Journal Pre-proof

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PII: S0223-5234(20)30935-1

DOI: https://doi.org/10.1016/j.ejmech.2020.112963

Reference: EJMECH 112963

To appear in: *European Journal of Medicinal Chemistry*

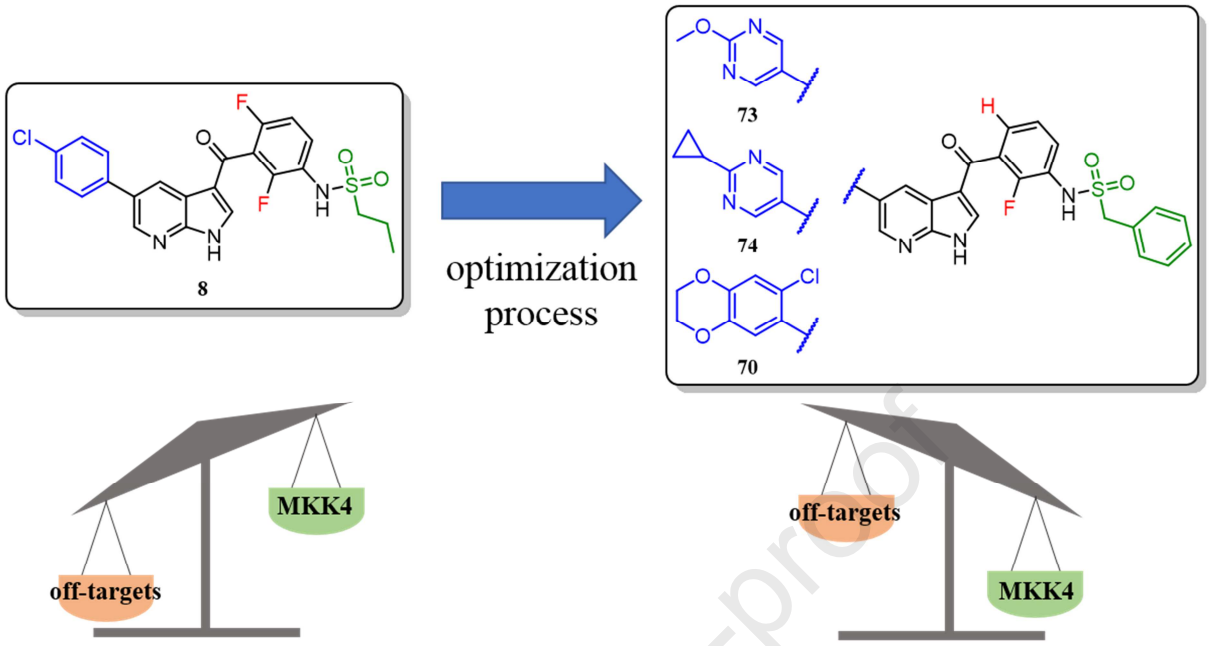
Received Date: 24 July 2020

Revised Date: 19 October 2020

Accepted Date: 20 October 2020

Please cite this article as: P. Klövekorn, B. Pfaffenrot, M. Juchum, R. Selig, W. Albrecht, L. Zender, S.A. Laufer, From off-to on-target: New BRAF-inhibitor-template-derived compounds selectively targeting mitogen activated protein kinase kinase 4 (MKK4), *European Journal of Medicinal Chemistry*, https://doi.org/10.1016/j.ejmech.2020.112963.

GRAPHICAL ABSTRACT.



From off- to on-target: New BRAF-inhibitor-template-derived compounds selectively targeting mitogen activated protein kinase kinase 4 (MKK4)

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KEYWORDS.

Acute and chronic liver failure, liver failure, NAFLD, NASH, liver regeneration, MEK4, MKK4, inhibitors, Vemurafenib

ABSTRACT.

The mitogen-activated protein kinase (MAP) kinase 4 (MKK4) was found to be a major regulator of liver regeneration and could be a valuable drug target addressing liver related diseases by restoring its intrinsic regenerative capacity. We report on the synthesis and optimization of novel MKK4 inhibitors following a target-hopping strategy from the FDA-approved $BRAF^{V600E}$ inhibitor PLX4032 (**8**). Applying an iterative multi-parameter optimization process we carved out essential structural features yielding in compounds with a low nanomolar affinity for MKK4 and excellent selectivity profiles against the main off-targets MKK7 and JNK1, which, upon relevant inhibition, would totally abrogate the pro-regenerative effect of MKK4 inhibition, as well as against the off-targets MAP4K5, ZAK and BRAF with selectivity factors ranging from 40 – 430 for our best-balanced compounds **70** and **73**.

INTRODUCTION.

The liver harbors an enormous regenerative capacity in response to injury, but after chronic liver damage this regenerative ability can collapse with a mostly fatal outcome for the patient. Driven by obesity and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) including its progressive form, non-alcoholic steatohepatitis (NASH), belong to the major health issues in industrialized countries affecting nearly 2 billion people worldwide [1,2].

While viral infection can be cured with antiviral drugs, the treatment of NASH is limited to drastic lifestyle changes and prevention [3]. Based on the medical need for treatment of NASH or its prevention, several therapeutic concepts are currently under clinical investigation. Most of these candidates address established metabolic disease targets such as subtypes of peroxisome proliferator-activated receptors (elafibranor / α/δ, lanifibranor /α/γ/δ, or saroglitazar / α/γ), the farnesoid x receptor (obeticholic acid, cilofexor or tropifexor), acetyl-CoA carboxylase (firsocostat) and others.

Wüstefeld *et al*. identified mitogen-activated protein (MAP) kinase kinase 4 (MKK4) as a key promotor for liver regeneration with beneficial effects on hepatocyte regeneration, robustness, fibrosis and Fas-mediated apoptosis [4]. On the molecular level, silencing of MKK4 via shRNA results in increased signaling through apoptosis signal-regulating kinase 1 (ASK1) and mitogen activated protein (MAP) kinas kinase 7 (MKK7) and thus yielding in higher phosphorylation of c-Jun-N-terminal kinase 1 (JNK1). Thereby, phosphorylation of ETS transcription factor (ELK1) and activating transcription factor 2 (ATF2) is intensified, which leads to a reinforced hepatocyte proliferation. Due to the involved signaling network MKK7 and JNK1 have to be considered as major off-targets (see **Figure 1**).

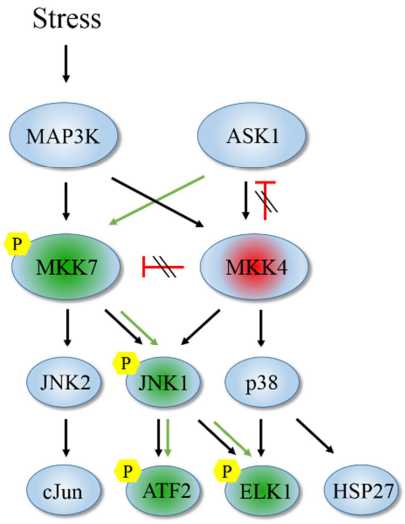


Figure 1. Schematic visualization of signal transduction upon MKK4 silencing modified from Wüstefeld *et al.* [4].

Since MKK4 plays a pivotal role in cell growth, differentiation and inflammation processes this kinase could represent a valuable drug target for different diseases [5-7]. However, only a handful of inhibitors are published until now (see **Figure 2**). Bayer published MKK4 and MKK7 inhibitors based on 9*H*-pyrimido[4,5-*b*]indol-6-ol scaffold (**1** and **2**) with IC_{50} values below 1 µM [8,9]. Also, natural products like isoflavones (THIF **3**) show inhibitory potency towards MKK4 but with lacking selectivity [10]. Recently, Deibler *et al*. published arylindazoles showing a great selectivity profile within the MAP2-kinase family and low nanomolar IC_{50} range (exemplary **7**) [11,12]. These structures were deduced from known MKK4 inhibitors like pazopanib (**4**), PLX4720 (**5**) and LY333531 (**6**).

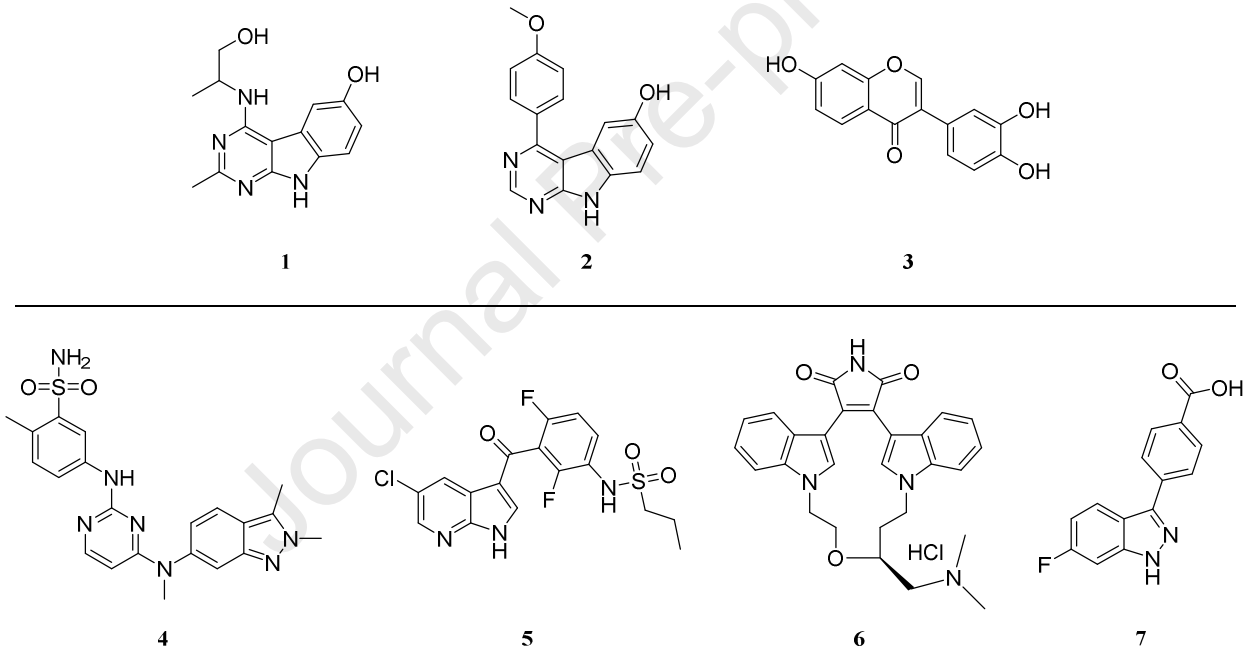
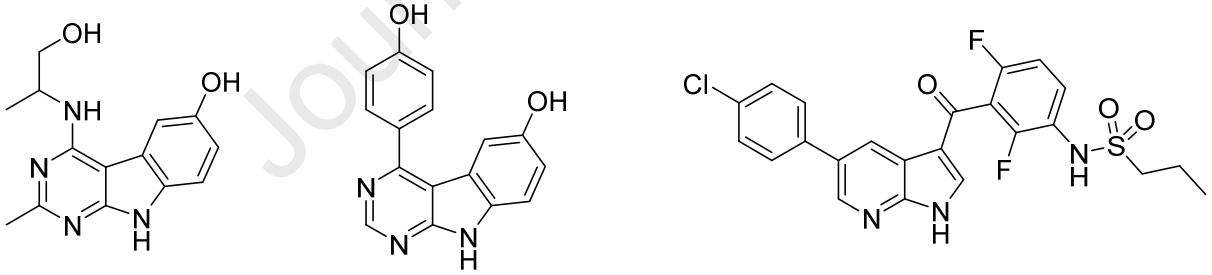


Figure 2. Published inhibitors for MKK4. Top: published MKK4/MKK7 dual-inhibitors (**1** and **2**) and THIF (**3**) by Kim *et al*.; bottom: inhibitors with off-target-inhibition for MKK4 used by Deibler *et al*. for *in silico* design of novel small molecules.

In this work, we describe the optimization process of **8**, an approved v-Raf murine sarcoma viral oncogene homolog B1 ($BRAF^{V600E}$) kinase inhibitor for the treatment of malignant melanoma, towards a high affine and selective MKK4 inhibitor. Initially we tested **8** and compounds **1** and **2** on a panel of important off-targets, namely BRAFwt, MEK kinase kinase

5 (MAP4K5), sterile alpha motif and leucine zipper containing kinase (ZAK), MKK7 and JNK1 regarding their binding affinities. Among other MAP4 and MAP3 kinases upstream of JNK both MAP4K5 and ZAK are known activators of JNK. Therefore, to achieve a beneficial pharmacological effect as obtained with shRNA-mediated MKK4-suppression, the small molecule MKK4 inhibitor should exhibit sufficient selectivity against MAP4K5 and ZAK [13]. Therefore, hit optimization included the determination of the affinity to all known potential off-targets employing the KINOMEscan technology by Eurofins DiscoverX. Binding affinities are given as percentage of control (POC) values. In the assay, the compounds compete with a proprietary immobilized multikinase inhibitor for the binding site of the DNA-tagged kinase. The readout is via quantitative PCR and the POC is calculated from the DMSO control. So, a POC of 0 is equal to a complete displacement of the ligand from the kinase (complete binding) and a POC of 100 is equal to no binding of the compound to the kinase [14].

Table 1. Initial testing of **1**, **2** and **8** as potential starting points for further optimization.



1 **2** **8**

No.	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
	% Ctrl at 100 nM[a]					
1	91	95	**100**	100	88	81
2	82	92	**48**	100	80	84
8	16	48	**14**	100	94	5.3

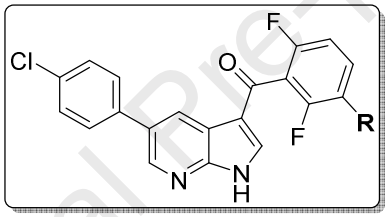
[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate.

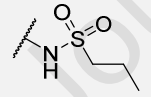
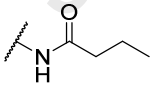
RESULTS AND DISCUSSION.

Biological evaluation. In the following all structural features of **8** (sulfonamide residue, substitution of the moiety in 5 position of the azaindole and substitution pattern of the difluoro phenyl part) will be analyzed successively taking affinity and selectivity towards all before mentioned off-targets, as well as MKK4 into account, while maintaining the azaindole scaffold.

Modification of the sulfonamide. At first, we evaluated the role of the sulfonamide residue of **8** with regards to affinity and selectivity towards MKK4. The substitution of the sulfonamide by an amide eliminates the affinity towards MKK4 (entry **9**, **Table 2**).

Table 2. Investigations on the sulfonamide structural elements.



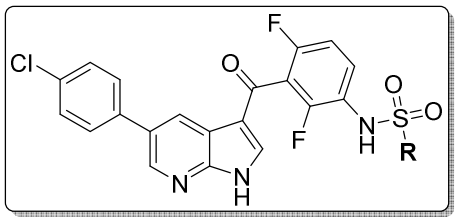
No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
		% Ctrl at 100 nM[a]					
8		16	48	**14**	100	94	5.3
9		82	91	**100**	94	61	78

[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate.

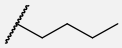
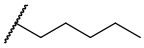
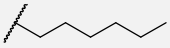
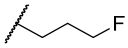
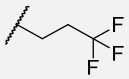
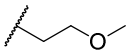
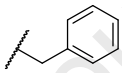
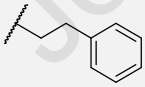
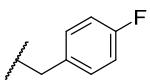
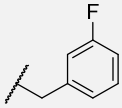
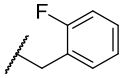
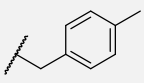
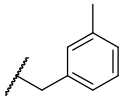
The propyl sulfonamide chain in **8** was optimized for a unique pocket in the BRAF family [15]. We speculated that modifications of this propyl side chain would increase selectivity, especially over BRAF. Therefore, chain lengths, aromatic modifications and incorporation of polar heteroatoms were examined on their binding effects to MKK4. We started by varying the length of the alkyl chains from methyl to hexyl. Especially for BRAF, we could observe an effect on the structure-activity-relationship. With altering the propyl chain, the binding affinity drops dramatically from POC 16 to at least 89 on BRAF (entries **10 – 14**, **Table 3**).

Regarding MKK4, the propyl chain exhibits the highest affinity and modifications thereof are more tolerated as for BRAF, while the hexyl moiety is the least tolerated larger side chain. Fluorination of the propyl sidechain gave varying results. MKK4 affinity of the monofluorinated compound **15** is comparable to **8**, but selectivity against BRAF and ZAK is reduced. The trifluoro compound **16** in contrast, showed a highly increased affinity for MKK4, while the affinity for BRAF dropped by factor 2. Polar modifications such as the methoxyethyl chain (entry **17**, **Table 3**) were not well tolerated by MKK4. To install a bulkier residue, we attached a phenyl ring to the sulfonamide with variation in spacer length (n = 0 – 2, entries **18 – 20**, **Table 3**). Compared to **8** the affinity towards MKK4 increased by a factor of 2 for the benzyl group (**19**) and 4 for the phenyl group (**18**), respectively. The ethylene linker (**20**) led to a loss in affinity to MKK4. Compound **19** showed improved affinity (POC^{MKK4} = 5.9) and the best selectivity profile among these modifications. Whether substitution of the benzyl moiety has a further impact on selectivity, this modification was investigated more detailed with compounds **21 – 25**. Fluorine was chosen as substituent to further increase affinity according to **15** and **16**, but no striking effect could be observed. Even though **21**, **24** and **25** showed a higher selectivity against ZAK, the affinity for MKK4 was lower compared to the unsubstituted compound **19**. Just **23** has a comparable profile to **19**.

Table 3. Scope of sulfonamide substitution patterns.



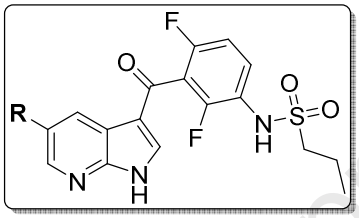
No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
		% Ctrl at 100 nM[a]					
10		93	63	**32**	87	100	2.6

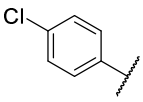
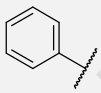
11		93	82	**43**	89	100	8.3
8		16	48	**14**	100	94	5.3
12		89	75	**23**	100	100	29
13		96	98	**29**	89	100	55
14		96	99	**45**	81	100	73
15		6.6	80	**10**	100	95	1.4
16		32	54	**2.8**	100	100	3.5
17		91	100	**47**	75	100	58
18		22	83	**3.3**	83	100	4.9
19		100	94	**5.9**	100	100	30
20		99	100	**24**	97	100	53
21		95	n.d.	**15**	100	100	61
22		100	n.d.	**13**	99	97	36
23		100	n.d.	**6**	97	100	23
24		100	n.d.	**19**	90	99	87
25		100	n.d.	**16**	100	100	64

[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate; n.d.= not determinded.

