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Design and synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines targeting mitogen-activated protein kinase kinase 4 (MKK4) - A promising target for liver regeneration

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A B S T R A C T

Currently, the therapeutic options for treatment of liver failure are very limited. As mitogen-activated protein kinase kinase 4 (MKK4) has recently been identified by *in vivo* RNAi experiments to be a major regulator in hepatocyte regeneration, we pursued the development of a small molecule targeting this protein kinase. Starting from the approved BRAF^{V600E} inhibitor vemurafenib (**8**), that showed a high off-target affinity to MKK4 in an initial screening, we followed a scaffold-hopping approach, changing the core heterocycle from 1*H*-pyrrolo[2,3-*b*]pyridine to 1*H*-pyrazolo[2,3-*b*]pyridine (**10**). Affinity to MKK4 could be conserved while the selectivity against off-target protein kinases was slightly improved. Further modifications led to **58** and **59** showing high affinity to MKK4 in the low nanomolar range and excellent selectivity profile from mandatory multiparameter-optimization for the essential anti-targets (MKK7, JNK1) and off-targets (BRAF, MAP4K5, ZAK) in the MKK4 pathway. Herein we report the first selective MKK4 inhibitors in this class.

1. Introduction

About 1 million deaths per year are associated with chronic or acute liver failure with main causes being viral infections (hepatitis B/C), non-alcoholic fatty liver disease (NAFLD) or metabolic syndrome. Since there is no medical treatment for liver failure currently available, the identification of a molecular target is being pursued. Wuestefeld et al. discovered mitogen-activated protein kinase kinase 4 (MKK4) to play a pivotal role in liver regeneration using RNAi experiments. Silencing MKK4 expression with short-hairpin RNA (shRNA) resulted in an increase in robustness and regenerative potential of the liver via amplified hepatocyte proliferation. MKK4 silencing is expected to lead to a higher activation of mitogen-activated protein kinase kinase 7 (MKK7) and thus to a higher phosphorylation and activation of the downstream c-Jun-N-terminal protein kinase 1 (JNK1). Therefore, phosphorylation of ETS transcription factor (ELK1) and activating transcription factor 2 (ATF2) is increased, which appears to be the reason for the elevated hepatocyte proliferation. Because of their opposite role, MKK7 and JNK1 are considered as anti-targets in the development of small molecule MKK4 inhibitors (see Fig. 1) [1,2].

To date, only few MKK4 inhibitors have been published (Fig. 2). In 2004 Bayer described 4-phenyl-pyrimido[4,5-*b*]indole (**1**) with IC$_{50}$ values $\leq$ 1 μM for both MKK4 and MKK7. In 2013 Krishna et al.

Abbreviations: MKK4/7, mitogen-activated protein kinase kinase 4/7; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; JNK1, c-Jun-N-terminal protein kinase 1; MAP4K5, MEK kinase kinase 5; ZAK, sterile alpha motif and leucine zipper containing kinase.

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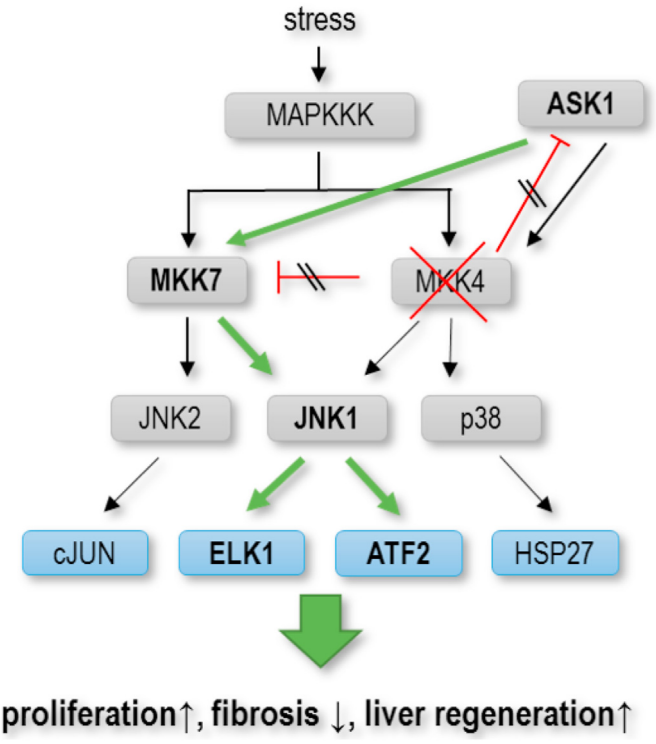


