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.44 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 1.8 Hz, 2H), 7.99 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.75 (dd, J = 8.4, 1.4 Hz, 1H), 4.18 (d, J = 6.7 Hz, 2H), 3.92 (s, 3H), 2.10 (dt, J = 13.4, 6.6 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H).

3-(6-Isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (90c). Prepared from **89c** using the procedures described for **78a** as an off-white solid (18.5 mg, 85%): MS (ESI) *(m/z)*: 323.3 $(M-H)^+$.

3-(5-Chloro-6-(cyclopropylmethoxy)pyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (90d). Prepared from **89d** using the procedures described for **78a** as an off-white solid (151.4 mg, 99%): MS (ESI) *(m/z)*: 357.1 $(M+H)^+$.

3-(6-Isobutoxy-5-methoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (90e). Prepared from **89e** using the procedures described for **78a** (25.0 mg, 61%): MS (ESI) *(m/z)*: 355.3 $(M+H)^+$.

3-(5-Chloro-6-(2-hydroxy-2-methylpropoxy)pyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (90f). Prepared from **89f** using the procedures described for **78a** (55.4 mg, 89%): MS (ESI) *(m/z)*: 375.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d6) δ 8.12 (s, 1H), 8.05 (s, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 4.85 (s, 1H), 4.11 (s, 2H), 3.90 (s, 3H), 1.17 (s, 6H).

5-Bromo-3-chloro-2-isobutoxypyridine (92). The mixture of cesium carbonate (5.31 g, 16.29 mmol), 5-bromo-3-chloro-2-fluoropyridine (**91**, 2.857 g, 13.6 mmol) and 2-methylpropan-1-ol (2.012 g, 27.1 mmol) in DMSO (10 mL) was stirred at 90 °C for 10 h. The reaction was diluted with water and extract with diethyl ether three times. The diethyl ether layer was combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by FCC to afford the desired product (3.26 g, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 4.14 (d, *J* = 6.8 Hz, 2H), 2.15 (dquin, *J* = 13.4, 6.7 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 6H).

1-((5-Bromo-3-chloropyridin-2-yl)oxy)-2-methylpropan-2-ol (94). The mixture of potassium carbonate (0.340 g, 2.461 mmol), 5-bromo-3-chloropyridin-2-ol (**93**, 0.513 g, 2.461 mmol) and 2,2-dimethyloxirane (0.202 g, 2.80 mmol) in 2-butanone (5 mL) was heated at 80 °C for 5 h. The reaction was continued at this temperature for 16 h. The reaction was diluted with EtOAc and washed with water three times. The EtOAc layer was separated, filtered and concentrated. Flash column eluted with EtOAc in hexane from 0 to 50% and gave the desired product (130.0 mg, 19%). MS (ESI) *(m/z)*: 280.1 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.64 (d, J = 2.5 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 4.06 (s, 2H), 2.78 (br. s., 1H), 1.29 (s, 6H).

3-Chloro-2-(2,2-difluoroethoxy)pyridine (96a). The mixture of cesium carbonate (1.918 g, 5.89 mmol), 3-chloro-2-fluoropyridine (**95**, 0.774 g, 5.89 mmol) and 2,2-difluoroethanol (0.966 g, 11.77 mmol) in DMSO (3 mL) was stirred at 80 °C for 18 h. The reaction was diluted with EtOAc and washed three times with water. The EtOAc layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column eluted with ethyl acetate in hexane from 0 to 10% to afford the desired product (0.79 g, 69%). MS (ESI) *(m/z)*: 194.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.05 (dd, J = 4.9, 1.6 Hz, 1H), 7.68 (dd, J = 7.7, 1.6 Hz, 1H), 6.93 (dd, J = 7.7, 4.9 Hz, 1H), 6.35 - 6.03 (m, 1H), 4.62 (td, J = 13.3, 4.3 Hz, 2H); ^{19}F NMR (376MHz, $CDCl_3$) δ -125.54 (s, 2F).