Variation of the phenyl ring in position 5 of the azaindole core. The impact of the moiety in position 5 of the azaindole of **8** regarding binding affinity and selectivity was further examined. Initially, the 4-chlorophenyl moiety of **8**, was replaced with a phenyl ring (**26**) and the corresponding isosteric alkyne (**27**). Furthermore, 2-furyl- (**28**) and 2-thiophenyl (**29**) compounds were prepared (see **Table 4**).

Table 4. Isosteric replacement of the 4-chlorophenyl part of **8**.



No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
		% Ctrl at 100 nM[a]					
8		16	48	**14**	100	94	5.3
26		21	29	**2.9**	100	81	0.5
27		8.2	89	**11**	100	84	1.4
28		9	78	**7.3**	95	94	2.1
29		13	48	**4.5**	98	100	2.9

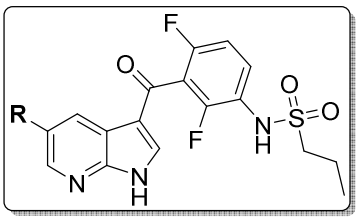
[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate.

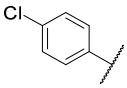
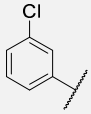
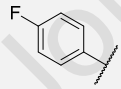
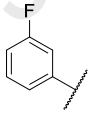
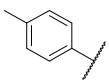
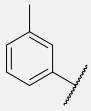
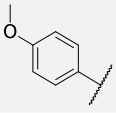
The unsubstituted isosteric derivatives **26 – 29** are showing higher affinity values for MKK4 compared to **8**. Therefore, we further investigated the substitution pattern of the phenyl moiety in the 5 position of the azaindole (**Table 5**). First, we elaborated the effect of monosubstituted derivatives and proceeded with di- and trisubstitution to combine beneficial moieties of each optimization cycle. Altering substituents in the *para*-position of the 5-phenyl

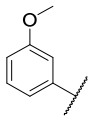
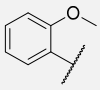
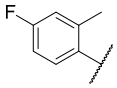
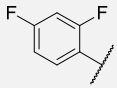
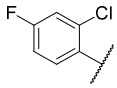
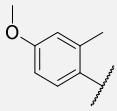
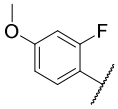
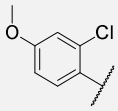
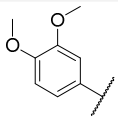
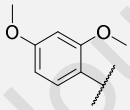
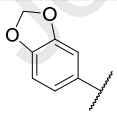
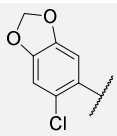
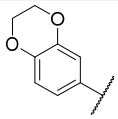
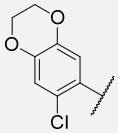
moiety increases the affinity towards MKK4 when chlorine is substituted by fluorine, methyl or a methoxy group (entries **32, 35** and **38**, **Table 5**). Among the regioisomeric mono-substitution patterns the *meta*-position (**30**, **33**, **36**, **Table 5**) has no relevant effect, except for the *m*-methoxy derivative (entry **39**, **Table 5**) that has a higher affinity to MKK4, but unfortunately also to BRAF and MAP4K5 compared to **8**. The *ortho*-regioisomers are showing a positive effect on the selectivity towards BRAF and slightly on ZAK. Substitution patterns containing *o*-chloro, *o*-fluoro, *o*-methyl and *o*-methoxy (entries **31**, **34**, **37** and **40**, **Table 5)** led to decrease in binding affinity for BRAF compared to the *meta*- and *para*-isomers. This '*ortho*-effect' was further investigated by the combination of **32** and **38** with compounds **31**, **34** and **37** (entries **41 – 46**, **Table 5**). Entries **45** and **46** represent the most superior derivatives of these combinations in terms of selectivity and affinity towards MKK4. The *m*- and *o*-methoxy derivatives were also combined with *p*-methoxy residues (entries **47** and **48**, **Table 5**). Herein, the *meta* substituted compound (**47**) had a higher selectivity towards ZAK but low selectivity towards BRAF, while selectivity to ZAK and BRAF was opposite for the *ortho*-methoxy compound (**48**). Bridging the 3,4-dimethoxy groups with a methylene and ethylene linker (entries **49** and **51**, **Table 5**), increased the selectivity to BRAF but also increased the affinity to ZAK. Ongoing modifications with *o*-chloro substituents led to a further increase of selectivity (**50** and **52**, **Table 5)**. These combinations afforded highly affine inhibitors of MKK4 sparing BRAF, MAP4K5, MKK7, JNK1 and ZAK moderately. In this example, the *ortho* chlorine was identified as an outstanding selectivity driver. We also focused on heteroaromatic moieties like pyridine, pyridazine and pyrimidine (entries **53 – 57**, **Table 5**). Entries **56** and **57** were inspired by **38** and PLX8394, a further derivative of **8**, which inhibits ERK-signaling without undesired JNK-activation and is currently under clinical investigations [16-18]. Compared to the substituted phenyl derivatives, the heteroaromatic compounds have a higher affinity towards MKK4, but also with a higher binding to the off-targets as well. Among this series, compound **57** showed an improvement

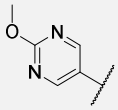
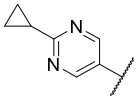
of ZAK-selectivity compared to **38** and **56**. We assume, that the attached cyclopropyl moiety could be in tight proximity to the extended p-loop of ZAK and thus clash with the protein [19].

Table 5. Investigation on the 5-position of the azaindole scaffold.



No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
		% Ctrl at 100 nM[a]					
8		16	48	**14**	100	94	5.3
30		47	n.d.	**24**	85	100	2.2
31		65	79	**6.2**	100	93	7.6
32		27	67	**4.3**	100	96	0.9
33		31	45	**9.9**	90	98	0.8
34		47	n.d.	**4.1**	86	69	2.9
35		11	28	**5**	89	76	0.85
36		29	28	**13**	97	92	0.7
37		72	67	**10**	100	88	6.9
38		6.7	38	**6.3**	70	89	0

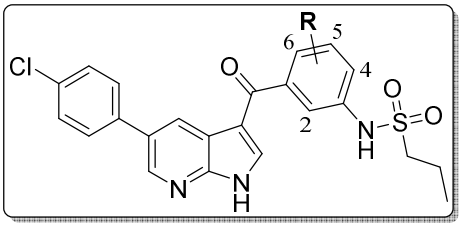
39		10	18	**5.4**	100	77	23
40		64	43	**2.8**	100	80	16
41		69	100	**8.8**	100	97	14
42		46	n.d.	**4.2**	93	87	5.9
43		85	100	**18**	100	100	19
44		75	n.d.	**7.7**	97	100	13
45		29	n.d.	**2.4**	85	85	6
46		70	100	**2.7**	100	97	18
47		0.55	14	**1.3**	84	65	18
48		31	84	**4.5**	87	76	1.6
49		13	76	**3.1**	90	94	0.45
50		85	99	**11**	100	100	26
51		5.7	84	**2.9**	100	96	2.2
52		72	98	**5.3**	97	99	20
53		1.4	80	**1.7**	81	65	3.5
54		8.7	92	**11**	90	83	39

55		2.2	75	**2.5**	83	74	11
56		0.75	86	**0.3**	84	73	8.9
57		1.1	n.d.	**0.2**	87	100	30

[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate; n.d.= not determinded.

Alteration of the difluoro pattern. In the ongoing course of our studies, we examined the impact of the difluorophenyl moiety of **8**. This part is considered to have an impact on the hydrophobic interaction, since the fluorine atoms are embedded in a hydrophobic pocket in BRAF [15]. To identify the relevant substitution, we initially tested the unsubstituted compound **58**. Removing the fluorine atoms led to a significant drop in affinity towards BRAF but also to a loss in affinity to the whole panel of kinases, including MKK4. Concluding the necessity of the fluorine from these results, mono substitution patterns (**59** – **64**, **Table 6**) were investigated, which revealed that the position 2 needs to be substituted with fluorine (**8**, **59**) in order to maintain affinity towards MKK4. Substituting fluorine in 2-position with chlorine or methyl (**63**, **64**) led to a loss in affinity for MKK4. Compound **59** (2-fluorophenyl) has a comparable affinity to MKK4 as **8**, but with improved selectivity against BRAF by factor 2.

Table 6. Altered substitution pattern at the difluorophenyl part of **8**.



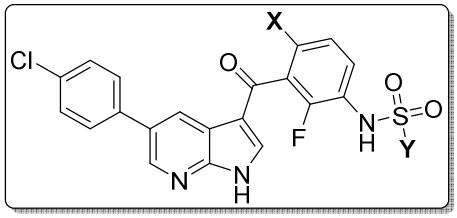
No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK

		% Ctrl at 100 nM[a]					
8	2,6-F	16	48	**14**	100	94	5.3
58	-H	100	44	**53**	100	98	n.d.
59	2-F	31	51	**16**	92	97	5
60	4-F	94	76	**32**	93	95	37
61	5-F	91	99	**100**	93	100	n.d.
62	6-F	82	60	**45**	92	100	16
63	2-Cl	31	79	**78**	100	100	68
64	2-CH_3	94	40	**92**	91	n.d.	n.d.

[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate; n.d.= not determinded.

Combinatorial approach. From previous results, we combined structural elements which improved affinity on MKK4 and/or led to a markedly better selectivity profile. By combination of the 2-fluorophenyl moiety of **59** and the benzyl sulfonamide group of **19** (yielding entry **66**, **Table 7**) the affinity towards MKK4 was increased by the factor of 2 while the selectivity ratio to all other kinases improved by a factor range of 7 – 11, compared to **8**. In comparison to the difluorophenyl derivative **19**, the monofluorophenyl compound **66** showed an improved selectivity against ZAK with comparable affinity towards MKK4. The combination of the benzyl sulfonamide and 2-fluoro phenyl moiety yielded an excellent selectivity profile and was thus used for the final modifications.

Table 7. Monofluoro substituted compounds **59, 65** and **66** in comparison to their difluoro counterparts.



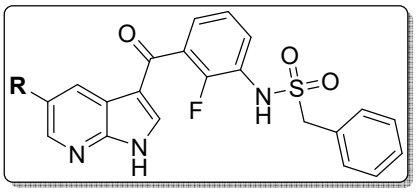
No.	X	Y	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
			% Ctrl at 100 nM[a]					
8	-F	-propyl	16	48	**14**	100	94	5.3
59	-H	-propyl	31	51	**16**	92	97	5
10	-F	-methyl	93	63	**32**	87	100	2.6
19	-F	-benzyl	100	94	**5.9**	100	100	30
65	-H	-methyl	91	78	**28**	81	100	27
66	-H	-benzyl	100	72	**8.9**	97	100	66

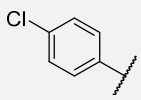
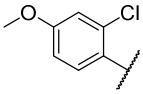
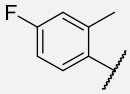
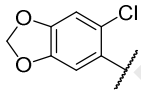
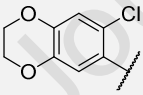
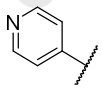
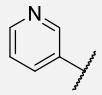
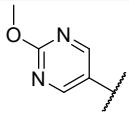
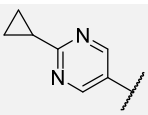
[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate.

Final modifications. As last stage of this optimization study, we combined the selectivity and affinity increasing residues from **66** (benzylsulfonamide and 2-fluorophenyl moiety) with aryl residues of the 5 position of the azaindole from **Table 5**, that were found to have an already high affinity to MKK4 but with still lacking selectivity, especially towards BRAF and ZAK. We selected the residues from **41**, **46**, **50** and **52** of the 5-position of the azaindole to combine with the 2-fluorophenyl linker and the benzylsulfonamide from **66** (Entries **67 – 70, Table 8**). Within this selection entries **68** and **70** are excellent compounds showing high affinity to MKK4 and a good selectivity profile within the kinase panel. Furthermore, the 5-position of the azaindole was substituted with pyridines (entries **71** and **72**, **Table 8**) and the residues from **56** and **57** were chosen for this combination (entries **73** and **74**, **Table 8**). Pyridines **71** and **72** showed a high affinity for MKK4, but also a strong affinity towards ZAK. Furthermore, MAP4K5 arises as an undesired off-target affinity for these compounds.

The combined 4-methoxy and 4-cyclopropyl pyrimidine compounds **73** and **74** have outstandingly high affinity to MKK4, while the critical off-targets were discriminated by the factor >190, making these compounds the best compounds from all compounds prepared, concerning affinity and selectivity for MKK4.

Table 8. Combinational compounds derived from **66**.

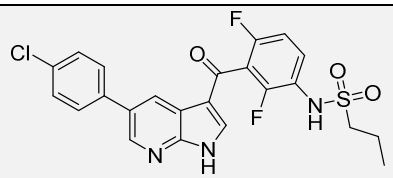
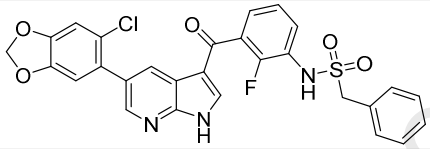
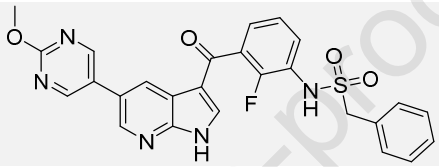
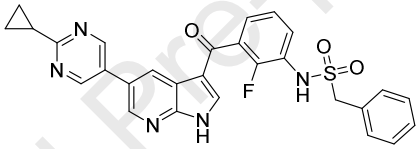


No.	R	BRAF	MAP4K5	MKK4	MKK7	JNK1	ZAK
		% Ctrl at 100 nM[a]					
8	-	16	48	**14**	100	94	5.3
66		100	72	**8.9**	97	100	66
67		96	79	**2.4**	100	100	87
68		100	97	**3.3**	98	100	90
69		98	66	**2.9**	100	97	80
70		99	98	**2.2**	100	97	94
71		86	26	**0**	95	75	0.95
72		91	20	**0**	85	55	1.7
73		84	86	**0.2**	70	86	38
74		83	82	**0.35**	86	92	80

[a]Binding affinities from KINOMEscan assay at a compound concentration of 100 nM. Values are shown as POC determined in duplicate.

For a further biological characterization of the most potent compounds, we determined Kd-values for MKK4 for **70**, **73** and **74** as well as for **8** for comprehension (see **Table 9**).

Table 9. Comparison of Kd-values (MKK4) for the most potent compounds.

No.	Structure	Kd-Value (nM)[a]
8		8.2
70		3.5
73		0.85
74		1.1

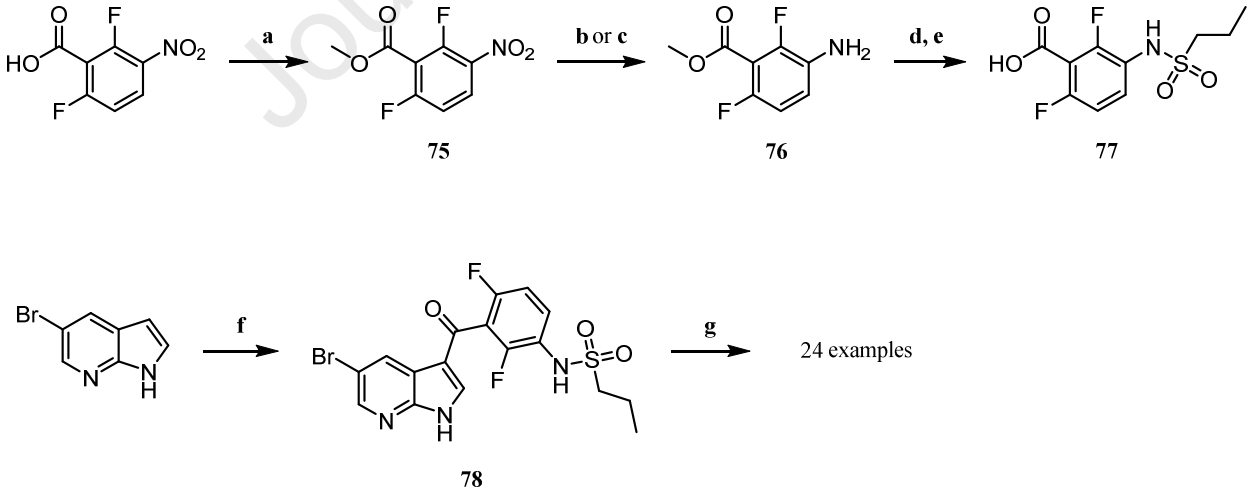
[a]Kd-values for MKK4 from KINOMEscan, determined in duplicates.

The Kd-values for MKK4 were within in the low one-digit nanomalor range for all tested compounds. Our newly developed compounds outperformed **8** with a gain in affinity towards MKK4 up to factor 10 (**73**), combined with a superior selectivity profile. Compounds **73** and **74**, showing Kd-values of 0.85 and 1.1 respectively, can be seen as equal in affinity towards MKK4. From the previous testing (see **Table 8**), **74** was the compound with the best selectivity and also one with the highest affinity for MKK4. We determined the kinome selectivity for **74** using the scanEDGE assay provided by DiscoverX at a concentration of 1 µM (1000x Kd-value). The panel consists of 97 kinases, from which 90 are non-mutant kinases. In this panel, a POC lower than 35 was measured only for 5 kinases (1 mutant-kinase, see SI), whereas a POC lower than 10 was not observed. This leads to a selectivity score of (S35) = 0.044 at 1 µM.

CHEMISTRY.

The synthetic route was mainly adapted from the procedures published in the corresponding patent [20]. Due to strategic issues, the order of introducing building blocks was modified in particular cases. **Scheme 1** displays the synthetic route to obtain 2,6-difluoro-3-(propylsulfonamido)benzoic acid (**77**), which was used in a subsequent Friedel-Crafts acylation (FC acylation) under standard conditions using $AlCl_3$ as mediator for acylation. The benzoic acid **77** was synthesized following the procedure of Wenglowsky *et al*. [21]. The intermediate **78** was finally modified using the corresponding boronic acids or the pinacol ester thereof according to the procedure from Buck *et al.* under microwave irradiation conditions [22]. This procedure was also applied to synthesize all modified benzoic acids used for the synthesis of compounds **58 – 64**. For compound **63** the reduction step (**Scheme 1**, b or c) was performed using a Béchamp-like procedure to avoid hydrodehalogenation.