Fig. 1. Illustration of the MKK4 silencing pathway modified from Wuestefeld et al. [1]. Genetic silencing of MKK4 leads to an increased activity of MKK7 via increased induction of MKK7 and apoptosis signal-regulating kinase 1 (ASK1). This results in an amplification of the MKK7 pathway, a higher activity of JNK1 and a higher phosphorylation of ELK1 and ATF2.

reported trihydroxyisoflavones (**2**, exemplary) as inhibitors of MKK4, but no selectivity was given. In 2014 the protoberberin derivative HWY336 (**3**) was published by Kim et al. with low micromolar IC_{50} values for both MKK4 and MKK7. Deibler et al. modified published kinase inhibitors AST-487 (**6**), PLX4720 (**5**) and pazopanib (**7**) for the development of MKK4 inhibitors generating derivatives with IC_{50} values in the low micromolar range against MKK4. Most recently (2019) Deibler et al. reported 3-arylindazoles (**4**, exemplary) as selective MKK4 inhibitors having two- to three-digit IC_{50} values in the nanomolar range [3–6].

In this study, we describe the development of a highly affine small molecule MKK4 inhibitor derived from the approved v-Raf murine sarcoma viral oncogene homolog B1 ($BRAF^{V600E}$) kinase inhibitor vemurafenib (**8**) by variation of the core heterocycle (hinge-binding scaffold) and further optimizations. We used the commercially available KINOMEscan technology by DiscoverX, Fremont CA to determine binding affinities (expressed as percent of control (POC) values). A POC of 100 refers to no binding of the compound to the kinase, whereas 0 refers to complete binding to the kinase [7]. Besides BRAFwt, we also chose MEK kinase kinase 5 (MAP4K5) and sterile alpha motif and leucine zipper containing kinase (ZAK) as off targets, as these kinases are assumed to reduce JNK activity via suppression of the MKK4/7 pathway if inhibited [8].

2. Results and discussion

Biological evaluation. In our first approach, we compared binding affinities of different hinge-binding scaffold derived from 1*H*-pyrrolo[2,3-*b*]pyridine (**8**) to 5*H*-pyrrolo[2,3-*b*]pyrazin **9** and 1*H*-pyrazolo[2,3-*b*]pyridin **10** (Table 1). Pyrrolopyrazin **9** showed almost no affinity towards MKK4 at a concentration of 100 nM, while pyrazolopyridine **10** had similar affinity to MKK4 and a slightly lower affinity to BRAF when related with **8**. Also, almost no binding of JNK1 and MKK7 was observed for **10**. Consequently, we chose **10** as a new compound class for the further development.

First, we designed a set of compounds - based on the pyrazolopyridine as hinge-binding scaffold - that differed in the substitution pattern of the aromatic residue in the 5-position. For the substitution of the *para*, *ortho* and *meta* position, wo chose chloro- (**10**, **12**, **13**), fluoro- (**14**–**16**), methyl- (**17**–**19**), methoxy- (**20**–**22**), hydroxy- (**23**–**25**) and amino (**26**–**28**) residues. We also included dimethylamino- (**29**, **30**), trifluoromethyl- (**40**, **41**) and nitrogroups (**42**, **43**) for the *meta* and *para* position. Additionally, we selected bulky and multiple-substituted (**31**–**39**) as well as sulfone- and sulfamoyl- (**44**, **45**) substituted residues to generate a first profile. For evaluation of the binding data, the compounds were grouped based on the residues' properties.