3-Chloro-2-(2,2,2-trifluoroethoxy)pyridine (96b). Prepared from **95** using the procedures described for **96a** (214.5 mg, 12%): ^{1}H NMR (400MHz, $CDCl_3$) δ 8.05 (dd, J = 4.9, 1.6 Hz, 1H), 7.71 (dd, J = 7.7, 1.6 Hz, 1H), 6.96 (dd, J = 7.7, 4.9 Hz, 1H), 4.84 (q, J = 8.5 Hz, 2H); ^{19}F NMR (376MHz, $CDCl_3$) δ -73.78 (s, 3F).

3-Chloro-2-(2,2-difluoroethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (97a). The mixture of (1,5-cyclooctadiene)(methoxy)iridium(i) dimer (0.081 g, 0.122 mmol), bis(pinacolato)diboron (1.239 g, 4.88

mmol), 3-chloro-2-(2,2-difluoroethoxy)pyridine (**96a**, 0.787 g, 4.06 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.033 g, 0.122 mmol) in *tert*-butylmethyl ether (12 mL) underwent vacuum/N_2 fill cycle four times. The reaction was heated at 80 °C for 0.5 h. The solvent was removed via vacuum and the crude was purified by flash column eluted with EtOAc in hexane from 0 to 30% to afford the desired product (0.41 g, 32%). MS (ESI) *(m/z)*: 320.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.38 (d, J = 1.5 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 6.35 - 6.01 (m, 1H), 4.64 (td, J = 13.2, 4.1 Hz, 2H), 1.36 - 1.33 (m, 12H); ^{19}F NMR (376MHz, $CDCl_3$) δ -125.53 (s, 2F).

3-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethoxy)pyridine (97b). Prepared from **96b** using the procedures described for **97a** (133.0 mg, 39%): ^{1}H NMR (400MHz, $CDCl_3$) δ 8.38 (d, J = 1.8 Hz, 1H), 8.05 (d, J = 1.5 Hz, 1H), 4.86 (q, J = 8.4 Hz, 2H), 1.35 (s, 12H); ^{19}F NMR (376MHz, $CDCl_3$) δ -73.74 (s, 3F).

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-5-fluoro-1-methyl-1H-indole-6-carboxylate (98a). Prepared from **86** using the procedures described for **87a** as light tan solid (56.0 mg, 47% for two steps): MS (ESI) *(m/z)*: 391.0 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 5.8 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.49 (d, J = 11.8 Hz, 1H), 7.36 (s, 1H), 4.21 (d, J = 6.7 Hz, 2H), 3.99 (s, 3H), 3.90 (s, 3H), 2.20 (hept, J = 6.7 Hz, 1H), 1.09 (d, J = 6.7 Hz, 6H); 19F NMR (376 MHz, $CDCl_3$) δ -121.23.

Methyl 5-fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylate (98b). Prepared from **86** using the procedures described for **87a** as light tan solid (65.5 mg, 60% for two steps): MS (ESI) *(m/z)*: 357.0 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.34 (m, 1H), 8.01 (d, J = 5.8 Hz, 1H), 7.77 (dd, J = 8.6, 2.5 Hz, 1H), 7.50 (d, J = 12.0 Hz, 1H), 7.35 (s, 1H), 6.85 (dd, J = 8.5, 0.7 Hz, 1H), 4.13 (d, J = 6.7 Hz, 2H), 3.99 (s, 3H), 3.90 (s, 3H), 2.15 (hept, J = 6.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.69.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-5-fluoro-1-methyl-1H-indole-6-carboxylic acid (99a). Prepared from **98a** using the procedures described for **78a** as a light yellow solid (57 mg, 100%): MS (ESI) *(m/z)*: 375.1 $(M-H)^+$.

5-Fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indole-6-carboxylic acid (99b). Prepared from **98a** using the procedures described for **78a** as a light yellow solid (65 mg, 100%): MS (ESI) *(m/z)*: 343.1 $(M+H)^+$.