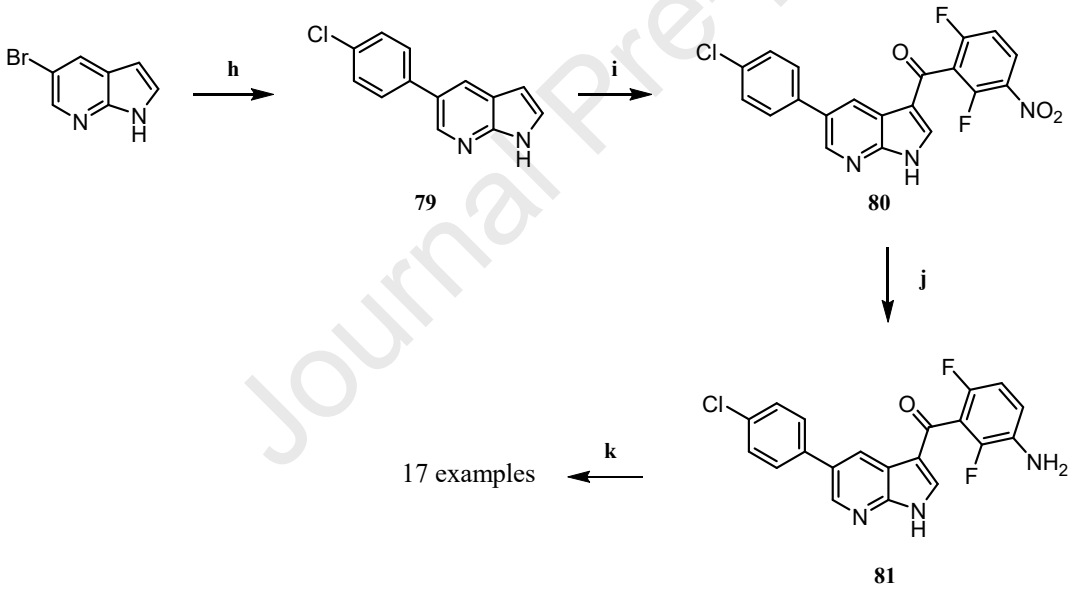
Scheme 1. Top: Synthesis of substituted carboxylic acids; here, exemplary synthesis of 2,6-difluoro-3-(propylsulfonamido)benzoic acid; bottom: synthesis and modification of **81** using microwave irradiation.[a]



[a]**Reagents and conditions:** (a) Oxalyl chloride, DMF, DCM, RT, then MeOH (quant.); (b) Pd/C, H_2, EtOH (quant.); (c) Fe, 1M $HCl_{aq.}$, EtOH (98%); (d) 1-Propanesulfonyl chloride, TEA, DCM, RT (85%); (e) 4N $NaOH_{aq.}$, THF/MeOH (4:1, v/v), RT (80%); (f) **77**, oxalyl chloride, DMF, $AlCl_3$, DCM, RT (85%); (g) corresponding boronic acid/pinacol ester boronate, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane/H_2O (4:1), µw, 120°C, 15 – 90 minutes, (25 – 91%).

For varying the sulfonamide substitution pattern, the commercially available 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine was substituted in the first step with (4-chlorophenyl)boronic acid applying Suzuki coupling resulting **79** in high yields (**Scheme 2**). Using the FC acylation according to the procedure of Zhang *et al.*, the 2,6-difluoro-3-nitrobenzoic acid was introduced (**79** to **80**) [18]. Using nitromethane as solvent allowed a workup without the need for further column purification. After reduction of the nitro group in **80** to the corresponding aniline **81** with $SnCl_2$ dihydrate, the desired sulfonyl chlorides were used to assemble the sulfonamides.

Scheme 2: Synthesis of the common precursor **81** varying the sulfonamide residue.[a]

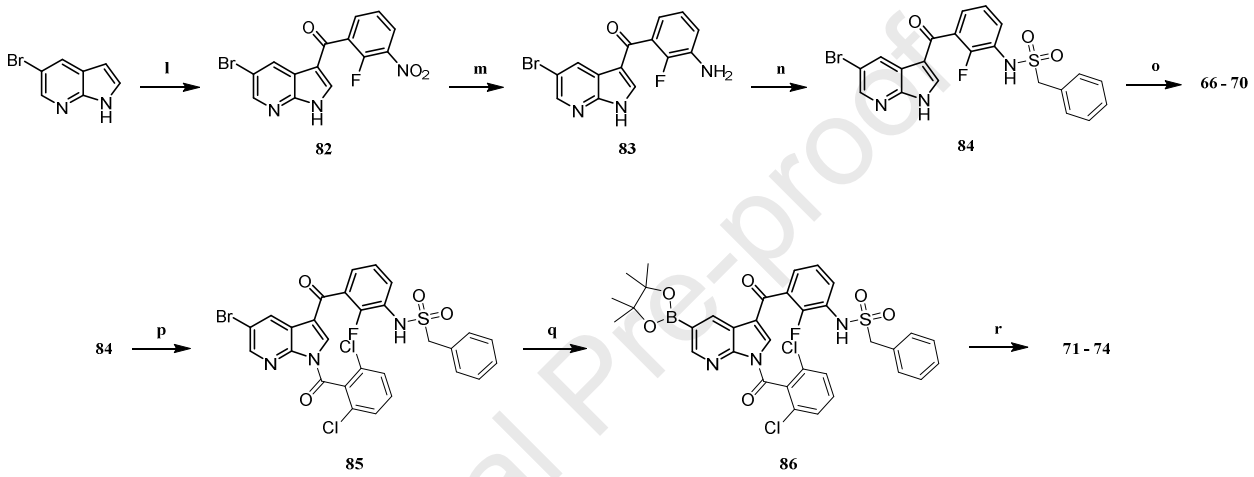


[a]**Reagents and conditions:** (h) (4-Chlorophenyl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, $MeCN/H_2O$ (4:1, v/v), 60°C (87%); (i) 2,6-difluoro-3-nitrobenzoic acid, oxalyl chloride, DMF, $AlCl_3$, $MeNO_2$, 60°C (67%); (j) $SnCl_2$ dihydrate, THF/EtOAc (1:1, v/v), 60°C (89%); (k) corresponding sulfonyl chloride, pyridine, 60°C (27 – 91%).

The synthetic strategy for compounds **66 – 74** is depicted in **Scheme 3**. All steps to intermediate **84** were performed as shown above. Suzuki coupling was again performed under microwave irradiation to introduce the favored boronic acids within a short reaction time. For compounds **71** – **74** the route was altered by a protection step of the pyrrole NH introducing

2,6-dichlorobenzoyl protection group, followed by a Miyaura borylation, yielding the intermediate **86** in high yields. For final modifications the corresponding hetero aryl bromides were used, reacting in the presence of $Pd(dppf)Cl_2$ and the crude product was deprotected with K_2CO_3 in MeOH.

Scheme 3: Synthesis of **66 – 74** from commercially available 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine.[a]



[a]**Reagents and conditions:** (l) 2-fluoro-3-nitrobenzoic acid, oxalyl chloride, DMF, $AlCl_3$, DCM, RT (84%); (m) $SnCl_2$ dihydrate, THF/EtOAc (1:1, v/v), 60°C (76%); (n) phenylmethanesulfonyl chloride, pyridine, 60°C (64%); (o) corresponding boronic acid/pinacol ester boronate, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane/H_2O (4:1), µw, 120°C, 15 – 90 min, (33 – 64%); (p) 2,6-dichlorobenzoyl chloride, TEA, THF, 4-DMAP, 0°C – RT (93%); (q) bis(pinacolato)diboron, AcOK, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, 80°C (60%); (r) aryl bromides, K_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane/H_2O (4:1, v/v), 60°C, then K_2CO_3, MeOH (29 – 55%, over two steps).

CONCLUSION.

In this work, we reported on the development of novel inhibitors with a high affinity to the on-target MKK4 and an outstanding selectivity profile towards the off-targets MKK7, JNK1, BRAFwt, MAP4K5 and ZAK, all derived from the $BRAF^{V600E}$ inhibitor-template **8**. Our synthetic efforts yielded a set of compounds, which points out structural hot spots driving affinity and selectivity. We performed a multi-parameter optimization process emphasizing a distinct SAR. With compound **70**, **73** and **74** we demonstrated the design of new inhibitors

with a high affinity to MKK4 (POC^{MKK4} = 2.2, 0.2 and 0.35 @ 0.1 µM) while sparing the off-targets in the range of factor 40 to 190. To our knowledge, these compounds are the first-in-class inhibitors selectively targeting MKK4 for the purpose of hepatocyte proliferation to restore the liver's intrinsic regenerative capacity. The findings of our work could be implemented in further investigations on the valuable drug target MKK4 in terms of using **70**, **73** and **74** as tool compounds.

EXPERIMENTAL SECTION.

General. All commercially purchased chemicals and solvents were used as received without further purification. Air- or moisture-sensitive reactions were performed under argon atmosphere and in anhydrous solvents (Acros Organics, AcroSeal). Organic extracts were dried over anhydrous sodium sulfate which was filtered off afterwards. For reaction controls, thin layer chromatography was applied using TLC Silica Gel 60 F_{254} aluminum sheets provided by Merck, detection at λ = 254 nm und 366 nm. Flash chromatography was performed manually or with Interchim PuriFlash F430 systems and Grace Davison Davisil LC60A 20 – 45 microns silica. Purity determination of all final compounds was measured with HPLC analysis on Agilent 1100 Series Liquid Chromatograph using a Phenomenex Luna C8 150x4.6 mm, 5-micron column with gradient elution (MeOH/0.01 M KH_2PO_4 buffer, pH 2.3, flow rate 1.5 mL/minute) and detection at λ = 230 and 254 nm. The minimum purity of all final compounds is >95%, if not otherwise quoted. Mass spectra (TLC-MS) for intermediates was performed on Advion DCMS interface (ESI voltage: 3.50 kV, capillary voltage: 187 V, source voltage: 44 V, capillary temperature: 250 °C, desolvation gas temperature: 250 °C, gas flowrate: 5L/minute N_2), using MeOH as elution solvent. High resolution mass spectra measurements for final compounds were performed by Mass Spectrometry Department, Eberhard Karls Universitaet Tuebingen on Bruker maXis 4G ESI-

TOF (capillary voltage: 4 kV, endplate voltage -500 V, source temperature 200°C, gas flow rate: 6 L/minute). NMR-spectra were measured on Bruker Avance 200 or 400, Avance III HDX 600 and 700. The chemical shifts (δ) are denoted by parts per million (ppm) relative to tetramethylsilane. Herein not listed intermediates and final compounds are described in the supporting information named **R** and/or with its given number from the text above.

Suzuki-coupling under microwave irradiation (General procedure A). A microwave tube was equipped with a magnetic stir bar. The vessel was charged with the corresponding 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**78** or **84**) (1.0 eq.), the appropriate boronic acid/ or pinacol ester boronate (1.2 eq.), solid K_2CO_3 (2.0 eq.) and 1,4-dioxane/water (4:1, v/v, 0.25 M). The suspension was purged with argon (5 minutes), the catalyst (10 mol%) was added, and the resulting mixture was heated to 120°C under microwave irradiation (50 W) for 30 minutes. When TLC revealed completion of the reaction, the crude was passed through a pad of Celite, diluted with EtOAc and neutralized with saturated aqueous NH_4Cl. The organic phase was separated and dried over sodium sulfate, and the solvent was removed under reduced pressure. All products were isolated applying flash chromatography.

Synthesis of the sulfonamides (General procedure B). To a solution of the corresponding aniline (**81** or **83**) (1.0 eq.) and pyridine (1 M), the appropriate sulfonyl chloride was added dropwise (1.1 eq). The resulting mixture was stirred at 60°C until TLC revealed complete consumption of the starting material (3-12 hrs). After cooling to RT, the crude was diluted with EtOAc, and then washed with aqueous 1M HCl solution. The organic layer was dried over sodium sulfate, and the solvent was evaporated. All products were isolated applying flash chromatography.

Suzuki-coupling using pinacol ester boronates at azaindole core (General procedure C). An oven-dried flask was charged with **86** / **R40** or **R45** (1.0 eq.), K_2CO_3 (2.0 eq.) and the appropriate aryl bromide (1.5 eq.). A mixture of 1,4-dioxane/H_2O (2:1, 1 M) was added, and the flask was evaporated and backfilled with argon (3x). $Pd(dppf)Cl_2$ (6 mol%) was added,

and the resulting suspension was heated to 60°C for 0.5 – 3h. After TLC revealed completion of the reaction, the crude was poured onto a pad of Celite, flushed with EtOAc, and the filtrate was evaporated to dryness. The residue was resolved in MeOH, K_2CO_3 (5.0 eq.) was added, and the reaction was stirred at RT for 3h, and then neutralized with aqueous 1M HCl solution. The mixture was extracted with EtOAc, the organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure. All compounds were isolated via flash chromatography.

Methyl 2,6-difluoro-3-nitrobenzoate (75). Oxalyl chloride (1.3 g, 10.4 mmol, 1.05 eq.) was added to a suspension of 2,6-difluoro-3-nitrobenzoic acid (2.0 g, 9.9 mmol, 1.0 eq.) in dry DCM (0.5 M), and some drops of DMF were added successively. The mixture was stirred at RT until the gas formation was complete. An excess of MeOH was added, and the solution was stirred for 5 minutes. All volatiles were removed under reduced pressure, and the product was obtained as a white solid without further purification. Yield: 2.1 g, 9.7 mmol, 98%. ^{1}H NMR (DMSO-d_6, 200 MHz, ppm): δ 8.45 (td, J = 9.0, 5.6 Hz, 1H), 7.52 (td, J = 9.4, 1.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 Hz, ppm): δ 162.1 (dd, J = 263.5, 5.7 Hz), 159.7, 153.6 (dd, J = 271.1, 7.6 Hz), 134.4 (dd, J = 7.5, 4.1 Hz), 130.6 (dd, J = 12.0, 1.5 Hz), 113.4 (dd, J = 23.8, 4.4 Hz), 112.2 (dd, J = 20.3, 18.0 Hz), 53.6.

Methyl 3-amino-2,6-difluorobenzoate (76). To a solution of **75** (2.1 g, 9.7 mmol, 1.0 eq.) in abs. EtOH (2 M), Pd on charcoal (Pd/C 10%, w/w, 514 mg, 485 µmol, 0.05 eq.) was added. The suspension was charged with H_2, and the reaction was stirred at RT until TLC revealed completion of the reduction. The crude was poured over a pad of Celite, flashed with EtOAc, and the filtrate was evaporated under reduced pressure to complete dryness. Yield: 1.8 g, 9.2 mmol, 95%.

Alternatively: **75** (1 g, 4.6 mmol, 1.0 eq.) was suspended in abs. Ethanol (0,25 M) and aqueous HCl solution (1 M, 4.6 ml, 1.0 eq.) and heated to 80°C. Fe^0 (282 mg, 5.1 mmol, 1.1 eq.) was added to the mixture and stirred at 80°C until complete consumption of the

starting material. The crude was poured through a pad of Celite and the filtrate dried *in vacuo*. The product was obtained as a white solid and was used without further purification steps. Yield: 843 mg, 4.5 mmol, 98%.

2,6-Difluoro-3-(propylsulfonamido)benzoic acid (77). The aniline **76** (1.7 g, 8.8 mmol, 1.0 eq.) was dissolved in DCM (0.25 M), treated with TEA (2.0 g, 19.4 mmol, 2.2 eq.) and cooled to 0°C. Propane-1-sulfonyl chloride (2.8 g, 19.4 mmol, 2.2 eq.) was added slowly to the solution at 0°C. The ice bath was removed, and the reaction was stirred at RT until TLC revealed completion of the reaction. Water was added, and the mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the intermediary formed disulfonamide was purified using flash chromatography (SiO_2, *n*Hex/EtOAc 9/1, v/v). This intermediate was suspended in THF/MeOH (4/1, v/v, 1 M), and aqueous 2 M NaOH solution (13 ml, 26 mmol, 3.0 eq.) was added and stirred at RT overnight. The organic solvents were evaporated, and the residue was acidified with aqueous 1 M HCl solution. The thus formed precipitate was filtered off, washed with water, and the white solid was dried in vacuum to dryness. Yield: 1.7 g, 6.0 mmol, 68% (over two steps). ^{1}H NMR (DMSO-d_6, 200 MHz, ppm): δ 14.01 (s, 1H), 9.74 (s, 1H), 7.54 (dd, *J* = 14.8, 8.7 Hz, 1H), 7.20 (t, *J* = 9.2 Hz, 1H), 3.15 – 3.02 (m, 2H), 1.85 – 1.63 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 50 Hz, ppm): δ 161.8, 157.3 (dd, *J* = 174.8, 6.9 Hz), 152.3 (dd, *J* = 178.1, 6.9 Hz), 129.8 (dd, *J* = 10.2, 2.2 Hz), 122.0 (dd, *J* = 13.5, 3.8 Hz), 112.8 (dd, *J* = 21.3, 19.3 Hz), 112.3 (dd, *J* = 22.6, 4.1 Hz), 53.8, 16.9, 12.6. $[M-H]^-$: 278,0.

***N*-(3-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (78).** An oven-dried flask was charged with **77** (15.6 g, 55.8 mmol, 1.1 eq), suspended in $MeNO_2$ (first half of total volume, 0.2 M) and treated with oxalyl chloride (7.1 g, 55.8 mmol, 1.1 eq.). Some drops of DMF were added to initiate the activation. A second oven dried flask was charged with 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (10.0 g, 50.8 mmol, 1.0 eq), $AlCl_3$ (40.6 g, 305 mmol, 6.0 eq.) and $MeNO_2$ (second half of total

volume, 0.2 M). This suspension was stirred for at least 30 minutes. Upon completion of gas formation of the activation step, the fully activated carboxylic acid solution was added to the second flask. The resulting mixture was stirred at 50°C overnight. After cooling the crude to 0°C, MeOH was slowly added. Finally, the suspension was diluted with water, and the resulting precipitate was filtered off. The solids were suspended in EtOAc, sonicated for 5 minutes and filtered off again to obtain the product which was dried in vacuum. Yield: 19.9 g, 43.3 mmol, 85%. ^{1}H NMR (DMSO-d_6, 200 MHz, ppm): δ 13.14 (s, 1H), 9.78 (s, 1H), 8.59 (d, *J* = 1.8 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 7.59 (td, *J* = 9.0, 6.4 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 1H), 3.19 – 3.06 (m, 2H), 1.86 – 1.62 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (DMSO-d_6, 50 Hz, ppm): δ 180.6, 156.6 (dd, *J* = 184.1, 7.6 Hz), 151.7 (dd, *J* = 187.1, 7.7 Hz), 147.8, 145.3, 139.3, 131.1, 128.9 (dd, *J* = 10.1, 2.1 Hz), 122.0 (dd, *J* = 13.6, 3.8 Hz), 119.0, 117.8 (dd, *J* = 24.3, 22.1 Hz), 114.9, 114.3, 112.4 (dd, *J* = 22.8, 3.8 Hz), 53.5, 16.8, 12.6. $[M-H]^-$: 456,1.

5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (79). A dry flask was charged with 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (7.0 g, 35.5 mmol, 1.0 eq.), K_2CO_3 (9.8 g, 71.1 mmol, 2.0 eq.) and (4-chlorophenyl)boronic acid (6.1 g, 39.1 mmol, 1.1 eq.). The solids were suspended in MeCN/H_2O (4/1, v/v, 36 ml), and the vessel was evacuated and backfilled with argon (3x). $Pd(PPh_3)_4$ (410 mg, 355 µmol, 1 mol%) was added, and the resulting mixture was heated to reflux overnight. After cooling the suspension to RT, the solids were filtered off and washed successively with water and cold MeCN. The obtained solids were dried in vacuum. Yield: 7.1 g, 31.0 mmol, 87%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 11.76 (s, 1H), 8.51 (d, *J* = 2.1 Hz, 1H), 8.20 (d, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.43 (m, 3H), 6.50 (dd, *J* = 3.2, 1.7 Hz, 1H).; ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 148.2, 141.4, 138.0, 131.7, 128.9, 128.6, 127.1, 126.9, 126.1, 119.7, 100.2. $[M-H]^-$: 227.0.