Regarding MKK4, *ortho* and *para* substitution of the phenyl residue with methoxy and nonpolar residues (fluorine (**14**, **16**), chlorine (**8**, **12**) and methyl (**17**, **19**)) lead to a higher affinity when compared to *meta* substitution regardless of the substituent (Table 2). The phenyl derivative **11** showed similar affinity to MKK4 like *ortho* and *para* substituted compounds. The corresponding chloro derivatives **8**, **12** and **13** showed lower affinity in the binding assays. From these findings, effects of methoxy/nonpolar substitution of the phenyl ring on MKK4 affinity can be ordered from

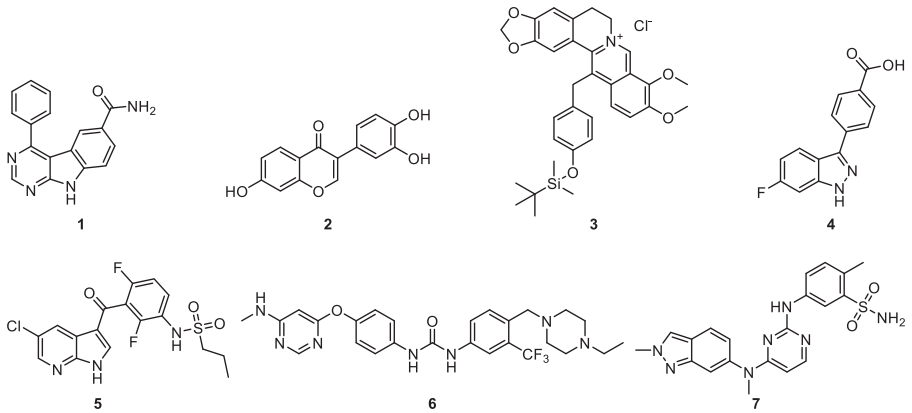
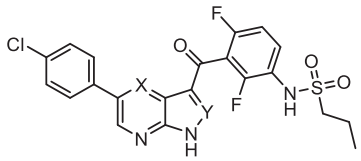


Fig. 2. Recently published MKK4 inhibitors according to references.

Table 1
Comparison of different hinge-binding scaffold derived from **8**.



No.	X =	Y =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
8	CH	CH	16	n.d.	48	**14**	100	n.d.
9	N	CH	91	96	100	**90**	100	100
10	CH	N	25	89	32	**12**	100	29

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

ortho ≥ *para* > *meta*. Selectivity over BRAF and ZAK was highest for *ortho*-substituted compounds having selectivity factors ranging from 7 to 70 for BRAF and 6–18 for ZAK at 100 nM, whereas fluoro, methyl and methoxy substitution in the *para* position increased affinity to both kinases. The affinity to JNK1 and MAP4K5 was low in case of compounds with higher affinity to MKK4. MKK7 had not been addressed in this series.

Compounds bearing polar hydroxy and amino residues in the *meta* (**24**, **27**) or *para* (**25**, **28**) position showed high affinity to MKK4 with POC values in the range of 0.1–2.2 at 100 nM (Table 3), with *para* substitutions having the highest impact on increased affinity. For the less polar dimethylamino compounds **29** and **30** the affinity to MKK4 was lower (POC 26 and 2.5 at 100 nM) when compared to the unsubstituted amines. Besides high affinity to MKK4, the polar *meta*- and *para*-substituted compounds showed low selectivity over BRAF and ZAK (POC values in the range of 1.3–11 for BRAF and 0–9.7 for ZAK at 100 nM), while selectivity over MKK7 and JNK1 was high, except for **28** having a POC of 28 at 100 nM. In summary, the compounds with polar substituents (Table 3) with compounds **25**, **27** and **28** as most potent structures showed high affinities for MKK4 but were less selective.

For compounds having bulky or multiple substituents (see Table 4) a drop in affinity to all tested kinases was observed, especially for the chloro compounds **31**–**33** when compared to the mono-substituted compounds (see Table 2). Addition of another methyl group (**34**) or increasing the size of the alkyl substituent to *iso*-propyl (**35**) or *tert*-butyl (**36**) led to a decrease in affinity to all tested kinases. Although the overall affinity of **35** is reduced compared to the *p*-methyl compound **19**, **35** showed a similar affinity towards MKK4 as **8** but with an improved selectivity profile. The substitution pattern given from a combination of compounds **16** and **17** lead to compound **38** which showed a good profile but a lower affinity to MKK4 than both parent molecules. **39** on the other hand (a combination of **22** and **12**), showed a similar affinity towards MKK4 as **22** with an excellent selectivity profile comparable with **12** and is the most potent compound within this set.