Methyl 3-bromo-1-isopropyl-1H-indole-6-carboxylate (100a). Prepared from **70** using the procedures described for **71** as a white solid (342 mg, 46%): MS (ESI) *(m/z)*: 298.1 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.87 (dd, J = 8.4, 1.4 Hz, 1H), 7.58 (dd, J = 8.5, 0.5 Hz, 1H), 7.39 (s, 1H), 4.78 (dt, J = 13.4, 6.7 Hz, 1H), 3.97 (s, 3H), 1.55 (d, J = 6.8 Hz, 6H).

Methyl 3-bromo-1-isobutyl-1H-indole-6-carboxylate (100b). Prepared from **70** using the procedures described for **71** as an off-white solid (318.7 mg, 44%): MS (ESI) *(m/z)*: 312.2 $(M+H)^+$; ^1H (400MHz, $CDCl_3$) δ 8.09 (d, J = 0.5 Hz, 1H), 7.86 (dd, J = 8.4, 1.4 Hz, 1H), 7.60 - 7.57 (m, 1H), 7.25 (s, 1H), 3.96 (s, 3H), 3.95 (d, J = 7.3 Hz, 2H), 2.20 (dt, J = 13.6, 7.0 Hz, 1H), 0.94 (d, J = 6.5 Hz, 6H).

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-isopropyl-1H-indole-6-carboxylate (101a). Prepared from **100a** using the procedures described for **77a** (58.9 mg, 13%): MS (ESI) *(m/z)*: 401.2 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.32 (d, J = 2.0 Hz, 1H), 8.22 (s, 1H), 7.90 - 7.86 (m, 2H), 7.84 - 7.81 (m, 1H), 7.49 (s, 1H), 4.90 - 4.74 (m, 1H), 4.21 (d, J = 6.8 Hz, 2H), 3.98 (s, 3H), 2.20 (dt, J = 13.4, 6.7 Hz, 1H), 1.61 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 6H).

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-isobutyl-1H-indole-6-carboxylate (101b). Prepared from **100b** using the procedures described for **77** as a colorless oil (47.0 mg, 23%): MS (ESI) *(m/z)*: 415.2 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.31 (d, J = 2.3 Hz, 1H), 8.15 (d, J = 0.5 Hz, 1H), 7.90 - 7.81 (m, 3H), 7.36 (s, 1H), 4.21 (d, J = 6.8 Hz, 2H), 4.03 (d, J = 7.5 Hz, 2H), 3.98 (s, 3H), 2.28 (dt, J = 13.5, 6.7 Hz, 1H), 2.19 (dt, J = 13.5, 6.7 Hz, 1H), 1.08 (d, J = 6.8 Hz, 6H), 0.99 (d, J = 6.5 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-isopropyl-1H-indole-6-carboxylic acid (102a). Prepared from **101a** using the procedures described for **78a** (54.0 mg, 73%): MS (ESI) *(m/z)*: 387.1 $(M+H)^+$; ^1H NMR (500MHz, DMSO-d_6) 8.45 - 8.42 (m, 1H), 8.18 (s, 1H), 8.17 - 8.14 (m, 1H), 8.11 - 8.09 (m, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 4.93 - 4.85 (m, 1H), 4.18 (d, *J* = 6.4 Hz, 2H), 2.14 - 2.03 (m, 1H), 1.54 (d, *J* = 6.7 Hz, 6H), 1.01 (d, *J* = 6.7 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-isobutyl-1H-indole-6-carboxylic acid (102b). Prepared from **101b** using the procedures described for **78a** as an off-white solid (45.2 mg, 100%): MS (ESI) *(m/z)*: 401.1 $(M+H)^+$.

6-Bromo-3-iodo-2-methyl-1H-indazole (104) and 6-bromo-3-iodo-1-methyl-2H-indazole (105). Potassium carbonate (1.146 g, 8.29 mmol) was added to the DMF (20 mL) solution of 6-bromo-3-iodo-1H-indazole (**103**, 2.231 g, 6.91 mmol) at room temperature. The mixture was stirred at rt for 30 min. Methyl iodide (0.52 mL, 8.29 mmol) was added to the reaction mixture and the reaction was stirred 72 h at rt. The reaction was diluted with water and extracted three times by diethyl ether. The diethyl ether layer was combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. The products were separated by flash column eluted with EtOAc in hexane from 0 to 25% to 40%. **104**: (0.331 g, 14%, yellow solid and more polar): MS (ESI) *(m/z)*: 336.8 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 - 7.83 (m, 1H), 7.28 - 7.24 (m, 1H), 7.21 - 7.17 (m, 1H), 4.23 (s, 3H). **105**: (1.115 g, 48%, yellow solid and less polar): MS (ESI) *(m/z)*: 336.8 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.58 (d, J = 0.8 Hz, 1H), 7.37 - 7.29 (m, 2H), 4.07 (s, 3H).