(5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)(2,6-difluoro-3-nitrophenyl)methanone (80). An oven-dried flask was charged with 2,6-difluoro-3-

nitrobenzoic acid (977 mg, 4.8 mmol, 1.1 eq), suspended in $MeNO_2$ (first half of total volume, 0.2 M) and treated with oxalyl chloride (658 mg, 4.8 mmol, 1.1 eq.). Some drops of DMF were added to initiate the activation. A second oven-dried flask was charged with **81** (1.0 g, 4.4 mmol, 1.0 eq.), $AlCl_3$ (3.5 g, 26.4 mmol, 6.0 eq.) and $MeNO_2$ (second half of total volume, 0.2 M). This suspension was stirred for at least 30 minutes. Upon completion of gas formation of the activation step, the fully activated carboxylic acid solution was added to the second flask. The resulting mixture was stirred at 50°C overnight. After cooling the crude to 0°C, MeOH was slowly added. Finally, the suspension was diluted with water, and the resulting precipitate was filtered off. The solids were suspended in EtOAc, sonicated for 5 minutes and filtered off again to obtain the product which was dried in vacuum. Yield: 1.2 g, 2.9 mmol, 67%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.13 (s, 1H), 8.75 – 8.68 (m, 2H), 8.50 – 8.38 (m, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.59 – 7.49 (m, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 178.8, 161.5 (dd, *J* = 257.1, 7.5 Hz), 152.7 (dd, *J* = 264.2, 9.4 Hz), 149.1, 144.1, 139.8, 136.9, 134.3 (dd, *J* = 7.6, 3.6 Hz), 132.5, 130.4, 129.0, 128.9, 127.2, 119.5 (dd, *J* = 25.1, 23.4 Hz), 117.4, 115.4, 113.2 (dd, *J* = 24.1, 3.7 Hz). $[M-H]^-$: 411.7.

(3-Amino-2,6-difluorophenyl)(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (81). A solution of **80** (1.2 g, 2.8 mmol, 1.0 eq.) in EtOAc (0.1 M) and THF (0.1 M) was heated to 60°C. $SnCl_2$ dihydrate (2.2 g, 9.8 mmol, 3.5 eq.) was added portion wise, and the resulting mixture was stirred at 60°C until TLC revealed completion of the reaction. The mixture was cooled to RT, and a half-saturated, aqueous sodium bicarbonate solution was added. The suspension was filtered, and the filtrate was washed with brine and water. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Yield: 970 mg, 2.5 mmol, 89%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.95 (s, 1H), 8.70 (d, *J* = 1.9 Hz, 1H), 8.64 (s, 1H), 8.12 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.00 – 6.87 (m, 2H), 5.24 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 182.2, 149.2 (dd, *J* = 235.1, 6.7 Hz), 148.9, 146.0 (dd, *J* = 241.2, 8.0 Hz), 143.7, 138.0, 137.1, 133.4

(dd, *J* = 13.1, 2.3 Hz), 132.4, 130.1, 129.0, 128.8, 127.0, 117.5, 116.6 (dd, *J* = 7.9, 6.2 Hz), 115.9, 111.3 (dd, *J* = 22.1, 3.3 Hz). $[M-H]^-$: 381.9.

(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)(2-fluoro-3-nitrophenyl)methanone (82). An oven-dried flask was charged with 2-fluoro-3-nitrobenzoic acid (3.1 g, 16.8 mmol, 1.1 eq), suspended in DCM (0.5 M) and treated with oxalyl chloride (2.1 g, 16.8 mmol, 1.1 eq.). Some drops of DMF were added to initiate the activation. A second oven-dried flask was charged with 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (3.0 g, 15.2 mmol, 1.0 eq.), $AlCl_3$ (10.0 g, 76 mmol, 5.0 eq.) and DCM (0.5 M). This suspension was stirred for at least 30 minutes. Upon completion of gas formation of the activation step, the fully activated carboxylic acid solution was added to the second flask. The resulting mixture was stirred at RT overnight. After cooling the crude to 0°C, MeOH was slowly added. Brine was added, and the mixture was extracted with EtOAc. The organic phases were dried over sodium sulfate, and the solvent was evaporated. The residue was suspended in EtOAc, sonicated for 5 minutes, and the solids were filtered off to obtain the product. Yield: 4.7 g, 12.8 mmol, 84%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.10 (s, 1H), 8.64 (s, 1H), 8.49 (s, 1H), 8.37 – 8.12 (m, 2H), 7.99 (s, 1H), 7.62 – 7.48 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 183.9, 151.7 (d, *J* = 264.4 Hz), 147.7, 145.1, 139.4, 137.5 (d, *J* = 8.2 Hz), 135.3 (d, *J* = 4.2 Hz), 131.3, 130.3 (d, *J* = 16.2 Hz), 127.8 (d, *J* = 2.0 Hz), 125.2 (d, *J* = 4.7 Hz), 119.4, 114.1, 114.0. $[M-H]^-$: 363.0.

(3-Amino-2-fluorophenyl)(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (83). A solution of **82** (4.7 g, 12.8 mmol, 1.0 eq.) in EtOAc (0.1 M) and THF (0.1 M) was heated to 60°C. $SnCl_2$ dihydrate (10.1 g, 44.8 mmol, 3.5 eq.) was added portion wise, and the resulting mixture was stirred at 60°C until TLC revealed completion of the reaction. The mixture was cooled to RT, and a half-saturated, aqueous sodium bicarbonate solution was added. The suspension was filtered, and the filtrate was washed with brine and water. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Yield: 3.3 g, 9.7 mmol, 76%. ^{1}H NMR (DMSO-d_6, 200 MHz, ppm): δ 12.90 (s, 1H), 8.58 (d, *J* = 2.2 Hz,

1H), 8.45 (d, *J* = 2.2 Hz, 1H), 8.02 (s, 1H), 7.03 – 6.90 (m, 2H), 6.69 – 6.64 (m, 1H), 5.36 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 186.8, 147.5, 147.0 (d, *J* = 241.6 Hz), 144.6, 137.6, 137.0 (d, *J* = 12.8 Hz), 131.2, 127.9 (d, *J* = 13.2 Hz), 124.1 (d, *J* = 3.6 Hz), 119.6, 118.0 (d, *J* = 4.9 Hz), 115.5, 114.4, 113.7. $[M-H]^-$: 333.0.

***N*-(3-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (84).** The aniline **83** (3.0 g, 9.0 mmol, 1.0 eq.) was dissolved in pyridine (1 M), and phenylmethanesulfonyl chloride (2.6 g, 13.5 mmol, 1.5 eq.) was added portion wise. The mixture was heated to 60°C until TLC revealed completion of the reaction. After cooling to RT, the mixture was diluted with EtOAc and washed with 1 M aqueous HCl solution. The organic phase was dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography (SiO_2, DCM/EtOAc 80/20, v/v). Yield: 2.8 g, 5.7 mmol, 64%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (d, *J* = 1.5 Hz, 1H), 9.87 (s, 1H), 8.62 (d, *J* = 2.2 Hz, 1H), 8.49 (d, *J* = 2.3 Hz, 1H), 8.08 (d, *J* = 1.3 Hz, 1H), 7.51 (td, *J* = 7.9, 1.4 Hz, 1H), 7.42 – 7.32 (m, 6H), 7.27 (t, *J* = 7.8 Hz, 1H), 4.56 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 185.5, 151.5 (d, *J* = 250.2 Hz), 147.6, 144.9, 138.2, 131.2, 130.9, 129.3, 128.5 (d, *J* = 15.0 Hz), 128.3, 128.2, 127.0, 126.0 (d, *J* = 13.0 Hz), 125.7 (d, *J* = 2.3 Hz), 124.5 (d, *J* = 4.3 Hz), 119.5, 114.2, 113.9, 58.4. $[M-H]^-$: 487.1.

***N*-(3-(5-bromo-1-(2,6-dichlorobenzoyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (85).** A solution of **84** (2.8 g, 5.7 mmol, 1.0 eq.) in THF (0.1 M) and TEA (604 mg, 6.0 mmol, 1.05 eq.) was cooled to 0°C. 2,6-Dichlorobenzoyl chloride (1.2 g, 5.8 mmol, 1.01 eq.) was added dropwise, followed by catalytic amounts of 4-DMAP (70 mg, 570 µmol, 10 mol%). The ice bath was removed, and the reaction mixture was stirred at RT until completion of the reaction. Water was added to crude, and EtOAc was used for extraction. The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated. The residue was purified via flash chromatography

(SiO_2, *n*Hex/EtOAc, 85/15 – 70/30, v/v). Yield: 3.5 g, 5.3 mmol, 93%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 9.94 (s, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.56 (s, 1H), 8.32 (s, 1H), 7.66 (s, 3H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 6.3 Hz, 1H), 7.43 – 7.28 (m, 6H), 4.58 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 186.1, 161.2, 151.7 (d, *J* = 252.3 Hz), 146.6, 145.1, 134.0, 133.4, 133.0 (d, *J* = 2.9 Hz), 130.9, 130.9, 129.2, 128.2 (d, *J* = 19.9 Hz), 128.2, 126.9 (d, *J* = 13.5 Hz), 126.4 (d, *J* = 12.6 Hz), 126.1, 124.6 (d, *J* = 4.0 Hz), 121.8, 118.9, 117.0, 58.5.

***N*-(3-(1-(2,6-dichlorobenzoyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (86).** An oven dried flask was charged with **85** (3.5 g, 5.3 mmol, 1.0 eq.), bis(pinacolato)diboron (1.2 g, 5.6 mmol, 1.05 eq.) and KOAc (1.6 g, 15.9 mmol, 3.0 eq.). Dry 1,4-dioxane (0.5 M) was added, the flask was evacuated and backfilled with argon (3x). $Pd(PPh_3)_2Cl_2$ (186 mg, 265 µmol, 0.05 eq.) was added, and the resulting mixture was heated to 80°C overnight. After cooling the crude to RT, it was passed through a pad of Celite and flashed with EtOAc. The filtrate was washed with brine and water, the organic phases were dried over Na_2SO_4, and the solvent was evaporated. Flash chromatography was applied for purification of the crude (SiO_2, *n*Hex/EtOAc, 90/10 – 70/30, v/v). Yield: 2.2 g, 3.1 mmol, 60%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 9.96 (s, 1H), 8.86 (d, *J* = 1.5 Hz, 1H), 8.52 (s, 1H), 8.32 (s, 1H), 7.65 (s, 3H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 6.2 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.36 – 7.29 (m, 4H), 4.59 (s, 2H), 1.30 (s, 12H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 186.6, 161.5, 151.6 (d, *J* = 252.2 Hz), 151.3, 148.3, 136.9, 133.8, 133.1, 132.7, 130.9, 130.8, 129.3, 128.2, 128.1, 127.9, 127.2 (d, *J* = 13.7 Hz), 126.4 (d, *J* = 12.6 Hz), 126.0, 124.6 (d, *J* = 3.8 Hz), 119.7, 84.2, 58.5, 24.5.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)butyramide (9).** To a suspension of **R5** (70 mg, 289 µmol, 1.1 eq.) in dry DCM (1 mL), oxalyl chloride (36 mg, 289 µmol, 1.1 eq.) and two drops of DMF were added. The mixture was stirred at RT until gas formation was complete. A second flask was charged

with **79** (60 mg, 262 µmol, 1.0 eq.), and $AlCl_3$ (173 mg, 1.3 mmol, 5.0 eq.) and dry DCM (1 ml) were added. This mixture was stirred for at least 30 minutes, and after that the first solution was added. The reaction was stirred at RT until TLC revealed complete consumption of the starting material. After cooling to 0°C, MeOH and brine were slowly added successively. The mixture was extracted with EtOAc, the combined organic layers were dried over sodium sulfate, and the solvent was evaporated. The product was isolated using flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 46 mg, 100 µmol, 38%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.01 (s, 1H), 9.80 (s, 1H), 8.71 (d, *J* = 1.7 Hz, 1H), 8.65 (s, 1H), 8.21 (s, 1H), 7.99 (dd, *J* = 14.8, 8.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.23 (t, *J* = 8.7 Hz, 1H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.67 – 1.55 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.9, 171.6, 154.6 (dd, *J* = 244.8, 5.5 Hz), 150.4 (dd, *J* = 249.4, 6.5 Hz), 148.9, 143.8, 138.6, 137.0, 132.5, 130.2, 129.0, 128.9, 127.1, 126.1 (dd, *J* = 6.4, 2.6 Hz), 123.2 (dd, *J* = 12.4, 3.4 Hz), 117.7 (dd, *J* = 19.8, 17.6 Hz), 117.5, 115.7, 111.5 (dd, *J* = 22.1, 2.6 Hz), 37.5, 18.5, 13.5. ESI-HRMS: m/z = 452.09880, calcd for $C_{24}H_{18}ClF_2N_3O_2$ m/z = 452.09828 $[M-H]^-$. IR (ATR) [cm^{-1}] 3276, 2955, 1657, 1590, 1482, 1411, 1207, 1016, 829, 683, 596, 521.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)methanesulfonamide (10).** Compound **10** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and mesyl chloride (33 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 74 mg, 160 µmol, 61%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 9.76 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.66 (s, 1H), 8.27 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.63 – 7.54 (m, 3H), 7.30 (t, *J* = 8.6 Hz, 1H), 3.08 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.1 (dd, *J* = 247.3, 6.8 Hz), 152.6 (dd, *J* = 249.8, 8.7 Hz), 149.0, 143.9, 138.9, 137.0, 132.5, 130.2, 129.0, 128.9, 127.5 (dd, *J* = 35.1, 2.0 Hz), 127.1, 121.9 (dd, *J* = 13.4, 3.8 Hz), 118.2 (dd, *J* = 24.9,

22.5 Hz), 117.5, 115.7, 112.3 (dd, *J* = 23.3, 4.0 Hz). ESI-HRMS: m/z = 460.03428, calcd for $C_{21}H_{14}ClF_2N_3O_3S$ m/z = 460.03397 $[M-H]^-$.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)ethanesulfonamide (11).** Compound **11** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and ethane-1-sulfonyl chloride (37 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 69 mg, 145 µmol, 56%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 9.78 (s, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.64 (s, 1H), 8.26 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.55 (m, 3H), 7.28 (t, *J* = 8.6 Hz, 1H), 3.15 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 6.9 Hz), 152.4 (dd, *J* = 249.3, 8.4 Hz), 149.0, 143.9, 138.8, 137.0, 132.5, 130.2, 129.0, 128.9, 127.0, 121.9 (dd, *J* = 13.6, 3.4 Hz), 118.1 (dd, *J* = 24.2, 23.0 Hz), 117.4, 115.7, 112.3 (dd, *J* = 22.8, 3.0 Hz), 46.4, 7.9. IR (ATR) [cm^{-1}] 3114, 3022, 2839, 2722, 1615, 1457, 1324, 1149, 974, 816, 762, 650, 500.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)butane-1-sulfonamide (12).** Compound **12** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and butyl-1-sulfonyl chloride (44 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 49 mg, 97 µmol, 37%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 9.78 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.64 (s, 1H), 8.26 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.64 – 7.51 (m, 3H), 7.29 (t, *J* = 8.6 Hz, 1H), 3.17 – 3.07 (m, 2H), 1.70 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.43 – 1.30 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 7.1 Hz), 152.3 (dd, *J* = 249.7, 8.5 Hz), 149.0, 143.9, 138.8, 137.0, 132.5, 130.2, 129.0, 128.9, 128.7 (m), 127.0, 121.9 (dd, *J* = 13.8, 3.4 Hz), 118.5 – 117.7 (m), 117.4, 115.7, 112.3 (dd, *J* = 23.1, 3.5 Hz), 51.6, 25.0, 20.7, 13.4. ESI-HRMS: m/z = 502.08140, calcd for $C_{24}H_{20}ClF_2N_3O_3S$ m/z = 502.08092 $[M-H]^-$. IR (ATR) [cm^{-1}] 3226, 3097, 2868, 1628, 1478, 1328, 1149, 974, 820, 512.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)pentane-1-sulfonamide (13).** Compound **13** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and **R1** (49 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 73 mg, 141 µmol, 54%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 9.78 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.64 (s, 1H), 8.26 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.64 – 7.51 (m, 3H), 7.29 (t, *J* = 8.6 Hz, 1H), 3.17 – 3.07 (m, 2H), 1.70 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.43 – 1.30 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 7.1 Hz), 152.3 (dd, *J* = 249.7, 8.5 Hz), 149.0, 143.9, 138.8, 137.0, 132.5, 130.2, 129.0, 128.9, 128.7 (m), 127.0, 121.9 (dd, *J* = 13.8, 3.4 Hz), 118.5 – 117.7 (m), 117.4 (s), 115.7, 112.3 (dd, *J* = 23.1, 3.5 Hz), 51.6, 25.0, 20.7, 13.4. ESI-HRMS: m/z = 516.09704, calcd for $C_{25}H_{22}ClF_2N_3O_3S$ m/z = 516.09657 $[M-H]^-$. IR (ATR) [cm^{-1}] 3201, 3093, 2947, 2868, 2722, 1653, 1478, 1411, 1320, 1124, 916, 829, 621, 496.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)hexane-1-sulfonamide (14).** Compound **14** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and **R2** (53 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 88 mg, 165 µmol, 63%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.78 (s, 1H), 8.71 (d, *J* = 2.1 Hz, 1H), 8.63 (s, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.66 – 7.50 (m, 3H), 7.29 (t, *J* = 8.7 Hz, 1H), 3.18 – 3.07 (m, 2H), 1.76 – 1.63 (m, 2H), 1.40 – 1.27 (m, 2H), 1.26 – 1.15 (m, 4H), 0.79 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 247.0, 6.9 Hz), 152.3 (dd, *J* = 249.9, 8.3 Hz), 149.0, 143.9, 138.7, 137.0, 132.5, 130.2, 129.1, 128.9, 128.7 (m), 127.0, 121.9 (dd, *J* = 13.8, 3.5 Hz), 118.1 (dd, *J* = 36.3, 12.7 Hz), 117.5, 115.7, 112.3 (dd, *J* = 22.8, 3.5 Hz), 51.9, 30.6, 27.0, 23.0, 21.7, 13.7. ESI-HRMS: m/z = 530.11245, calcd for $C_{26}H_{24}ClF_2N_3O_3S$ m/z = 530.11222 $[M-H]^-$. IR (ATR) [cm^{-1}] 3197, 2856, 2714, 1644, 1478, 1416, 1312, 1128, 916, 827, 625, 517.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-3-fluoropropane-1-sulfonamide (15).** Compound **15** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and 3-fluoropropane-1-sulfonyl chloride (46 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 73 mg, 144 µmol, 55%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.97 (s, 1H), 9.94 (s, 1H), 8.66 (d, *J* = 2.2 Hz, 1H), 8.60 (s, 1H), 8.13 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.57 (td, *J* = 9.0, 5.9 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.27 (t, *J* = 8.3 Hz, 1H), 4.54 (t, *J* = 5.9 Hz, 1H), 4.46 (t, *J* = 5.9 Hz, 1H), 3.24 – 3.21 (m, 2H), 2.14 – 2.09 (m, 1H), 2.09 – 2.04 (m, 1H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 181.4, 156.8 (dd, *J* = 247.5, 7.3 Hz), 153.1 (dd, *J* = 249.9, 8.9 Hz), 149.3, 144.5, 139.4, 137.3, 133.2, 131.0, 129.8 (d, *J* = 10.3 Hz), 129.7, 129.4, 127.7, 122.0 (dd, *J* = 13.9, 3.9 Hz), 118.5 (dd, *J* = 25.2, 22.6 Hz), 118.0, 116.2, 113.0 (dd, *J* = 23.0, 4.0 Hz), 82.3 (d, *J* = 162.9 Hz), 48.6 (d, *J* = 5.6 Hz), 25.0 (d, *J* = 20.7 Hz). ESI-HRMS: m/z = 506.05620, calcd for $C_{23}H_{17}ClF_3N_3O_3S$ m/z = 506.05585 $[M-H]^-$. IR (ATR) [cm^{-1}] 3243, 3114, 3014, 2839, 1632, 1490, 1420, 1320, 1141, 962, 825, 687, 512.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-3,3,3-trifluoropropane-1-sulfonamide (16).** Compound **16** was prepared following **general procedure B** using **81** (70 mg, 182 µmol, 1.0 eq.) and 3,3,3-trifluoropropane-1-sulfonyl chloride (39 mg, 201 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 86 mg, 158 µmol, 86%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 13.04 (d, *J* = 2.5 Hz, 1H), 10.11 (s, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.66 (s, 1H), 8.31 (d, *J* = 2.8 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.62 (td, *J* = 9.0, 6.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 8.6 Hz, 1H), 3.51 – 3.40 (m, 2H), 2.87 – 2.69 (m, 2H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.4, 156.5 (dd, *J* = 247.5, 7.0 Hz), 152.8 (dd, *J* = 249.6, 8.5 Hz), 149.0, 143.8, 138.9, 137.0, 132.5, 130.3, 129.6 (d, *J* = 9.5 Hz), 129.0, 128.9, 127.1, 126.0 (q, *J* = 276.6 Hz), 121.0 (dd, *J* = 13.6, 3.5 Hz), 118.2 (dd, *J* = 24.3, 22.7 Hz), 117.4, 115.7, 112.5 (dd, *J* = 22.9, 3.5 Hz), 44.7, 28.0 (dd, *J* = 61.0, 30.7 Hz). ESI-HRMS: m/z = 542.03708, calcd for $C_{23}H_{15}ClF_5N_3O_3S$ m/z =