For compounds having electron withdrawing groups, no clear trend could be observed (Table 5). The trifluoromethyl compounds **40** and **41** showed low affinity to the tested kinases. The 4-nitro compound **43** exhibited a higher affinity to MKK4 by factor 2 than the corresponding 3-nitro compound **42** (POC value of 4.2 vs. 15 at 100 nM). Compounds **44** and **45** with sulfur-based residues had very low POC values of 1.5 and 0.25 at 100 nM for MKK4, but also high affinity to BRAF with POC values in the range of 0.45–0.9 at 100 nM. Compound **28** and **45** showed the lowest POC values for MKK4 at 100 nM, a high selectivity over MAP4K5 and MKK7, and a moderate selectivity over JNK1. Moreover, **45** was the first compound to show a very high affinity to MKK4 (POC 0.25 at 100 nM) with superior ZAK selectivity (POC 91 at 100 nM). As a result, we chose **45** as a new starting point for the further development of selective MKK4 inhibitors.

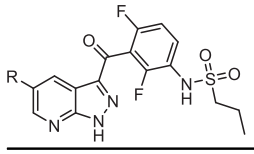
For **28** and **45** POC values for MKK4 were determined again at a lower concentration of 10 nM for better comprehension. It was observed that both compounds were still binding MKK4 with a high affinity reflected in POC values in the range of 3.7–5.1 at 10 nM (see Table 6).

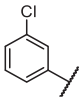
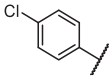
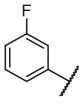
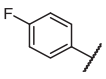
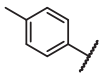
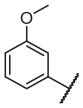
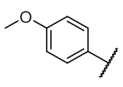
Modifications of the sulfamoylphenyl residue. To further investigate the influence of the sulfaomyl residue, we chose to vary the amino function by *N*-alkylation (**46**, **47**, loss of a hydrogen bond donor) and *N*-acylation (**48**, loss of hydrogen bond donor and increase of acidity). We also inverted the sulfamoyl group (**49**) and employed other more acidic residues like tetrazol (**50**) and carboxylic acid (**51**), as well as the neutral amide (**52**) (see Table 7).

From the previous testing, we observed that a loss of the amino function (**44**, Table 5) resulted in reduced affinity to MKK4 and selectivity for MAP4K5 and ZAK. The *N*-alkyl compounds **46** and **47** gave similar results, while the affinity to MKK4 was reduced with increasing chain lengths. The results for the "inverted sulfonamide" (**49**) were comparable to the *N*-alkylated compounds, but with an increased affinity towards MAP4K5 and ZAK. The acidic *N*-acetyl compound **48** had a higher affinity to MKK4 when compared to **45** with a POC value of 0.5 at 10 nM, with a very high affinity to BRAF (POC value of 0 at 100 nM) and a slightly higher affinity to ZAK. The data for the tetrazole **50** and the carboxylic acid compound **51** is in line with the data generated from the acidic *N*-acetylated sulfonamide **48** having a high affinity to MKK4 (POC values from 0.2 to 1.1 at 100 nM). These acidic compounds also had low POC values for BRAF (1.2–1.4 at 100 nM) and a moderate affinity to ZAK (POC 7.5–20 at 100 nM). Also, significant binding to MKK7 at 100 nM was observed for compound **51**. The amide **52** had a profile comparable to the acid **51** but with a higher affinity to MAP4K5. From these data, we decided to pursue the further development of a selective MKK4 inhibitor based on compound **45** as **45** showed a better selectivity profile with high binding to MKK4 and extraordinary ZAK selectivity. In the next step we took the information from Table 2 that *ortho* substitution of the phenyl residue with nonpolar substituents leads to a reduced binding to BRAF generating the equivalent sulfamoyl derivatives as depicted in Table 8.

As expected, *ortho* substitution of **45** (**53**–**55**, Table 8) leads to a decrease in BRAF affinity (POC values from 2.2 to 21 vs. 0.9 (**45**) at 100 nM). The affinity to MKK4 was also decreased, with POC values ranging from 1 to 3.4 vs. 0.25 (**45**) at 100 nM, while maintaining high selectivity over MKK7 and ZAK. Also, the selectivity for JNK1 was improved for all compounds. Due to the decreased binding affinity to MKK4 by *ortho*-substitution, we used another approach to increase the selectivity of **45**.