6-Bromo-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole (106). The mixture of sodium carbonate (0.064 mL, 0.128 mmol), $PdCl_2$(dppf) (2.3 mg, 3.19 μmol), (4-(trifluoromethyl)phenyl)boronic acid (14.5 mg, 0.077 mmol) and 6-bromo-3-iodo-1-methyl-1H-indazole (**105**, 21.5 mg, 0.064 mmol) in dioxane (0.5 mL) was heated at 80 °C for 1 h. The reaction was diluted with EtOAc, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column eluted with EtOAc in hexane from 0 to 10% (11.2 mg, 49%). MS (ESI) *(m/z)*: 355.1 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 1.0 Hz, 1H), 7.36 (dd, J = 8.8, 1.5 Hz, 1H), 4.12 (s, 3H); ^{19}F NMR (376MHz, $CDCl_3$) δ -62.55 (s, 3F).

Methyl 3-bromo-2-methyl-2H-indazole-6-carboxylate (108) and **methyl 3-bromo-1-methyl-1H-indazole-6-carboxylate (109).** Sodium hydride (0.152 g, 3.79 mmol) was added to the THF (10 mL) solution of methyl 3-bromo-1H-indazole-6-carboxylate (**107**, 0.645 g, 2.53 mmol) at 0 °C. The reaction was stirred for 10 min before addition of methyl iodide (0.237 mL, 3.79 mmol) to the reaction mixture. The reaction was stirred overnight while it was warmed up to rt. The solvent was removed via vacuum and the crude was partitioned between water and EtOAc. The aqueous layer was separated and extracted two more times with EtOAc. The EtOAc layer was combined, dried (Na_2SO_4), filtered and concentrated to give the crude products as a mixture. The starting material was mainly remained in aqueous layer. The product was purified by flash column eluted with EtOAc in hexane from 0 to 25%. Two products were isolated and the structure elucidation was carried out by NOE studies. **108**:

(0.121 g, 18%, off-white solid and more polar): MS (ESI) *(m/z)*: 270.9 $(M+H)^+$; ^1H NMR (500MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.76 (dd, J = 8.9, 1.2 Hz, 1H), 7.55 (dd, J = 8.9, 0.8 Hz, 1H), 4.25 (s, 3H), 3.98 (s, 3H). **109**: (0.228 mg, 34%, white solid and less polar): MS (ESI) *(m/z)*: 270.9 $(M+H)^+$; ^1H NMR (500MHz, $CDCl_3$) δ 8.14 (d, J = 0.8 Hz, 1H), 7.87 - 7.83 (m, 1H), 7.64 (dd, J = 8.5, 0.8 Hz, 1H), 4.12 (s, 3H), 3.99 (s, 3H).

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole-6-carboxylate (110). Prepared from **109** using the procedures described for **34** (36.4 mg, 37%): MS (ESI) *(m/z)*: 374.1 $(M+H)^+$.

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole-6-carboxylic acid (111). Prepared from **110** using the procedures described for **78a** (33.5 mg, 49%): MS (ESI) *(m/z)*: 358.1 $(M-H)^+$.