542.04428 [M-H]$^-$. IR (ATR) [cm^{-1}] 3609, 3105, 2826, 1636, 1590, 1482, 1420, 1324, 1220, 1133, 1095, 970, 854, 633.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-2-methoxyethane-1-sulfonamide (17).** Compound **17** was prepared following **general procedure B** using **81** (100 mg, 261 µmol, 1.0 eq.) and **R3** (46 mg, 287 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 59 mg, 116 µmol, 44%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 9.83 (s, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.65 (s, 1H), 8.24 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.65 – 7.52 (m, 3H), 7.28 (t, *J* = 8.7 Hz, 1H), 3.70 (t, *J* = 6.1 Hz, 2H), 3.45 (t, *J* = 6.1 Hz, 2H), 3.20 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 155.9 (dd, *J* = 246.3, 7.1 Hz), 152.2 (dd, *J* = 249.0, 7.7 Hz), 149.0, 143.9, 138.7, 137.0, 132.5, 130.2, 129.0, 128.9, 128.3 (d, *J* = 8.7 Hz), 127.0, 121.9 (dd, *J* = 13.5, 3.5 Hz), 118.1 (dd, *J* = 24.2, 22.3 Hz), 117.5, 115.7, 112.2 (dd, *J* = 22.6, 3.5 Hz), 65.7, 57.9, 51.8. ESI-HRMS: m/z = 504.06000, calcd for $C_{23}H_{18}ClF_2N_3O_4S$ m/z = 504.06018 [M-H]$^-$. IR (ATR) [cm^{-1}] 3130, 3005, 2839, 2718, 1624, 1586, 1474, 1407, 1336, 1153, 1108, 970, 879, 816, 492.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)benzenesulfonamide (18).** Compound **18** was prepared following **general procedure B** using **81** (70 mg, 182 µmol, 1.0 eq.) and benzenesulfonyl chloride (35 mg, 201 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 48 mg, 92 µmol, 50%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.03 (s, 1H), 10.29 (s, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.60 (s, 1H), 7.86 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.61 – 7.53 (m, 4H), 7.45 (td, *J* = 8.9, 6.0 Hz, 1H), 7.26 (t, *J* = 8.3 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.3, 156.3 (dd, *J* = 247.8, 6.5 Hz), 152.6 (dd, *J* = 251.2, 9.2 Hz), 148.9, 143.9, 139.6, 138.4, 136.9, 133.0, 132.5, 130.2, 129.4 (dd, *J* = 7.9, 3.1 Hz), 129.2, 129.0, 128.8, 127.0, 126.6, 121.2 (dd, *J* = 12.7, 3.8 Hz), 117.3, 115.5, 112.3 (dd, *J* = 22.4, 3.9 Hz). ESI-HRMS: m/z = 522.05033, calcd for

$C_{26}H_{16}ClF_2N_3O_3S$ m/z = 522.04962 $[M-H]^-$. IR (ATR) [cm^{-1}] 3236, 3101, 2999, 2840, 2725, 1626, 1483, 1172, 1095, 825, 682, 576.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-phenylmethanesulfonamide (19).** Compound **19** was prepared following **general procedure B** using **81** (70 mg, 182 µmol, 1.0 eq.) and phenylmethanesulfonyl cloride (38 mg, 201 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 59 mg, 110 µmol, 60%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.05 (d, *J* = 2.2 Hz, 1H), 9.84 (s, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.67 (s, 1H), 8.23 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.52 (td, *J* = 9.0, 6.0 Hz, 1H), 7.41 – 7.33 (m, 5H), 7.26 – 7.20 (m, 1H), 4.54 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 155.7 (dd, *J* = 246.0, 7.0 Hz), 151.8 (dd, *J* = 249.7, 8.7 Hz), 149.0, 143.9, 138.7, 137.0, 132.5, 130.9, 130.3, 129.3, 129.0, 128.9, 128.3, 128.2, 127.7 (d, *J* = 9.1 Hz), 127.1, 122.2 (dd, *J* = 13.4, 3.4 Hz), 118.0 (dd, *J* = 24.3, 22.4 Hz), 117.5, 115.7, 112.1 (dd, *J* = 22.5, 3.1 Hz), 58.2. ESI-HRMS: m/z = 536.06580, calcd for $C_{27}H_{18}ClF_2N_3O_3S$ m/z = 536.06527 $[M-H]^-$. IR (ATR) [cm^{-1}] 3101, 3007, 2848, 1638, 1491, 1418, 1336, 1152, 1136, 890, 825.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-2-phenylethane-1-sulfonamide (20).** Compound **20** was prepared following **general procedure B** using **81** (70 mg, 182 µmol, 1.0 eq.) and **R4** (see **SI**; 41 mg, 201 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 63 mg, 114 µmol, 63%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (s, 1H), 9.96 (s, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.64 (s, 1H), 8.30 (s, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.62 (dd, J = 15.1, 9.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.32 – 7.17 (m, 6H), 3.42 (dd, J = 9.9, 6.3 Hz, 2H), 3.05 (dd, J = 9.8, 6.4 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.1 (dd, J = 246.1, 6.6 Hz), 152.5 (dd, J = 249.8, 8.3 Hz), 149.0, 143.9, 138.8, 138.0, 137.0, 132.5, 130.2, 129.1 (d, J = 9.5 Hz), 129.0, 128.9, 128.5, 128.3, 127.0, 126.5, 121.7 (dd, J = 13.3, 2.8 Hz), 118.5 – 117.9 (m), 117.4, 115.7, 112.3 (dd, J = 22.6, 2.6 Hz), 52.9, 29.1. ESI-HRMS: m/z = 550.08092, calcd for

$C_{28}H_{20}ClF_2N_3O_3S$ m/z = 550.08147 $[M-H]^-$. IR (ATR) [cm^{-1}] 3363, 3109, 2999, 2848, 1626, 1479, 1413, 1144, 980, 821, 686, 514.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-(4-fluorophenyl)methanesulfonamide (21).** Compound **21** was prepared following **general procedure B** using **81** (80 mg, 209 µmol, 1.0 eq.) and (4-fluorophenyl)methansulfonyl chloride (65 mg, 313 µmol, 1.5 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 36 mg, 66 µmol, 31%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.83 (s, 1H), 8.72 (s, 1H), 8.67 (s, 1H), 8.24 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.61 – 7.48 (m, 3H), 7.46 – 7.39 (m, 2H), 7.25 (t, *J* = 8.8 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 4.55 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.5, 162.1 (d, *J* = 244.9 Hz), 155.7 (dd, *J* = 246.4, 6.9 Hz), 151.8 (dd, *J* = 249.8, 8.3 Hz), 148.9, 143.9, 138.6, 137.0, 132.9 (d, *J* = 8.5 Hz), 132.5, 130.2, 129.0, 128.8, 127.8 (d, *J* = 9.1 Hz), 127.0, 125.7 (d, *J* = 3.0 Hz), 122.1 (dd, *J* = 13.5, 3.5 Hz), 118.0 (dd, *J* = 24.5, 22.5 Hz), 117.4, 115.7, 115.1 (d, *J* = 21.6 Hz), 112.1 (dd, *J* = 23.0, 3.5 Hz), 57.3. ESI-HRMS: m/z = 554.05649, calcd for $C_{27}H_{17}ClF_3N_3O_3S$ m/z = 554.05585 $[M-H]^-$. IR (ATR) [cm^{-1}] 3268, 3010, 2839, 1644, 1490, 1465, 1341, 1141, 1004, 899, 812, 575, 504, 471.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-(3-fluorophenyl)methanesulfonamide (22).** Compound **22** was prepared following **general procedure B** using **81** (80 mg, 209 µmol, 1.0 eq.) and (3-fluorophenyl)methanesulfonyl chloride (65 mg, 313 µmol, 1.5 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 53 mg, 95 µmol, 45%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.90 (s, 1H), 8.72 (d, *J* = 1.9 Hz, 1H), 8.67 (s, 1H), 8.25 (d, *J* = 1.7 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.52 (m, 3H), 7.40 (dd, *J* = 14.2, 7.8 Hz, 1H), 7.30 – 7.15 (m, 4H), 4.60 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 161.8 (d, *J* = 243.6 Hz), 155.8 (dd, *J* = 246.4, 7.0 Hz), 151.9 (dd, *J* = 249.8, 8.2 Hz), 149.0, 143.9, 138.7, 137.0, 132.5, 131.9 (d, *J* = 8.1 Hz), 130.2 (d, *J* = 4.1 Hz), 130.1, 129.0, 128.9, 127.9 (d, *J* =

10.6 Hz), 127.1, 122.0 (dd, *J* = 13.4, 3.4 Hz), 118.1 (dd, *J* = 24.3, 22.3 Hz), 117.7, 117.4, 115.7, 115.1 (d, *J* = 20.8 Hz), 112.1 (dd, *J* = 22.7, 3.0 Hz), 57.5. ESI-HRMS: m/z = 554.05623, calcd for $C_{27}H_{17}ClF_3N_3O_3S$ m/z = 554.05585 $[M-H]^-$. IR (ATR) [cm^{-1}] 3255, 3039, 1636, 1490, 1416, 1328, 1141, 829, 654, 492.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-(2-fluorophenyl)methanesulfonamide (23).** Compound **23** was prepared following **general procedure B** using **81** (80 mg, 209 µmol, 1.0 eq.) and (2-fluorophenyl)methanesulfonyl chloride (65 mg, 313 µmol, 1.5 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 52 mg, 93 µmol, 44%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 10.02 (s, 1H), 8.72 (d, *J* = 2.1 Hz, 1H), 8.67 (s, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.61 – 7.52 (m, 3H), 7.51 – 7.38 (m, 2H), 7.31 – 7.15 (m, 3H), 4.60 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 160.9 (d, *J* = 248.0 Hz), 155.7 (dd, *J* = 246.3, 7.1 Hz), 151.8 (dd, *J* = 249.7, 8.6 Hz), 148.9, 143.9, 138.6, 137.0, 133.1 (d, *J* = 2.9 Hz), 132.5, 130.8 (d, *J* = 8.3 Hz), 130.3, 129.0, 128.9, 127.3 (d, *J* = 10.3 Hz), 127.1, 124.4 (d, *J* = 3.4 Hz), 122.1 (dd, *J* = 13.3, 3.7 Hz), 118.1 (dd, *J* = 24.5, 22.5 Hz), 117.4, 116.6 (d, *J* = 14.9 Hz), 115.7, 115.5, 115.3, 112.1 (dd, *J* = 22.5, 3.3 Hz), 51.7. ESI-HRMS: m/z = 554.05664, calcd for $C_{27}H_{17}ClF_3N_3O_3S$ m/z = 554.05585 $[M-H]^-$. IR (ATR) [cm^{-1}] 3243, 3105, 1632, 1486, 1411, 1336, 1228, 1137, 1087, 832, 770, 558, 483.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-(*p*-tolyl)methanesulfonamide (24).** Compound **24** was prepared following **general procedure B** using **81** (80 mg, 209 µmol, 1.0 eq.) and (*p*-tolyl)methansulfonyl chloride (47 mg, 229 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 31 mg, 56 µmol, 27%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.78 (s, 1H), 8.72 (d, J = 2.2 Hz, 1H), 8.66 (s, 1H), 8.24 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.52 (td, J = 9.0, 6.0 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.16 (d, J = 7.9 Hz, 2H), 4.48 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 157.1 – 154.4 (m), 151.8

(dd, J = 248.1, 6.9 Hz), 149.0, 143.9, 138.6, 137.6, 137.0, 132.5, 130.8, 130.3, 129.0, 128.9, 128.9, 127.7 (d, J = 8.7 Hz), 127.1, 126.2, 122.2 (dd, J = 13.5, 3.4 Hz), 118.0 (dd, J = 24.3, 22.2 Hz), 117.5, 115.7, 112.1 (dd, J = 22.2, 3.1 Hz), 57.9, 20.7. ESI-HRMS: m/z = 550.08118, calcd for $C_{28}H_{20}ClF_2N_3O_3S$ m/z = 550.08092 $[M-H]^-$. IR (ATR) [cm^{-1}] 1636, 1486, 1457, 1169, 970, 816, 679, 625, 504.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-(*m*-tolyl)methanesulfonamide (25).** Compound **25** was prepared following **general procedure B** using **81** (80 mg, 209 µmol, 1.0 eq.) and (*m*-tolyl)methanesulfonyl chloride (44 mg, 313 µmol, 1.1 eq.). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 31 mg, 57 µmol, 27%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.82 (s, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 8.24 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.50 (m, 3H), 7.28 – 7.12 (m, 5H), 4.49 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 181.2, 156.2 (dd, *J* = 246.8, 7.7 Hz), 152.2 (dd, *J* = 250.0, 9.2 Hz), 149.4, 144.4, 139.2, 138.0, 137.5, 133.0, 131.9, 130.8, 129.6, 129.4, 128.7, 128.5, 128.1 (d, *J* = 8.9 Hz), 127.6, 122.7 (dd, *J* = 13.6, 3.5 Hz), 118.5 (dd, *J* = 24.5, 22.2 Hz), 118.0, 116.2, 112.6 (dd, *J* = 23.0, 3.3 Hz), 58.7, 21.2.ESI-HRMS: m/z = 550.08150, calcd for $C_{28}H_{20}ClF_2N_3O_3S$ m/z = 550.08092 $[M-H]^-$. IR (ATR) [cm^{-1}] 3272, 3014, 2831, 1648, 1486, 1336, 1149, 986, 890, 824, 691, 549, 503.

***N*-(2,4-difluoro-3-(5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (26).** Compound **35** was prepared following **general procedure A** using **78** (150 mg, 327 µmol, 1.0 eq.), phenylboronic acid (48 mg, 393 µmol, 1.2 eq.), K_2CO_3 (90 mg, 654 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (37 mg, 33 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 59 mg, 130 µmol, 40%. ^{1}H NMR (DMSO-d6, 400 MHz, ppm): δ 13.00 (s, 1H), 9.78 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.63 (s, 1H), 8.23 (s, 1H), 7.74 (d, J = 7.3 Hz, 2H), 7.59 (td, J = 9.0, 5.9 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 3.12 (dd, J = 8.7, 6.7 Hz, 2H), 1.80 – 1.66 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d6, 101 Hz, ppm): δ 180.7, 156.1 (dd, J = 246.6, 6.9 Hz),

152.4 (dd, J = 249.7, 8.6 Hz), 148.9, 144.1, 138.6, 138.2), 131.6, 129.2, 128.8 (d, J = 10.1 Hz), 127.6, 127.2, 127.1, 122.0 (dd, J = 13.7, 3.5 Hz), 118.2 (dd, J = 24.6, 22.6 Hz), 117.5, 115.7, 112.3 (dd, J = 22.7, 3.6 Hz), 53.6, 16.8, 12.6. ESI-HRMS: m/z = 454.10424, calcd for $C_{23}H_{19}F_2N_3O_3S$ m/z = 454.11152 $[M-H]^-$. IR (ATR) [cm-1] 3230, 2872, 1640, 1582, 1486, 1407, 1316, 1153, 966, 762, 696, 512.

***N*-(3-(5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (27).**[22] A microwave vessel was charged with **78** (100 mg, 218 µmol, 1.0 eq.), CuI (8 mg, 43 µmol, 0.2 eq.) and $Pd(PPh_3)_2Cl_2$ (31 mg, 43 µmol, 0,2 eq.), TEA (55 mg, 546 µmol 2.5 eq.) and trimethylsilylacetylene (64 mg, 655 µmol, 3.0 eq.). The resulting mixture was irradiated (50 W) in a microwave oven at 130°C for 60 minutes. The crude was passed through at pad of Celite, flushed with EtOAc and the filtrate was washed with brine. The organic phase was dried over sodium sulfate, and the solvent was evaporated. The residue was suspended in MeOH, K_2CO_3 (78 mg, 436 µmol, 2.0 eq.) was added, and the suspension was stirred at RT until complete cleavage of TMS. The solvent was removed and the product was isolated applying flash chromatography (SiO_2, DCM/MeOH 100/0 – 97/3, v/v). Yield: 45 mg, 112 µmol, 51%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.15 (s, 1H), 9.79 (s, 1H), 8.52 (d, *J* = 1.6 Hz, 1H), 8.50 (s, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 7.59 (td, *J* = 9.0, 6.0 Hz, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 4.34 (s, 1H), 3.16 – 3.06 (m, 2H), 1.79 – 1.67 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 181.0, 156.2 (dd, *J* = 245.2, 6.2 Hz), 152.6 (dd, *J* = 249.9, 8.2 Hz), 148.6, 148.0, 139.2, 132.4, 129.2 (d, *J* = 10.4 Hz), 122.1 (dd, *J* = 13.8, 3.3 Hz), 118.1 (dd, *J* = 24.5, 21.9 Hz), 117.0 (s, *J* = 5.5 Hz), 115.5, 113.8, 112.6 (dd, *J* = 22.8, 3.5 Hz), 82.3, 81.5, 53.9, 17.0, 12.7. ESI-HRMS: m/z = 402.07328, calcd for $C_{19}H_{15}F_2N_3O_3S$ m/z = 402.08022 $[M-H]^-$. IR (ATR) [cm^{-1}] 3243, 3097, 2968, 2872, 2722, 1619, 1486, 1465, 1411, 1316, 1149, 974, 895, 608, 508.