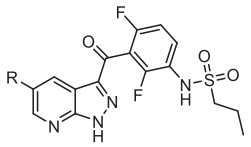
Table 2
Binding affinities for single nonpolar and hydrogen accepting substituted derivatives.

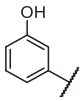
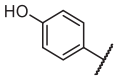
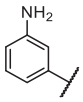
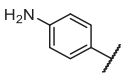
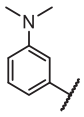
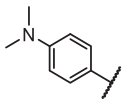


No.	R =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
11		29	70	24	**2.4**	100	1.9
12		70	100	96	**9.3**	100	64
13		72	90	69	**40**	100	16
10		25	89	32	**12**	100	29
14		40	97	59	**2**	83	32
15		4.9	85	65	**8.2**	97	12
16		28	83	59	**2.1**	100	4.8
17		65	90	67	**7**	100	41
18		38	90	18	**15**	100	5.5
19		16	73	25	**5.4**	100	5.9
20		70	54	34	**1.9**	100	36
21		23	73	24	**6.3**	100	23
22		5.9	69	28	**4.2**	100	1.9

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

Table 3
Binding affinities for single polar and hydrogen accepting/donating and weakly basic substituted derivatives.



No.	R =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
23		71	79	39	**9**	100	9.7
24		11	63	8	**2.2**	100	0.95
25		8.7	65	9.4	**0.75**	87	0
26		99	80	73	**23**	95	40
27		3.5	65	3.8	**1.6**	86	2.3
28		1.3	28	1.3	**0.1**	93	2.7
29		22	86	11	**26**	100	9.7
30		1.9	100	31	**2.5**	100	2.2

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

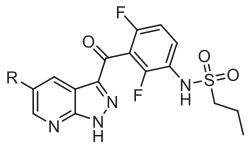
Variation of the sulfonamide sidechain. The *n*-propanesulfonamide sidechain in **8** is known to be optimized to fit the *raf-selectivity-pocket* which is unique to the Raf kinase family [9]. We tried to decrease the BRAF binding of **45** by varying the length and bulkiness of the sulfonamide sidechain. In a focused library, we chose methyl, *n*-butyl and benzyl residues to investigate the effects on BRAF affinity. The results are given in Table 9. Regarding BRAF affinity, the longer *n*-butyl sidechain (**57**) yielded only a slight reduction in affinity to BRAF, while shortening the sidechain to methyl (**56**) led to a higher reduction in affinity (POC values 2.1 and 16 at 100 nM). Also, selectivity over JNK1 was slightly increased for **56** and **57** compared with **45**. With benzyl (**58**) we achieved an excellent selectivity profile showing POC values of 76 for BRAF and 0.4 for MKK4 at 100 nM and 10 at 10 nM. The selectivity over JNK1 could be further increased when compared to **45**, **56** and **57**. Moreover, affinities to MKK7 and ZAK were not detectable at 100 nM.

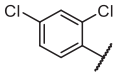
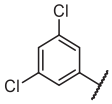
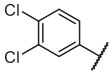
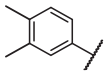
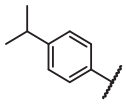
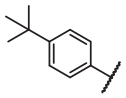
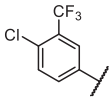
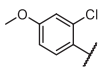
The benzylsulfonamide moiety was then applied to the high affinity compound **28** from the first set of compounds (*vide supra*, Tables 3 and 6). The combination compound **59** showed a drastically improved selectivity profile when compared to **28**, especially for BRAF and MAP4K5, retaining a high affinity for MKK4 with POC values of 0.1 at 100 nM and 11 at 10 nM (see Table 10.). Only the affinities for ZAK and MAP4K5 were still equally high compared to the parent compound.