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-2-methyl-2H-indazole-6-carboxylate (112). Prepared from **108** using the procedures described for **34** (17.0 mg, 62%): MS (ESI) *(m/z)*: 374.1 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.51 (t, J = 1.0 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.8, 1.3 Hz, 1H), 7.56 (dd, J = 8.9, 0.9 Hz, 1H), 4.26 (d, J = 6.5 Hz, 2H), 4.22 (s, 3H), 3.97 (s, 3H), 2.22 (dt, J = 13.4, 6.7 Hz, 1H), 1.10 (d, J = 6.8 Hz, 6H).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-2-methyl-2H-indazole-6-carboxylic acid (113). Prepared from **112** using the procedures described for **78a** (16.2 mg, 99%): MS (ESI) *(m/z)*: 358.1 $(M-H)^+$.

6-Bromo-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole (114a). Prepared from **105** using the procedures described for **106** (63.5 mg, 73%): MS (ESI) *(m/z)*: 360.2 $(M+H)^+$; ^1H NMR (400MHz, $CDCl_3$) δ 8.69 (d, J = 2.0 Hz, 1H), 8.11 (dd, J = 8.7, 2.4 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 1.3 Hz, 1H), 7.31 (dd, J = 8.7, 1.6 Hz, 1H), 6.88 (dd, J = 8.5, 0.5 Hz, 1H), 4.14 (d, J = 6.8 Hz, 2H), 4.08 (s, 3H), 2.14 (dt, J = 13.4, 6.7 Hz, 1H), 1.06 (d, J = 6.8 Hz, 6H).

6-Bromo-3-(5-chloro-6-isobutoxypyridin-3-yl)-3a,7a-dihydro-1H-indazole (114b). Prepared from **103** using the procedures described for **106** (79.0 mg, 24%): MS (ESI) *(m/z)*: 382.1 $(M+H)^+$.

2-Fluoro-4-methyl-5-nitrobenzoic acid (116). In a 250 mL round-bottomed flask was 2-fluoro-4-methylbenzoic acid (**115**, 4.0 g, 26.0 mmol) dissolved in 40 mL concentrated sulfuric acid at 0 °C (completely dissolved) was added dropwise a mixture of H_2SO_4 (1.70 ml, 31.1 mmol) and nitric acid (2.50 ml, 38.9 mmol) (70%). After stirring for 3

h at 0 °C, an excess of ice water was added. The resulting solid was filtered and dried to obtain the desired product (5.18 g, 100%) as a white solid.

Methyl 2-fluoro-4-methyl-5-nitrobenzoate (117). In a 500 mL round-bottomed flask was 2-fluoro-4-methyl-5-nitrobenzoic acid (**116**, 5.18 g, 26 mmol) in MeOH (40 mL) to give a colorless solution. H_2SO_4 (7.1 mL, 130 mmol) was slowly added. The reaction was heated to 65 °C overnight for 20 h. The mixture was concentrated, diluted with ice and water, filtered and rinsed several times with cold water, and air-dried overnight to afford the desired product (5.12 g, 92%) as a white solid: MS (ESI) *(m/z)*: 212.1 $(M-H)^+$.

Methyl 5-amino-2-fluoro-4-methylbenzoate (118). In a 250 mL round-bottomed flask was methyl 2-fluoro-4-methyl-5-nitrobenzoate (**117**, 1.38 g, 6.47 mmol) in EtOAc (40 mL) to give a colorless solution. Pd/C (0.069 g, 0.065 mmol) was added. After vacuum and refill, the mixture was stirred under hydrogen (balloon) for 20 h. After vacuum and refilled with nitrogen, the mixture was filtered and rinsed with EtOAc. The combined organic solution was concentrated to the desired product (1.13 g, 95%) as an off-white solid: MS (ESI) *(m/z)*: 184.1 $(M+H)^+$.

Methyl 5-fluoro-1H-indazole-6-carboxylate (119). In a 500 mL round-bottomed flask was methyl 5-amino-2-fluoro-4-methylbenzoate (**118**, 1.13 g, 6.17 mmol) and potassium acetate (0.061 g, 0.617 mmol) in $CHCl_3$ (62 mL) to give a colorless suspension. Acetic acid (3.53 mL, 61.7 mmol) was added and the mixture was cooled to 0 °C. Isoamyl nitrite (1.25 mL, 9.25 mmol) was added dropwise. After stirring for 10 min, ice bath was removed and the reaction was stirred at rt for 3 h. The reaction was quenched with aqueous ammonia (the color changed to very dark). Layers were carefully separated. Aqueous phase was extracted 4 times with CH_2Cl_2. Combined organics were dried, and concentrated to a black oil. The crude oil was purified by FCC up to 100% EtOAc to afford the desired product (0.155 g, 13%) as a tan solid. MS (ESI) *(m/z)*: 195.1 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.18 (dt, J = 5.5, 0.8 Hz, 1H), 8.13 (d, J = 1.1 Hz, 1H), 7.56 - 7.46 (m, 1H), 4.01 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.16.