***N*-(2,4-difluoro-3-(5-(furan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (28).** Compound **28** was prepared following

general procedure A using **78** (60 mg, 131 µmol, 1.0 eq.), 2-furanylboronic acid (18 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 35 mg, 79 µmol, 61%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (s, 1H), 9.79 (s, 1H), 8.83 (d, *J* = 2.1 Hz, 1H), 8.70 (s, 1H), 8.23 (d, *J* = 1.2 Hz, 1H), 7.82 (d, *J* = 1.1 Hz, 1H), 7.59 (td, *J* = 8.9, 6.0 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.65 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.17 – 3.07 (m, 2H), 1.74 (dq, *J* = 14.9, 7.4 Hz,21H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 6.7 Hz), 152.3 (dd, *J* = 249.4, 8.1 Hz), 151.3, 148.5, 143.2, 141.5, 138.6, 128.8 (d, *J* = 9.8 Hz), 123.5, 122.3, 121.9 (dd, *J* = 13.3, 3.8 Hz), 118.5 – 117.8 (m), 117.3, 115.7, 112.5 – 112.2 (m), 112.2, 105.9, 53.5, 16.8, 12.6. ESI-HRMS: m/z = 444.08386, calcd for $C_{21}H_{17}F_2N_3O_4S$ m/z = 444.08351 $[M-H]^-$. IR (ATR) [cm^{-1}] 3097, 2839, 1640, 1490, 1416, 1328, 1145, 979, 879, 733, 558, 496.

***N*-(2,4-difluoro-3-(5-(thiophen-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (29).** Compound **29** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), 2-thiophenylboronic acid (20 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 48 mg, 104 µmol, 79%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.79 (s, 1H), 8.78 (d, *J* = 2.2 Hz, 1H), 8.60 (s, 1H), 8.24 (s, 1H), 7.65 – 7.53 (m, 3H), 7.29 (t, *J* = 8.7 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.16 – 3.08 (m, 2H), 1.80 – 1.68 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.4, 7.1 Hz), 152.3 (dd, *J* = 249.6, 8.4 Hz), 148.7, 142.7, 140.7, 138.7, 128.8 (d, *J* = 10.2 Hz), 128.7, 126.0, 125.5, 124.1, 121.93 (dd, *J* = 13.8, 4.0 Hz), 117.5, 115.5, 112.3 (dd, *J* = 22.6, 3.0 Hz), 53.5, 16.8, 12.5. ESI-HRMS: m/z = 460.06115, calcd for $C_{21}H_{17}F_2N_3O_3S_2$ m/z = 460.06066 $[M-H]^-$. IR (ATR) [cm^{-1}] 2843, 1632, 1582, 1495, 1461, 1411, 1336, 1145, 999, 974, 887, 704, 558.

***N*-(3-(5-(3-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (30).** Compound **30** was prepared following **general procedure A** using **78** (100 mg, 218 µmol, 1.0 eq.), (3-chlorophenyl)boronic acid (41 mg, 262 µmol, 1.2 eq.), K_2CO_3 (60 mg, 436 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (25 mg, 22 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v).

Yield: 50 mg, 102 µmol, 47%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.04 (s, 1H), 9.78 (s, 1H), 8.74 (d, *J* = 1.9 Hz, 1H), 8.66 (s, 1H), 8.27 (s, 1H), 7.83 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.52 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 8.6 Hz, 1H), 3.18 – 3.07 (m, 2H), 1.74 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.7, 156.0 (dd, *J* = 247.1, 6.9 Hz), 152.4 (dd, *J* = 249.9, 8.6 Hz), 149.1, 144.1, 140.4, 138.8, 133.9, 130.9, 130.1, 128.9 – 128.7 (m), 127.4, 127.4, 126.8, 125.9, 122.0 (dd, *J* = 13.5, 3.5 Hz), 118.1 (dd, *J* = 24.3, 22.7 Hz), 117.5, 115.8, 112.3 (dd, *J* = 22.6, 3.5 Hz), 53.6, 16.8, 12.6. ESI-HRMS: m/z = 488.06545, calcd for $C_{23}H_{18}ClF_2N_3O_3S$ m/z = 488.06527 $[M-H]^-$. IR (ATR) [cm^{-1}] 3213, 2856, 1649, 1486, 1399, 1141, 962, 791, 683, 571, 504.

***N*-(3-(5-(2-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (31).** Compound **31** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), (2-chlorophenyl)boronic acid (25 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 42 mg, 86 µmol, 66%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.07 (s, 1H), 9.78 (s, 1H), 8.49 (s, 1H), 8.46 (d, *J* = 2.1 Hz, 1H), 8.28 (s, 1H), 7.66 – 7.54 (m, 3H), 7.52 – 7.43 (m, 2H), 7.28 (t, *J* = 8.7 Hz, 1H), 3.16 – 3.08 (m, 2H), 1.80 – 1.68 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 7.1 Hz), 152.3 (dd, *J* = 249.6, 8.5 Hz), 148.6, 145.4, 138.7, 137.3, 132.0, 131.8, 129.8, 129.8, 129.7, 129.6, 128.7 (d, *J* = 8.4 Hz), 127.6, 121.9 (dd, *J* = 13.6, 3.6 Hz), 118.1 (dd, *J* = 24.3, 22.6 Hz), 116.8, 115.6, 112.27 (dd, *J* = 22.7, 3.6 Hz), 53.5, 16.8, 12.5. ESI-HRMS: m/z = 488.06560, calcd for

$C_{23}H_{18}ClF_2N_3O_3S$ m/z = 488.06527 $[M-H]^-$. IR (ATR) [cm^{-1}] 3014, 2856, 1628, 1486, 1403, 1324, 1145, 1020, 762, 496.

***N*-(2,4-difluoro-3-(5-(4-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (32).** Compound **32** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), (4-fluorophenyl)boronic acid (22 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 55 mg, 115 µmol, 88%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.99 (s, 1H), 9.78 (s, 1H), 8.69 (d, *J* = 2.2 Hz, 1H), 8.62 (s, 1H), 8.25 (s, 1H), 7.80 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.59 (td, *J* = 9.0, 5.9 Hz, 1H), 7.35 (t, *J* = 8.8 Hz, 2H), 7.29 (t, *J* = 8.7 Hz, 1H), 3.15 – 3.10 (m, 2H), 1.80 – 1.69 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 161.9 (d, *J* = 244.6 Hz), 156.0 (dd, *J* = 246.4, 6.9 Hz), 152.3 (dd, *J* = 249.6, 8.6 Hz), 148.8, 143.9, 138.6, 134.6 (d, *J* = 3.0 Hz), 130.6, 129.1 (d, *J* = 8.2 Hz), 128.7 (dd, *J* = 10.8, 4.2 Hz), 127.0, 121.9 (dd, *J* = 13.6, 3.6 Hz), 118.1 (dd, *J* = 24.4, 22.6 Hz), 117.4, 115.9 (d, *J* = 21.4 Hz), 115.6, 112.2 (dd, *J* = 22.9, 3.2 Hz), 53.5, 16.8, 12.5. ESI-HRMS: m/z = 472.09507, calcd for $C_{23}H_{18}F_3N_3O_3S$ m/z = 472.09482 $[M-H]^-$. IR (ATR) [cm^{-1}] 3022, 2851, 2714, 1632, 1478, 1328, 1149, 1016, 833, 716, 504.

***N*-(2,4-difluoro-3-(5-(3-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (33).** Compound **33** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (3-fluorophenyl)boronic acid (44 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 55 mg, 115 µmol, 44%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 13.03 (s, 1H), 9.77 (s, 1H), 8.74 (d, *J* = 2.2 Hz, 1H), 8.66 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 7.65 – 7.54 (m, 4H), 7.29 (t, *J* = 8.7 Hz, 1H), 7.25 (td, *J* = 8.7, 2.2 Hz, 1H), 3.14 – 3.11 (m, 2H), 1.79 – 1.66 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.7, 162.7 (d, *J* = 243.7 Hz),

156.0 (dd, *J* = 246.5, 7.4 Hz), 152.4 (dd, *J* = 249.4, 8.9 Hz), 149.1, 144.2, 140.7 (d, *J* = 8.3 Hz), 139.0, 131.1 (d, *J* = 8.9 Hz), 130.2 (d, *J* = 2.5 Hz), 128.8 (d, *J* = 10.5 Hz), 127.3, 123.3 (d, *J* = 2.9 Hz), 121.9 (dd, *J* = 14.0, 3.9 Hz), 118.1 (dd, *J* = 25.4, 22.6 Hz), 117.5, 115.7, 114.3 (d, *J* = 21.2 Hz), 113.9 (d, *J* = 22.4 Hz), 112.4 (dd, *J* = 23.1, 4.2 Hz), 53.5, 16.8, 12.6. ESI-HRMS: m/z = 472.09498, calcd for $C_{23}H_{18}F_3N_3O_3S$ m/z = 472.09482 $[M-H]^-$. IR (ATR) [cm^{-1}] 3222, 1640, 1586, 1478, 1399, 1141, 958, 779, 500.

***N*-(2,4-difluoro-3-(5-(2-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (34).** Compound **34** was prepared following **general procedure A** using **78** (100 mg, 218 µmol, 1.0 eq.), (2-fluorophenyl)boronic acid (37 mg, 262 µmol, 1.2 eq.), K_2CO_3 (60 mg, 436 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (25 mg, 22 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 31 mg, 66 µmol, 30%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.06 (s, 1H), 9.78 (s, 1H), 8.59 (s, 2H), 8.27 (s, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.59 (dd, *J* = 14.7, 8.8 Hz, 1H), 7.49 (dd, *J* = 12.3, 6.3 Hz, 1H), 7.38 (dd, *J* = 16.4, 8.7 Hz, 2H), 7.29 (t, *J* = 8.5 Hz, 1H), 3.18 – 3.07 (m, 2H), 1.74 (dq, *J* = 14.1, 7.0 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 181.1, 159.5 (d, *J* = 245.4 Hz), 156.3 (dd, *J* = 246.5, 7.2 Hz), 152.6 (dd, *J* = 250.1, 8.2 Hz), 148.9, 145.4 (d, *J* = 1.6 Hz), 138.9, 131.4 (d, *J* = 2.8 Hz), 130.3 (d, *J* = 8.1 Hz), 129.6 (d, *J* = 2.8 Hz), 129.2 (d, *J* = 9.1 Hz), 126.6, 126.0 (d, *J* = 13.5 Hz), 125.5 (d, *J* = 3.3 Hz), 122.1 (dd, *J* = 13.3, 3.6 Hz), 118.3 (dd, *J* = 24.4, 22.6 Hz), 117.4, 116.4 (d, *J* = 22.3 Hz), 115.9, 112.6 (dd, *J* = 22.8, 3.1 Hz), 53.9, 17.0, 12.8. ESI-HRMS: m/z = 472.09558, calcd for $C_{23}H_{18}F_3N_3O_3S$ m/z = 472.09482 $[M-H]^-$. IR (ATR) [cm^{-1}] 3238, 1648, 1490, 1411, 1323, 1149, 965, 820, 753, 707, 553, 499.

***N*-(2,4-difluoro-3-(5-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (35).** Compound **35** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (*p*-tolyl)boronic acid (42 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2,

DCM/MeOH 100/0 - 97/3, v/v). Yield: 73 mg, 156 µmol, 60%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.97 (s, 1H), 9.76 (s, 1H), 8.68 (d, *J* = 2.2 Hz, 1H), 8.59 (s, 1H), 8.22 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.59 (td, *J* = 9.0, 5.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 8.5 Hz, 1H), 3.14 – 3.10 (m, 2H), 2.37 (s, 3H), 1.78 – 1.70 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 7.3 Hz), 152.3 (dd, *J* = 249.1, 9.2 Hz), 148.8, 143.9, 138.7, 136.9, 135.2, 131.5, 129.8, 128.8 (dd, *J* = 15.8, 4.2 Hz), 127.0, 126.7, 121.9 (dd, *J* = 14.1, 4.0 Hz), 118.2 (dd, *J* = 24.7, 22.8 Hz), 117.5, 115.6, 112.3 (dd, *J* = 23.0, 4.1 Hz), 53.5, 20.7, 16.8, 12.6. ESI-HRMS: m/z = 468.12022, calcd for $C_{24}H_{21}F_2N_3O_3S$ m/z = 468.11989 $[M-H]^-$. IR (ATR) [cm^{-1}] 3234, 1640, 1482, 1395, 1149, 958, 812, 517.

***N*-(2,4-difluoro-3-(5-(*m*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (36).** Compound **36** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (*m*-tolyl)boronic acid (43 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 57 mg, 121 µmol, 46%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.98 (d, *J* = 1.8 Hz, 1H), 9.77 (s, 1H), 8.69 (d, *J* = 2.2 Hz, 1H), 8.61 (s, 1H), 8.23 (d, *J* = 2.5 Hz, 1H), 7.64 – 7.51 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 3.14 – 3.10 (m, 2H), 2.42 (s, 3H), 1.78 – 1.71 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.6, 7.2 Hz), 152.3 (dd, *J* = 249.3, 9.0 Hz), 148.9, 144.0, 138.8, 138.4, 138.1, 131.7, 129.1, 128.8 (dd, *J* = 11.7, 3.5 Hz), 128.2, 127.8, 127.0, 124.3, 121.9 (dd, *J* = 14.0, 3.9 Hz), 118.2 (dd, *J* = 25.4, 22.9 Hz), 117.5, 115.7, 112.4 (dd, *J* = 23.0, 4.2 Hz), 53.5, 21.1, 16.8, 12.60. ESI-HRMS: m/z = 468.12020, calcd for $C_{24}H_{21}F_2N_3O_3S$ m/z = 468.11989 $[M-H]^-$. IR (ATR) [cm^{-1}] 3218, 1619, 1595, 1403, 1332, 1145, 837, 783, 708, 512.

***N*-(2,4-difluoro-3-(5-(*o*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (37).** Compound **37** was prepared following **general procedure A** using **78**

(120 mg, 262 µmol, 1.0 eq.), (*o*-tolyl)boronic acid (43 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 75 mg, 160 µmol, 61%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 13.00 (d, *J* = 2.0 Hz, 1H), 9.76 (s, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 8.35 (s, 1H), 8.24 (d, *J* = 2.7 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.37 – 7.30 (m, 4H), 7.28 (t, *J* = 8.5 Hz, 1H), 3.15 – 3.06 (m, 2H), 2.26 (s, 3H), 1.78 – 1.69 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.8, 7.3 Hz), 152.3 (dd, *J* = 249.4, 9.1 Hz), 148.4, 145.4, 138.6, 138.6, 135.3, 132.2, 130.4, 130.2, 129.2, 128.8 (d, *J* = 12.1 Hz), 127.8, 126.2, 121.9 (dd, *J* = 14.0, 4.0 Hz), 118.2 (dd, *J* = 25.3, 23.2 Hz), 117.0, 115.6, 112.3 (dd, *J* = 23.0, 3.9 Hz), 53.5, 20.2, 16.8, 12.6. ESI-HRMS: m/z = 468.12014, calcd for $C_{24}H_{21}F_2N_3O_3S$ m/z = 468.11989 $[M-H]^-$. IR (ATR) [cm^{-1}] 1649, 1478, 1436, 1407, 1324, 1145, 983, 654, 504.

***N*-(2,4-difluoro-3-(5-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (38).** Compound **38** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), (4-methoxyphenyl)boronic acid (23 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 23 mg, 47 µmol, 36%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.96 (s, 1H), 9.78 (s, 1H), 8.67 (d, *J* = 1.7 Hz, 1H), 8.57 (s, 1H), 8.21 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.59 (dd, *J* = 14.8, 8.9 Hz, 1H), 7.28 (t, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 3.19 – 3.06 (m, 2H), 1.74 (dq, *J* = 14.7, 7.2 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.5, 159.0, 156.0 (dd, *J* = 246.6, 6.9 Hz), 152.4 (dd, *J* = 258.5, 8.9 Hz), 148.5, 143.7, 138.4, 131.3, 130.4, 128.7 (d, *J* = 8.7 Hz), 128.2, 126.4, 121.9 (dd, *J* = 13.1, 3.6 Hz), 118.2 (dd, *J* = 25.0, 23.0 Hz), 117.5, 115.6, 114.6, 112.2 (dd, *J* = 22.5, 3.3 Hz), 55.2, 53.5, 16.74, 12.5. ESI-HRMS: m/z = 484.11573, calcd for $C_{24}H_{21}F_2N_3O_4S$ m/z = 484.11481 $[M-H]^-$

. IR (ATR) [cm^{-1}] 2960, 2835, 1632, 1499, 1474, 1336, 1249, 1140, 979, 891, 812, 708, 554, 496.

***N*-(2,4-difluoro-3-(5-(3-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (39).** Compound **39** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (3-methoxyphenyl)boronic acid (48 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 72 mg, 149 µmol, 57%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 13.00 (s, 1H), 9.77 (s, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.61 (s, 1H), 8.24 (s, 1H), 7.59 (td, *J* = 9.0, 5.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.25 (m, 3H), 6.99 (ddd, *J* = 8.2, 2.4, 0.6 Hz, 1H), 3.86 (s, 3H), 3.15 – 3.10 (m, 2H), 1.77 – 1.70 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.6, 159.9, 156.0 (dd, *J* = 246.5, 7.3 Hz), 152.3 (dd, *J* = 249.4, 8.9 Hz), 149.0, 144.2, 139.7, 138.8, 131.5, 130.3, 128.8 (d, *J* = 11.5 Hz), 127.1, 121.9 (dd, *J* = 14.1, 3.8 Hz), 119.5, 118.2 (dd, *J* = 25.0, 22.6 Hz), 117.4, 115.7, 113.3, 112.6, 112.3 (dd, *J* = 22.7, 3.9 Hz), 55.2, 53.5, 16.8, 12.6. ESI-HRMS: m/z = 484.11526, calcd for $C_{24}H_{21}F_2N_3O_4S$ m/z = 484.11481 $[M-H]^-$. IR (ATR) [cm^{-1}] 3222, 1640, 1586, 1482, 1303, 1137, 966, 820, 783, 691, 596, 554, 496.