Methyl 5-fluoro-3-iodo-1-methyl-1H-indazole-6-carboxylate (120). The mixture of KOH (0.134 g, 2.395 mmol) and methyl 5-fluoro-1H-indazole-6-carboxylate (**119**, 0.155 g, 0.798 mmol) in DMF (2 mL) was stirred at rt for 30 min. Iodine (0.405 g, 1.597 mmol) was added to the reaction mixture at rt. The reaction was continue to stir

overnight for 16 h. LCMS showed the desired intermediate as the major peak (M - H = 318.96). MeI (0.100 mL, 1.597 mmol) was added. The mixture was stirred at rt overnight for 20 h. Excess water and EtOAc were added and the layers were separated. The organic layer was washed with brine, dried and concentrated. The residue was purified by FCC up to 50% EtOAc/hexane to afford the desired product (the less polar spot, 157.6 mg, 59%) as a tan solid. MS (ESI) *(m/z)*: 334.9 $(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 5.3 Hz, 1H), 7.19 (d, J = 10.2 Hz, 1H), 4.15 (s, 3H), 4.00 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -120.17. The undesired isomer (the more polar spot, 63.6 mg, 24%): MS (ESI) *(m/z)*: 334.9 $(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, J = 6.2, 0.6 Hz, 1H), 7.11 (dd, J = 10.7, 0.6 Hz, 1H), 4.29 (s, 3H), 3.98 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -120.00. The regiochemistry was proved by NOE studies.

Methyl 5-fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole-6-carboxylate (121a). Prepared from **120** using the procedures described for **106** as a white solid (25.8 mg, 91%): MS (ESI) *(m/z)*: 353.1 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 5.5 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 10.9 Hz, 1H), 4.21 (s, 3H), 4.03 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57, -120.36.

Methyl 5-fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole-6-carboxylate (121b). Prepared from **120** using the procedures described for **87a** (70.4 mg, 97%) as a white solid: MS (ESI) *(m/z)*: 358.2 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 2.4 Hz, 1H), 8.09 (dd, J = 8.6, 2.5 Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 7.64 (d, J = 10.9 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.18 - 4.14 (m, 5H), 4.01 (s, 3H), 2.14 (dp, J = 13.4, 6.7 Hz, 1H), 1.06 (d, J = 6.7 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.10.

5-Fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole-6-carboxylic acid (122a). Prepared from **121a** using the procedures described for **78a** (24.8 mg, 100%) as a white solid: MS (ESI) *(m/z)*: 339.1 $(M+H)^+$.

5-Fluoro-3-(6-isobutoxypyridin-3-yl)-1-methyl-1H-indazole-6-carboxylic acid (122b). Prepared from **121b** using the procedures described for **78a** (64.7 mg, 96%) as a white solid: MS (ESI) *(m/z)*: 344.1 $(M+H)^+$.

Methyl 1H-pyrrolo[2,3-b]pyridine-6-carboxylate (124). The mixture of 1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (**123**, 0.340 g, 2.097 mmol) and sulfuric acid (0.112 mL, 2.097 mmol) in MeOH (7 mL) was heated at 70 °C for 22 h. The solvent was removed via vacuum and the crude was used as it is. A small portion was further purified

by p-HPLC: MS (ESI) *(m/z)*: 177.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 12.07 (br. s., 1H), 8.10 - 8.06 (m, 1H), 8.02 - 7.98 (m, 1H), 7.83 - 7.79 (m, 1H), 6.61 (dd, J = 3.5, 2.0 Hz, 1H), 4.09 (s, 3H).

Methyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (125). Potassium hydroxide (0.588 g, 10.49 mmol) and methyl 1H-pyrrolo[2,3-b]pyridine-6-carboxylate (**124**, 0.369 g, 2.097 mmol) in DMF (7.0 mL) was stirred at rt for 1 h. Iodine (0.639 g, 2.52 mmol) was added to the reaction mixture and the reaction was stirred for another 3 h at rt. The reaction was diluted with water, filtered and washed with water. The solid was air dried to give the desired product (478 mg, 75%) as a brown solid. MS (ESI) *(m/z)*: 301.0 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.04 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 4.09 (s, 3H).

Methyl 3-iodo-1-methyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (126). Potassium carbonate (0.194 g, 1.401 mmol) was added to the DMF (3 mL) solution of methyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (**125**, 0.353 g, 1.168 mmol) at rt. The mixture was stirred at rt for 30 min. Methyl iodide (0.15 mL, 2.399 mmol) was added to the reaction mixture and the reaction was stirred for 18 h at rt. The reaction was diluted with water and extracted with diethyl ether three times. The diethyl ether layer was combined, washed with brine and dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column eluted with EtOAc in hexane from 0 to 50% to afford the desired product (322 mg, 87%) as an off-white solid. MS (ESI) *(m/z)*: 317.1 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H).

Methyl 3-(5-chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (127a). Prepared from **126** using the procedures described for **87a** (45.0 mg, 39%): MS (ESI) *(m/z)*: 374.1 $(M+H)^+$. ^{1}H NMR (500MHz, DMSO-d6) δ 8.50 (d, J = 2.1 Hz, 1H), 8.48 (d, J = 8.2 Hz, 1H), 8.29 (s, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 4.17 (d, J = 6.7 Hz, 2H), 3.93 (s, 3H), 3.93 (s, 3H), 2.10 (dt, J = 13.4, 6.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H).

Methyl 1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (127b). Prepared from **126** using the procedures described for **106** (27.0 mg, 55%): MS (ESI) *(m/z)*: 335.2 $(M+H)^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.30 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 2.5 Hz, 4H), 7.66 (s, 1H), 4.07 (s, 3H), 4.06 (s, 3H); ^{19}F NMR (376MHz, $CDCl_3$) δ -62.38 (s, 3F).

3-(5-Chloro-6-isobutoxypyridin-3-yl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (128a). Prepared from **127a** using the procedures described for **78a** (29.8 mg, 83%): MS (ESI) *(m/z)*: 360.2 $(M+H)^+$.

1-Methyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid (128b). Prepared from **127b** using the procedures described for **78a** (25.7 mg, 99%): MS (ESI) *(m/z)*: 321.2 $(M+H)^+$.

6-Bromo-3-iodo-1H-pyrrolo[3,2-b]pyridine (130). The mixture of KOH (0.569 g, 10.13 mmol) and 6-bromo-1H-pyrrolo[3,2-b]pyridine (**129**, 1.551 g, 7.87 mmol) in DMF (15 mL) was stirred at rt for 1 h. Iodine (2.00 g, 7.87 mmol) in DMF (7 mL) was added to the reaction mixture at rt. The reaction was continue to stir for 18 h. The reaction was poured into 200 mL ice water and the solid was filtered, washed with water. The solid was dissolved in EtOAc and dried with Na_2SO_4. The EtOAc layer was filtered and concentrated to give the crude product (2.43 g, 96%) as a brown solid. MS (ESI) *(m/z)*: 322.8 $(M+H)^+$; ^{1}H NMR (400MHz, DMSO-d6) δ 11.88 (br. s., 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.86 (s, 1H).