***N*-(2,4-difluoro-3-(5-(2-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (40).** Compound **40** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (2-methoxyphenyl)boronic acid (48 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 72 mg, 148 µmol, 57%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.94 (s, 1H), 9.76 (s, 1H), 8.48 (d, *J* = 1.8 Hz, 2H), 8.21 (s, 1H), 7.64 – 7.52 (m, 3H), 7.43 – 7.37 (m, 2H), 7.28 (t, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.09 (td, *J* = 7.4, 0.8 Hz, 1H), 3.80 (s, 3H), 3.14 – 3.08 (m, 2H), 1.77 – 1.70 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ESI-HRMS: m/z = 484.11495, calcd

for $C_{24}H_{21}F_2N_3O_4S$ m/z = 484.11481 $[M-H]^-$. IR (ATR) [cm^{-1}] 1632, 1482, 1407, 1328, 1245, 1141, 1024, 887, 754, 542, 492.

***N*-(2,4-difluoro-3-(5-(4-fluoro-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (41).** Compound **41** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), (4-fluoro-2-methylphenyl)boronic acid (24 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 47 mg, 96 µmol, 73%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (s, 1H), 9.78 (s, 1H), 8.37 (d, *J* = 1.6 Hz, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 7.58 (td, *J* = 8.9, 6.1 Hz, 1H), 7.35 (dd, *J* = 8.3, 6.2 Hz, 1H), 7.28 (t, *J* = 8.7 Hz, 1H), 7.23 (dd, *J* = 10.1, 2.4 Hz, 1H), 7.14 (td, *J* = 8.5, 2.5 Hz, 1H), 3.16 – 3.09 (m, 2H), 2.26 (s, 3H), 1.80 – 1.69 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 161.6 (d, *J* = 244.0 Hz), 156.0 (dd, *J* = 246.4, 6.9 Hz), 152.3 (dd, *J* = 249.5, 8.5 Hz), 148.4, 145.4, 138.5, 138.2 (d, *J* = 8.1 Hz), 134.9 (d, *J* = 2.9 Hz), 132.0 (d, *J* = 8.5 Hz), 131.2, 129.3, 128.7 (d, *J* = 9.8 Hz), 121.9 (dd, *J* = 13.6, 3.5 Hz), 118.1 (dd, *J* = 24.6, 22.3 Hz), 117.0, 116.73 (d, *J* = 21.1 Hz), 115.5, 112.7 (d, *J* = 20.9 Hz), 112.2 (dd, *J* = 22.7, 3.5 Hz), 53.5, 20.2, 16.8, 12.5. ESI-HRMS: m/z = 486.11076, calcd for $C_{24}H_{20}F_3N_3O_3S$ m/z = 486.11047 $[M-H]^-$. IR (ATR) [cm^{-1}] 3076, 2843, 1640, 1482, 1328, 1141, 974, 704, 492.

***N*-(3-(5-(2,4-difluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (42).** Compound **42** was prepared following **general procedure A** using **78** (100 mg, 218 µmol, 1.0 eq.), (2,4-difluorophenyl)boronic acid (41 mg, 262 µmol, 1.2 eq.), K_2CO_3 (60 mg, 436 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (25 mg, 22 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 50 mg, 101 µmol, 46%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.07 (s, 1H), 9.78 (s, 1H), 8.57 (s, 1H), 8.55 (s, 1H), 8.28 (d, *J* = 1.6 Hz, 1H), 7.73 (dd, *J* = 15.5, 8.7 Hz, 1H), 7.59 (td, *J* = 8.9, 6.1 Hz, 1H), 7.48 – 7.39 (m, 1H), 7.32 – 7.21 (m, 2H), 3.17 – 3.06 (m, 2H), 1.80 – 1.67

(m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 181.1, 162.2 (dd, *J* = 247.2, 12.3 Hz), 159.5 (dd, *J* = 248.3, 12.3 Hz), 156.3 (dd, *J* = 246.8, 7.0 Hz), 152.7 (dd, *J* = 250.0, 8.9 Hz), 148.9, 145.4 (d, *J* = 2.1 Hz), 138.9, 132.5 (dd, *J* = 9.7, 4.5 Hz), 129.6 (d, *J* = 2.5 Hz), 129.2 (d, *J* = 9.8 Hz), 125.8 (d, *J* = 0.9 Hz), 122.7 (dd, *J* = 13.7, 3.7 Hz), 122.1 (dd, *J* = 13.5, 3.5 Hz), 118.3 (dd, *J* = 24.2, 22.4 Hz), 117.4, 115.9, 112.6 (dd, *J* = 22.8, 3.5 Hz), 112.5 (dd, *J* = 21.2, 3.7 Hz), 105.2 – 104.1 (m), 53.9, 17.0, 12.8. ESI-HRMS: m/z = 490.08580, calcd for $C_{23}H_{17}F_4N_3O_3S$ m/z = 490.08540 $[M-H]^-$. IR (ATR) [cm^{-1}] 3263, 1644, 1490, 1461, 1403, 1320, 1137, 966, 820, 704, 612, 504.

***N*-(3-(5-(2-chloro-4-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (43).** Compound **43** was prepared following **general procedure A** using **78** (80 mg, 175 µmol, 1.0 eq.), (2-chloro-4-fluorophenyl)boronic acid (37 mg, 210 µmol, 1.2 eq.), K_2CO_3 (48 mg, 350 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (21 mg, 18 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 36 mg, 71 µmol, 41%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.07 (s, 1H), 9.77 (s, 1H), 8.47 (s, 1H), 8.43 (d, *J* = 1.2 Hz, 1H), 8.27 (s, 1H), 7.64 – 7.52 (m, 3H), 7.36 (td, *J* = 8.4, 2.0 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 1H), 3.18 – 3.04 (m, 2H), 1.74 (dq, *J* = 14.6, 7.2 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.7, 161.5 (d, *J* = 248.3 Hz), 156.0 (dd, *J* = 246.7, 6.8 Hz), 152.3 (dd, *J* = 249.8, 8.5 Hz), 148.7, 145.5, 138.7, 133.9 (d, *J* = 3.5 Hz), 133.3 (d, *J* = 9.0 Hz), 131.5 (d, *J* = 9.7 Hz), 129.8, 128.8, 128.8 – 128.7 (m), 122.0 (dd, *J* = 13.5, 3.3 Hz), 118.1 (dd, *J* = 24.2, 22.2 Hz), 117.0 (d, *J* = 25.1 Hz), 116.8, 115.6, 114.8 (d, *J* = 21.0 Hz), 112.3 (dd, *J* = 23.1, 3.1 Hz), 53.6, 16.8, 12.6. ESI-HRMS: m/z = 506.05592, calcd for $C_{23}H_{17}ClF_3N_3O_3S$ m/z = 506.05585 $[M-H]^-$. IR (ATR) [cm^{-1}] 3101, 2872, 1628, 1482, 1411, 1320, 1149, 887, 704, 537, 500.

***N*-(2,4-difluoro-3-(5-(4-methoxy-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (44).** Compound **44** was prepared following **general procedure A** using **78** (80 mg, 175 µmol, 1.0 eq.), (4-methoxy-2-

methylphenyl)boronic acid (35 mg, 210 µmol, 1.2 eq.), K_2CO_3 (48 mg, 350 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (21 mg, 18 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 50 mg, 96 µmol, 55%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.97 (s, 1H), 9.76 (s, 1H), 8.35 (d, *J* = 1.9 Hz, 1H), 8.31 (s, 1H), 8.22 (s, 1H), 7.58 (td, *J* = 9.0, 6.0 Hz, 1H), 7.27 (t, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.80 (s, 3H), 3.15 – 3.08 (m, 2H), 2.24 (s, 3H), 1.81 – 1.67 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.5, 158.7, 155.9 (dd, *J* = 246.5, 6.7 Hz), 152.2 (dd, *J* = 249.4, 8.4 Hz), 148.1, 145.5, 138.2, 136.6, 131.9, 131.2, 130.9, 129.1, 128.7 – 128.4 (m), 121.9 (dd, *J* = 13.7, 3.5 Hz), 118.2 (dd, *J* = 24.5, 22.5 Hz), 116.9, 115.7, 115.5, 112.2 (dd, *J* = 22.8, 3.6 Hz), 111.5, 55.0, 53.5, 20.3, 16.7, 12.5. ESI-HRMS: m/z = 498.13048, calcd for $C_{25}H_{23}F_2N_3O_4S$ m/z = 498.13046 $[M-H]^-$. IR (ATR) [cm^{-1}] 1636, 1478, 1407, 1328, 1245, 1153, 966, 841, 712, 621, 500.

***N*-(2,4-difluoro-3-(5-(2-fluoro-4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (45).** Compound **45** was prepared following **general procedure A** using **78** (80 mg, 175 µmol, 1.0 eq.), (2-fluoro-4-methoxyphenyl)boronic acid (36 mg, 210 µmol, 1.2 eq.), K_2CO_3 (48 mg, 350 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (21 mg, 18 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 42 mg, 84 µmol, 48%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.90 (s, 1H), 9.75 (s, 1H), 8.46 (s, 2H), 8.09 (s, 1H), 7.54 (td, *J* = 9.0, 5.9 Hz, 1H), 7.47 (t, *J* = 8.9 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 1H), 6.90 (dd, *J* = 22.0, 2.4 Hz, 1H), 6.90 (s, 1H), 3.77 (s, 3H), 3.07 – 3.04 (m, 2H), 1.77 – 1.57 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 181.9, 161.2 (d, *J* = 11.5 Hz), 160.5 (d, *J* = 245.4 Hz), 156.9 (dd, *J* = 247.6, 7.2 Hz), 153.2 (dd, *J* = 249.9, 8.9 Hz), 148.9, 145.8, 132.2 (d, *J* = 5.5 Hz), 130.0 (dd, *J* = 25.1, 13.9 Hz), 127.3, 122.4 (dd, *J* = 13.8, 3.8 Hz), 118.9 – 118.5 (m), 118.4 (d, *J* = 14.0 Hz), 118.02, 116.3, 113.4 – 113.0 (m), 112.0 (d, *J* = 3.2 Hz), 102.9, 102.8, 56.5, 54.4, 17.5, 13.3.

ESI-HRMS: m/z = 502.10560, calcd for $C_{24}H_{20}F_3N_3O_4S$ m/z = 502.10539 $[M-H]^-$. IR (ATR) [cm^{-1}] 3238, 2968, 2843, 1640, 1624, 1478, 1312, 1149, 970, 812, 567, 496.

***N*-(3-(5-(2-chloro-4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (46).** Compound **46** was prepared following **general procedure A** using **78** (80 mg, 175 µmol, 1.0 eq.), (2-chloro-4-methoxyphenyl)boronic acid (39 mg, 210 µmol, 1.2 eq.), K_2CO_3 (48 mg, 350 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (21 mg, 18 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 53 mg, 102 µmol, 58%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.01 (s, 1H), 9.75 (s, 1H), 8.44 (s, 1H), 8.41 (s, 1H), 8.23 (s, 1H), 7.58 (dd, *J* = 14.7, 8.7 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.27 (t, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.85 (s, 3H), 3.15 – 3.08 (m, 2H), 1.80 – 1.68 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 159.6, 156.0 (dd, *J* = 246.5, 6.8 Hz), 152.3 (dd, *J* = 249.3, 9.2 Hz), 148.4, 145.6, 138.5, 132.6, 132.4, 129.7, 129.7, 129.5, 128.8 – 128.6 (m), 121.9 (dd, *J* = 13.5, 3.8 Hz), 118.5 – 117.8 (m), 116.8, 115.6, 115.1, 113.8, 112.3 (dd, *J* = 22.8, 3.8 Hz), 55.7, 53.6, 16.8, 12.5. ESI-HRMS: m/z = 518.07571, calcd for $C_{24}H_{20}ClF_2N_3O_4S$ m/z = 518.07583 $[M-H]^-$. IR (ATR) [cm^{-1}] 3197, 6109, 2976, 2839, 1628, 1486, 1457, 1403, 1149, 1020, 712, 508, 562.

***N*-(3-(5-(3,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (47).** Compound **47** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (3,4-dimethoxyphenyl)boronic acid (57 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 100 mg, 187 µmol, 72%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.96 (s, 1H), 9.76 (s, 1H), 8.70 (d, *J* = 2.2 Hz, 1H), 8.55 (s, 1H), 8.21 (s, 1H), 7.59 (td, *J* = 9.0, 6.0 Hz, 1H), 7.31 – 7.24 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.14 – 3.10 (m, 2H), 1.80 – 1.63 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 180.6, 156.0 (dd, *J* =

246.5, 7.8 Hz), 152.3 (dd, *J* = 249.3, 8.9 Hz), 149.3, 148.6, 148.6, 144.0, 138.6, 131.6, 130.9, 128.8 (d, *J* = 12.1 Hz), 126.6, 121.9 (dd, *J* = 14.0, 4.0 Hz), 119.4, 118.3 (dd, *J* = 25.5, 23.5 Hz), 117.5, 115.6, 112.4, 112.3 (d, *J* = 3.7 Hz), 110.8, 55.7, 55.6, 53.5, 16.8, 12.6. ESI-HRMS: m/z = 514.12541, calcd for $C_{25}H_{23}F_2N_3O_5S$ m/z = 514.12537 $[M-H]^-$. IR (ATR) [cm^{-1}] 3263, 1649, 1486, 1403, 1245, 1145, 991, 887, 829, 562, 496.

***N*-(3-(5-(2,4-dimethoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (48).** Compound **48** was prepared following **general procedure A** using **78** (120 mg, 262 µmol, 1.0 eq.), (2,4-dimethoxyphenyl)boronic acid (57 mg, 314 µmol, 1.2 eq.), K_2CO_3 (72 mg, 524 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 26 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 98 mg, 191 µmol, 73%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.90 (s, 1H), 9.76 (s, 1H), 8.43 (d, *J* = 2.0 Hz, 2H), 8.18 (d, *J* = 1.2 Hz, 1H), 7.58 (td, *J* = 9.0, 5.9 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.13 – 3.08 (m, 2H), 1.77 – 1.69 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 181.0, 160.9, 157.7, 156.5 (dd, *J* = 246.3, 7.4 Hz), 152.8 (dd, *J* = 248.9, 9.2 Hz), 148.5, 146.3, 138.7, 131.8, 129.6, 129.2 (d, *J* = 23.5 Hz), 129.2, 122.4 (dd, *J* = 14.0, 4.0 Hz), 120.3, 117.4, 116.0, 112.8 (dd, *J* = 22.9, 4.1 Hz), 106.0, 99.5, 56.1, 55.8, 53.9, 17.3, 13.1. ESI-HRMS: m/z = 514,12583, calcd for $C_{25}H_{23}F_2N_3O_5S$ m/z = 514.12537 $[M-H]^-$. IR (ATR) [cm^{-1}] 1649, 1486, 1403, 1299, 1141, 1016, 883, 704, 500.

***N*-(3-(5-(benzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (49).** Compound **49** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), benzo[*d*][1,3]dioxol-5-ylboronic acid (26 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 59 mg, 119 µmol, 91%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.96 (s, 1H), 9.77 (s, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.56 (s, 1H), 8.20 (s, 1H), 7.67 – 7.50 (m, 1H), 7.33 (s, 1H), 7.28 (t,

J = 8.7 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 2H), 3.17 – 3.08 (m, 2H), 1.82 – 1.69 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.5, 156.0 (dd, *J* = 246.7, 7.3 Hz), 152.3 (dd, *J* = 249.7, 8.6 Hz), 148.6, 148.1, 147.0, 143.9, 138.4, 132.4, 131.5, 128.6 (d, *J* = 11.8 Hz), 126.8, 122.0 (dd, *J* = 13.8, 3.4 Hz), 120.8, 118.2 (dd, *J* = 24.5, 22.7 Hz), 117.4, 115.7, 112.2 (dd, *J* = 22.8, 3.4 Hz), 108.8, 107.5, 101.2, 53.6, 16.8, 12.5. ESI-HRMS: m/z = 498.09466, calcd for $C_{24}H_{19}F_2N_3O_5S$ m/z = 498.09407 $[M-H]^-$. IR (ATR) [cm^{-1}] 2851, 2722, 1644, 1465, 1411, 1228, 1141, 995, 866, 808, 567, 500.

***N*-(3-(5-(6-chlorobenzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (50).** Compound **50** was prepared following **general procedure A** using **78** (100 mg, 218 µmol, 1.0 eq.), **R35** (74 mg, 262 µmol, 1.2 eq.), K_2CO_3 (60 mg, 436 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (25 mg, 22 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 58 mg, 109 µmol, 50%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (s, 1H), 9.77 (s, 1H), 8.43 (s, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 8.24 (s, 1H), 7.58 (td, *J* = 8.9, 6.0 Hz, 1H), 7.27 (t, *J* = 8.7 Hz, 1H), 7.23 (s, 1H), 7.13 (s, 1H), 6.15 (s, 2H), 3.15 – 3.08 (m, 2H), 1.80 – 1.69 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.7, 7.3 Hz), 152.3 (dd, *J* = 249.5, 8.2 Hz), 148.5, 147.9, 147.0, 145.7, 138.6, 130.5, 130.0, 128.8 (d, *J* = 8.1 Hz), 123.8, 122.0 (dd, *J* = 13.8, 3.4 Hz), 118.1 (dd, *J* = 24.5, 22.7 Hz), 116.8, 115.6, 112.3 (dd, *J* = 23.1, 3.5 Hz), 111.1, 109.9, 102.3, 53.6, 16.8, 12.6. ESI-HRMS: m/z = 532.05513, calcd for $C_{24}H_{18}ClF_2N_3O_5S$ m/z = 532.05510 $[M-H]^-$. IR (ATR) [cm^{-1}] 3093, 2972, 2889, 2718, 1640, 1465, 1416, 1328, 1237, 1141, 1228, 877, 833, 696, 500.

***N*-(3-(5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (51).** Compound **51** was prepared following **general procedure A** using **78** (60 mg, 131 µmol, 1.0 eq.), (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (28 mg, 157 µmol, 1.2 eq.), K_2CO_3 (36 mg, 262 µmol, 2.0 eq.) and

$Pd(PPh_3)_4$ (15 mg, 13 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 60 mg, 117 µmol, 89%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 12.97 (s, 1H), 9.79 (s, 1H), 8.64 (d, *J* = 2.0 Hz, 1H), 8.55 (s, 1H), 8.21 (s, 1H), 7.65 – 7.51 (m, 2H), 7.28 (t, *J* = 8.5 Hz, 1H), 7.24 – 7.16 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.29 (s, 4H), 3.17 – 3.07 (m, 2H), 1.74 (dq, *J* = 14.9, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz, ppm): δ 180.6, 156.0 (dd, *J* = 246.4, 7.1 Hz), 152.4 (dd, *J* = 249.6, 8.3 Hz), 148.6, 143.9, 143.8, 143.3, 138.5, 131.4, 131.2, 128.7 (d, *J* = 11.8 Hz), 126.6, 122.0 (dd, *J* = 13.7, 3.4 Hz), 120.0, 118.24 (dd, *J* = 24.2, 22.1 Hz), 117.8, 117.5, 115.7, 115.6, 112.3 (dd, *J* = 23.0, 3.6 Hz), 64.2, 64.2, 53.6, 16.8, 12.6. ESI-HRMS: m/z = 512.11011, calcd for $C_{25}H_{21}F_2N_3O_5S$ m/z = 512.10972 $[M-H]^-$. IR (ATR) [cm^{-1}] 3010, 2722, 1640, 1482, 1411, 1312, 1245, 1137, 979, 887, 558, 496.

***N*-(3-(5-(7-chloro-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (52).** Compound **52** was prepared following **general procedure A** using **78** (150 mg, 327 µmol, 1.0 eq.), **R39** (116 mg, 393 µmol, 1.2 eq.), K_2CO_3 (90 mg, 654 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (38 mg, 33 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 105 mg, 192 µmol, 59%. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 13.02 (s, 1H), 9.77 (s, 1H), 8.43 (s, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 8.24 (s, 1H), 7.58 (td, *J* = 9.0, 5.9 Hz, 1H), 7.27 (td, *J* = 9.0, 1.3 Hz, 1H), 7.14 (s, 1H), 7.05 (s, 1H), 4.31 (s, 4H), 3.16 – 3.07 (m, 2H), 1.80 – 1.67 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 180.6, 156.0 (dd, *J* = 246.5, 6.9 Hz), 152.3 (dd, *J* = 249.7, 8.4 Hz), 148.5, 145.6, 143.8, 142.7, 138.5, 130.1, 129.8, 129.5, 128.8 (d, *J* = 9.9 Hz), 123.1, 122.0 (dd, *J* = 13.7, 3.7 Hz), 119.7, 118.1 (dd, *J* = 24.8, 22.5 Hz), 117.9, 116.8, 115.6, 112.3 (dd, *J* = 22.5, 3.1 Hz), 64.3, 64.2, 53.6, 16.8, 12.6. ESI-HRMS: m/z = 546.07088, calcd for $C_{25}H_{20}ClF_2N_3O_5S$ m/z = 546.07075 $[M-H]^-$. IR (ATR) [cm^{-1}] 3259, 3084, 2976, 2826, 2722, 1636, 1486, 1461, 1395, 1316, 1137, 1062, 887, 700, 562, 504.

***N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (66).** Compound **66** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0eq.), (4-chlorophenyl)boronic acid (38 mg, 246 µmol, 1.2 eq.), K_2CO_3 (57 mg, 410 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 55 mg, 105 µmol, 52%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 8.70 (d, *J* = 2.2 Hz, 1H), 8.68 (d, *J* = 2.2 Hz, 1H), 8.03 (s, 1H), 7.85 (dd, *J* = 20.1, 8.4 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.51 (td, *J* = 7.9, 1.4 Hz, 1H), 7.39 – 7.31 (m, 5H), 7.24 (t, *J* = 7.8 Hz, 1H), 4.51 (s, 2H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.9, 151.5 (d, *J* = 249.2 Hz), 148.9, 143.6, 138.0, 137.2, 132.4, 131.0, 130.0, 129.8, 129.1, 129.0, 128.9, 128.4, 128.3, 128.1, 127.7, 127.4, 127.3, 124.4 (d, *J* = 3.3 Hz), 118.0, 115.0, 58.2. ESI-HRMS: m/z = 518.07503, calcd for $C_{27}H_{19}ClFN_3O_3S$ m/z = 518.07469 $[M-H]^-$. IR (ATR) [cm^{-1}] 3243, 1644, 1416, 1332, 1278, 1145, 1095, 999, 891, 758, 637, 521.

***N*-(3-(5-(2-chloro-4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (67).** Compound **67** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0eq.), (4-chlorophenyl)boronic acid (38 mg, 246 µmol, 1.2 eq.), K_2CO_3 (57 mg, 410 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 68 mg, 124 µmol, 60%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 8.47 (d, *J* = 2.1 Hz, 1H), 8.38 (d, *J* = 2.1 Hz, 1H), 7.96 (s, 1H), 7.52 (td, *J* = 8.2, 1.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.34 – 7.26 (m, 6H), 7.20 (d, *J* = 2.6 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.97 (t, *J* = 6.0 Hz, 1H), 4.26 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 187.0, 159.5, 151.3 (d, *J* = 246.4 Hz), 148.3, 145.2, 137.3, 132.6, 132.5, 131.5 (d, *J* = 9.7 Hz), 130.8, 130.0, 129.7, 129.2, 128.8, 128.7, 128.0, 127.3, 123.9 (d, *J* = 3.3 Hz), 117.4, 115.1, 115.0, 113.8, 57.3, 55.7. ESI-HRMS: m/z = 548.08563, calcd for $C_{28}H_{21}ClFN_3O_4S$ m/z

= 548.08526 $[M-H]^-$. IR (ATR) [cm^{-1}] 1603, 1457, 1416, 1295, 1216, 1091, 1037, 891, 745, 691, 537, 483.

***N*-(2-fluoro-3-(5-(4-fluoro-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)-1-phenylmethanesulfonamide (68).** Compound **68** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0eq.), (4-fluoro-2-methylphenyl)boronic acid (38 mg, 246 µmol, 1.2 eq.), K_2CO_3 (57 mg, 410 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 67 mg, 130 µmol, 64%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.89 (s, 1H), 9.84 (s, 1H), 8.38 (d, *J* = 1.5 Hz, 1H), 8.35 (d, *J* = 1.5 Hz, 1H), 8.04 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.33 (m, 7H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 10.1, 2.2 Hz, 1H), 7.14 (td, *J* = 8.4, 2.3 Hz, 1H), 4.55 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.7, 161.6 (d, *J* = 243.9 Hz), 151.5 (d, *J* = 249.7 Hz), 148.3, 145.2, 138.3 (d, *J* = 8.1 Hz), 137.8, 135.1 (d, *J* = 2.8 Hz), 132.0 (d, *J* = 8.4 Hz), 131.0, 130.9, 129.6, 129.4, 128.9 (d, *J* = 15.2 Hz), 128.3, 128.3, 126.8, 126.0 (d, *J* = 13.0 Hz), 125.7, 124.5 (d, *J* = 3.7 Hz), 117.5, 116.8 (d, *J* = 21.1 Hz), 114.8, 112.8 (d, *J* = 20.9 Hz), 58.4, 20.3. ESI-HRMS: m/z = 516.12048, calcd for C $C_{28}H_{21}F_2N_3O_3S$ m/z = 516.11989 $[M-H]^-$. IR (ATR) [cm^{-1}] 3176, 3026, 1607, 1507, 1465, 1403, 1345, 1137, 904, 750, 687, 608, 537, 483.

***N*-(3-(5-(6-chlorobenzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (69).** Compound **69** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0eq.), **R35** (69 mg, 246 µmol, 1.2 eq.), K_2CO_3 (57 mg, 410 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 38 mg, 67 µmol, 33%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.91 (s, 1H), 9.84 (s, 1H), 8.47 (d, *J* = 2.1 Hz, 1H), 8.37 (d, *J* = 2.2 Hz, 1H), 8.04 (s, 1H), 7.62 (ddd, *J* = 7.0, 5.6, 4.0 Hz, 1H), 7.50 (td, *J* = 7.9, 1.5 Hz, 1H), 7.40 – 7.33 (m, 5H), 7.28 – 7.24 (m, 2H), 7.13 (s, 1H), 6.15 (s, 2H), 4.55 (s, 2H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 186.2, 152.0 (d, *J* = 249.8 Hz), 148.8, 148.3, 147.4, 145.9,

138.4, 132.0 (d, *J* = 9.8 Hz), 131.5, 131.1, 130.6, 130.2, 129.9, 129.3 (d, *J* = 15.1 Hz), 129.2 (d, *J* = 11.8 Hz), 128.8 128.7, 127.3, 126.5 (d, *J* = 13.0 Hz), 126.2, 125.0 (d, *J* = 3.8 Hz), 124.2, 117.7, 115.4, 111.6, 110.4, 102.8, 58.8. ESI-HRMS: m/z = 562.06520, calcd for $C_{28}H_{19}ClFN_3O_5S$ m/z = 562.06452 $[M-H]^-$. IR (ATR) [cm^{-1}] 3109, 2885, 1624, 1474, 1407, 1332, 1241, 1153, 1037, 887, 745, 696, 537, 479.

***N*-(3-(5-(7-chloro-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (70).** Compound **70** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0eq.), **R39** (73 mg, 246 µmol, 1.2 eq.), K_2CO_3 (57 mg, 410 µmol, 2.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 74 mg, 128 µmol, 62%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.89 (s, 1H), 9.83 (s, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.04 (s, 1H), 7.50 (td, *J* = 7.9, 1.5 Hz, 1H), 7.40 – 7.33 (m, 6H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.04 (s, 1H), 4.55 (s, 2H), 4.32 (s, 4H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.7, 151.5 (d, *J* = 249.7 Hz), 148.3, 145.3, 143.8, 142.7, 137.9, 131.0, 130.1 (d, *J* = 25.8 Hz), 129.3 (d, *J* = 33.2 Hz), 128.9 (d, *J* = 15.2 Hz), 128.3, 128.3, 126.8, 126.2 (d, *J* = 12.9 Hz), 125.6, 124.5 (d, *J* = 4.0 Hz), 123.1, 119.7, 117.9, 117.3, 114.9, 64.3, 64.1, 58.3. ESI-HRMS: m/z = 576,08059, calcd for $C_{29}H_{21}ClFN_3O_5S$ m/z = 576,08017 $[M-H]^-$. IR (ATR) [cm^{-1}] 3018, 2885, 1628, 1574, 1511, 1470, 1307, 1278, 1149, 1053, 887, 745, 700, 529.

***N*-(2-fluoro-3-(5-(pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)-1-phenylmethanesulfonamide (71).** Compound **71** was prepared following **general procedure A** using **84** (100 mg, 205 µmol, 1.0 eq.), pyridine-4-ylboronic acid (38 mg, 307 µmol, 1.5 eq.), K2CO3 (57 mg, 410 µmol, 2.0 eq.) and Pd XPhos G3 (17 mg, 21 µmol, 10 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 93/7, v/v). Yield: 55 mg, 112 µmol, 55%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.99 (s, 1H), 9.86 (s, 1H), 8.83 (d, *J* = 2.3 Hz, 1H), 8.82 (d, *J* = 2.3 Hz, 1H), 8.68 (dd, *J* = 4.5, 1.6 Hz, 2H), 8.08 (s, 1H), 7.82 (dd, *J* = 4.5, 1.6 Hz,

2H), 7.51 (td, *J* = 7.9, 1.5 Hz, 1H), 7.42 – 7.34 (m, 6H), 7.28 (t, *J* = 7.8 Hz, 1H), 4.56 (s, 2H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.7, 151.5 (d, *J* = 249.9 Hz), 150.3, 149.6, 145.4, 143.8, 138.3, 131.0, 129.4, 128.8 (d, *J* = 15.1 Hz), 128.4, 128.3, 128.2, 127.7, 127.0, 126.0 (d, *J* = 13.0 Hz), 125.8, 124.6 (d, *J* = 3.9 Hz), 121.6, 118.0, 115.1, 58.4. ESI-HRMS: m/z = 485.10931, calcd for $C_{26}H_{19}FN_4O_3S$ m/z = 485.10891 $[M-H]^-$. IR (ATR) [cm^{-1}] 3326, 1599, 1515, 1411, 1332, 1149, 891, 762, 696, 537.

***N*-(2-fluoro-3-(5-(pyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)-1-phenylmethanesulfonamide (72).** Compound **72** was prepared following **general procedure C** using **86** (150 mg, 212 µmol, 1.0 eq.), 3-bromopyridine (37 mg, 233 µmol, 1.1 eq.), K_2CO_3 (59 mg, 424 µmol, 2.0 eq.) and Pd(dppf)Cl_2 (10 mg, 13 µmol, 6 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 93/7, v/v). Yield: 41 mg, 84 µmol, 40%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.95 (s, 1H), 9.85 (s, 1H), 8.97 (d, *J* = 1.9 Hz, 1H), 8.75 (d, *J* = 2.2 Hz, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.63 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.20 – 8.16 (m, 1H), 8.07 (d, *J* = 1.3 Hz, 1H), 7.55 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.51 (td, *J* = 7.9, 1.4 Hz, 1H), 7.41 – 7.37 (m, 3H), 7.37 – 7.34 (m, 3H), 7.28 (t, *J* = 7.8 Hz, 1H), 4.56 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 Hz, ppm): δ 185.7, 151.5 (d, *J* = 249.6 Hz), 149.0, 148.6, 147.9, 143.8, 138.1, 134.7, 134.0, 131.0, 129.4, 128.9 (d, *J* = 15.4 Hz), 128.4, 128.3 (d, *J* = 6.6 Hz), 127.7, 126.9, 126.0 (d, *J* = 13.4 Hz), 125.7 (d, *J* = 2.6 Hz), 124.6 (d, *J* = 4.7 Hz), 124.0, 118.0, 115.0, 58.4. ESI-HRMS: m/z = 485.10973, calcd for $C_{26}H_{19}FN_4O_3S$ m/z = 485.10891 $[M-H]^-$. IR (ATR) [cm^{-1}] 3025, 2883, 2819, 1643, 1494, 1416, 1338, 1136, 895, 743, 697, 534.

***N*-(2-fluoro-3-(5-(2-methoxypyrimidin-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)phenyl)-1-phenylmethanesulfonamide (73).** Compound **73** was prepared following **general procedure C** using **86** (200 mg, 282 µmol, 1.0 eq.), 5-bromo-2-chloropyrimidine (60 mg, 310 µmol, 1.1 eq.), K_2CO_3 (78 mg, 564 µmol, 2.0 eq.) and Pd(dppf)Cl_2 (12 mg, 17 µmol, 6 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 43 mg, 83 µmol, 29%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ

12.94 (d, *J* = 1.9 Hz, 1H), 9.84 (s, 1H), 9.00 (s, 2H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.06 (d, *J* = 1.9 Hz, 1H), 7.51 (td, *J* = 7.9, 1.4 Hz, 1H), 7.41 – 7.37 (m, 3H), 7.37 – 7.34 (m, 3H), 7.27 (t, *J* = 7.8 Hz, 1H), 4.56 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.6, 164.6, 157.7, 151.5 (d, *J* = 249.5 Hz), 149.0, 143.5, 138.1, 131.0, 129.4, 128.9 (d, *J* = 15.6 Hz), 128.3, 128.3, 127.3, 127.0, 126.0, 126.0 (d, *J* = 13.9 Hz), 125.7 (d, *J* = 2.6 Hz), 125.2, 124.6 (d, *J* = 4.6 Hz), 118.0, 115.0, 58.4, 54.8. ESI-HRMS: m/z = 516.11531, calcd for $C_{26}H_{20}FN_5O_4S$ m/z = 516.11473 $[M-H]^-$. IR (ATR) [cm^{-1}] 3121, 3027, 2900, 1605, 1499, 1466, 1413, 1339, 1155, 877, 743, 698, 604.

***N*-(3-(5-(2-cyclopropylpyrimidin-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2-fluorophenyl)-1-phenylmethanesulfonamide (74).** Compound **74** was prepared following **general procedure C** using **86** (300 mg, 424 µmol, 1.0 eq.), 5-bromo-2-cyclopropylpyrimidine (93 mg, 466 µmol, 1.1 eq.), K_2CO_3 (117 mg, 848 µmol, 2.0 eq.) and Pd(dppf)Cl_2 (19 mg, 25 µmol, 6 mol%). Flash chromatography (SiO_2, DCM/MeOH 100/0 - 97/3, v/v). Yield: 115 mg, 218 µmol, 52%. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 12.96 (s, 1H), 9.85 (s, 1H), 9.02 (s, 2H), 8.74 (d, *J* = 2.2 Hz, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 1.1 Hz, 1H), 7.51 (td, *J* = 7.9, 1.4 Hz, 1H), 7.41 – 7.37 (m, 3H), 7.37 – 7.34 (m, 3H), 7.27 (t, *J* = 7.8 Hz, 1H), 4.56 (s, 2H), 2.28 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.12 – 1.08 (m, 2H), 1.08 – 1.05 (m, 2H). ^{13}C NMR (DMSO-d_6, 151 Hz, ppm): δ 185.6, 169.9, 155.0, 151.5 (d, *J* = 249.5 Hz), 149.1, 143.6, 138.1, 131.0, 129.4, 128.9 (d, *J* = 15.4 Hz), 128.6, 128.4, 128.3, 127.5, 127.0, 126.0 (d, *J* = 13.4 Hz), 125.7 (d, *J* = 2.2 Hz), 125.4, 124.6 (d, *J* = 4.7 Hz), 118.0, 115.0, 58.4, 17.7, 10.5. ESI-HRMS: m/z = 526.13647, calcd for $C_{28}H_{22}FN_5O_3S$ m/z = 526.13546 $[M-H]^-$. IR (ATR) [cm^{-1}] 3219, 2819, 2721, 1634, 1458, 1413, 1319, 1204, 902, 747, 694, 538.

Supporting Information. Synthesis of intermediates **R1** – **R49**, information of synthesis of final compounds **1**, **2**, **53** – **64** and results from scanEDGE assay

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Funding Sources

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's excellence strategy – EXC 2180 – 390900677 [Image Guided and Functionally Instructed Tumour Therapies" (iFIT)]

Notes

Compounds were tested for PAINS with the ZINC15 database and neither PAINS nor aggregators were identified [24].

ACKNOWLEDGMENT

We thank Kristine Schmidt for editing and language check services.

ABBREVIATIONS

MAPK, mitogen-activated protein kinase; MKK4, mitogen-activated protein kinase kinase 4; shRNA, short hairpin RNA; ASK1, signaling through apoptosis signal-regulating kinase 1; MKK7, mitogen-activated protein kinase kinase 7; JNK1, c-Jun-N-terminal kinase 1; ELK1, ETS transcription factor; ATF2, activating transcription factor 2; MAP4K5, mitogen-activated protein kinase kinase kinase kinase 5, ZAK, sterile alpha motif and leucine zipper-containing kinase; NAFLD, non-alcoholic liver diseases; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; POC, percentage of control; n.d., not determined; DMF, N,N-

dimethylformamide; DCM, dichloromethane; TEA, triethylamine; RT, room temperature; THF, tetrahydrofuran; EtOAc, ethylacetate; 4-DMAP, 4-dimethylaminopyridine.

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HIGHLIGHTS.

- MKK4 is a major driver in hepatocyte regeneration process.
- Silencing MKK4 induces proliferation and regeneration of hepatocytes.
- Novel strategy for the treatment of liver related diseases using MKK4 inhibitors.
- Optimization and synthesis of highly affine and selective compounds for MKK4.

Declaration of interests

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

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

SL is stock owner <3% of Heparegenix GmbH.
However this relationship has not influenced any work related to this manuscript.