6-Bromo-3-iodo-1-methyl-1H-pyrrolo[3,2-b]pyridine (131). Potassium carbonate (1.198 g, 8.67 mmol) was added to the DMF (20 mL) solution of 6-bromo-3-iodo-1H-pyrrolo[3,2-b]pyridine (**130**, 2.333 g, 7.22 mmol) at rt. The mixture was stirred at rt for 30 min. Methyl iodide (0.542 mL, 8.67 mmol) was added to the reaction mixture and the reaction was stirred at rt overnight for 18 h. The reaction was diluted with water and filtered. The solid was washed by water and air-dried to afford the desired product (2.33 g, 96%) as a brown solid. MS (ESI) *(m/z)*: 336.8 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, *J* = 1.8 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 6.85 (s, 1H), 3.06 (s, 3H).

Methyl 3-iodo-1-methyl-1H-pyrrolo[3,2-c]pyridine-6-carboxylate (133). The mixture of KOH (1.097 g, 19.56 mmol) and methyl 1-methyl-1H-pyrrolo[3,2-c]pyridine-6-carboxylate (**132**, 1.24 g, 6.52 mmol) in DMF (15 mL) was stirred at rt. Iodine (3.31 g, 13.04 mmol) in DMF (5 mL) was added to the reaction mixture at rt. The reaction was continue to stir overnight for 16 h. Sodium sulfite solution was added to quench excess iodine and water was added. Solids were filtered, rinsed with water, and further dried overnight to afford the desired product (1.218 g, 59%) as a tan solid: MS (ESI) *(m/z)*: 316.6 $(M-H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.21 (s, 1H), 7.35 (s, 1H), 4.07 (s, 3H), 3.93 (s, 3H).

Methyl 1-methyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxylate (134). Prepared from **133** using the procedures described for **106** (5.0 mg, 11%) as a white solid: MS (ESI) *(m/z)*: 335.2 $(M+H)^+$; ^1H (400 MHz, $CDCl_3$) δ 9.28 (d, J = 0.9 Hz, 1H), 8.31 (d, J = 1.0 Hz, 1H), 7.77 (s, 4H), 7.51 (s, 1H), 4.09 (s, 3H), 3.99 (s, 3H); 19F NMR (376 MHz, Chloroform-d) δ -62.44.

1-Methyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[3,2-c]pyridine-6-carboxylic acid (135). Prepared from **134** using the procedures described for **78a** (25.7 mg, 99%): MS (ESI) *(m/z)*: 321.2 $(M+H)^+$.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at:

Molecular formula strings (cvs).

Notes

The authors declare no competing financial interest.

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scale synthesis of compound **29**, and Spectrix chemists for all the final compound purification and characterization.

ABBREVIATIONS

SAR, structure-activity relationship; EP, electrophysiology; DRG, dorsal root ganglion; TGG, trigeminal ganglion; TTX, tetrodotoxin; EtOAc, ethyl acetate; TEA, triethylamine; TFA, trifluoroacetic acid; DIAD, diisopropyl azodicarboxylate; rt, room temperature; CYP, cytochrome P450 enzymes; PO, oral administration; SC, subcutaneous injection; IP, intraperitoneal; PK/PD, Pharmacokinetic/Pharmacodynamic; Pgp, P-glycoprotein; FCC, flash column chromatography; HPLC, high pressure liquid chromatography; LCMS, liquid chromatography mass spectrometry; NMR, nuclear magnetic resonance.

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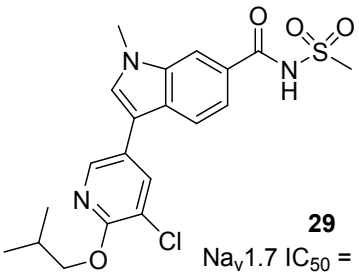
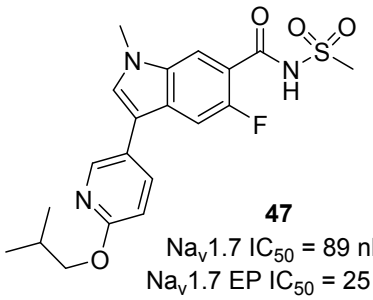
Table of Contents Graphic



29
$Na_v1.7$ IC_{50} = 108 nM
$Na_v1.7$ EP IC_{50} = 8 nM
Efficacious in three pain models



47
$Na_v1.7$ IC_{50} = 89 nM
$Na_v1.7$ EP IC_{50} = 25 nM