For a further compound characterization, we determined Kd-values for **58** and **59** (see. Table 11). The Kd-values are in line with the POC values given in Table 10. Both compounds exhibit a one-digit nanomolar Kd-value for MKK4. For **59** the selectivity over the anti-targets JNK1 and MKK7 is relatively high for JNK1 with two orders of magnitude and excellent for MKK7 with a factor of >3000. Nevertheless, the selectivity for MAP4K5 and ZAK is low, expressed by selectivity factors of only around 5 and 9, respectively. The remarkable selectivity of **58** over the off- and anti-targets is represented by the factors of >100, >250, >600 and almost 3000 against JNK1, BRAF, MAP4K5, MKK7 and ZAK respectively. **58** was also screened against a panel of 97 kinases using scanEDGE assay at a concentration of 1 μM, which is over 500 times higher than the Kd-value for MKK4. At this concentration, only 2 kinases (AURKB and SNARK) showed a POC-value <35%, resulting in a selectivity factor of S(35) = 0.022 (see supporting information for details).

To determine the inhibitory activity, we performed ^{33}PanQinase assay [10] with the highly selective and most promising compound **58**, the *n*-propyl parent compound **45** as well as with compound **48**,

Table 4
Binding affinities for bulky or multiple-substituted derivatives.



No.	R =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
31		82	100	100	**22**	96	99
32		99	94	99	**73**	100	66
33		57	100	100	**45**	100	85
34		21	84	20	**20**	100	24
35		65	78	89	**17**	98	92
36		92	73	97	**46**	100	77
37		18	78	16	**15**	100	20
38		97	98	55	**14**	100	65
39		73	92	53	**5.3**	100	74

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

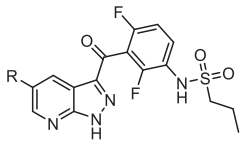
one the compounds with the highest affinity towards MKK4 (Table 12). Consistent with the determination of POC values, a decrease in potency from an IC_{50} of 89 nM−146 nM for MKK4 was observed when the sulfonamide side chain was varied from *n*-propyl (**45**) to the selectivity driving benzyl residue (**58**). Compound **48** with a POC value of 0.5 at 10 nM (10-fold lower than **45**) exhibited a low two-digit nanomolar IC_{50} value of 29 nM for MKK4. Due to the different nature of the assays, the results cannot be compared quantitively, but their outcomes are qualitatively in line.

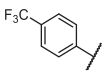
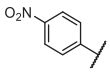
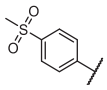
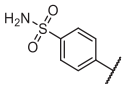
CHEMISTRY. Compound **9** was prepared according to the procedures described in the literature [11]. Although the preparation of a precursor of the pyrazolopyridine compounds was partially described by Ibrahim et al. [12], the published route was found to be unreliable and unreproducible. A new synthetic route for the preparation of the pyrazolopyridine compounds was established.

[a]**Reagents and conditions:** (a) I_2, KOH, DMF, RT (92%); (b) 1.) $CO_{(g)}$, Xantphos, $Pd(OAc)_2$, Et_3N, MeOH, DMF, 60 °C, 2.) NaOH, H_2O, 95 °C − RT (quant.); (c) CDI, *N*,*O*-dimethylhydroxylamine hydrochloride, 60 °C (85%); (d) 1.) 2,4-difluoroaniline, *n*-BuLi, TMS-Cl, NaH, −78 °C to −15 °C, 2.) conc. HCl, RT (70%); (e) appropriate sulfonyl chloride, 4-DMAP, pyridine, 65 °C (38−65%); (f) appropriate boronic acid or pinacol boronate, $Pd(PPh_3)_4$, XPhos Pd G3/G4 or P(*t*-Bu)$_3$ Pd G3, K_2CO_3 or K_3PO_4, 1,4-dioxane, H_2O, μw, 100−130 °C (24−87%); (g) DHP, *p*-TsOH, DCM, reflux (75%); (h) B_2Pin_2, AcOK, $Pd(dppf)Cl_2$, 1,4-dioxane, 85 °C (91%); (i) 1.) appropriate aryl bromide, $Pd(PPh_3)_4$ or XPhos Pd G3, K_2CO_3, 1,4-dioxane, H_2O, 55 °C, 2.) HCl, *i*-PrOH, 70 °C (31−58%, two steps).

Scheme 1 depicts the synthesis used in the preparation of the testing compounds. In the first step, the 3-iodo compound **61** was generated by iodination of **60** with elemental iodine and potassium hydroxide in *N*,*N*-dimethylformamide following a modified literature procedure [13]. The conversion to the corresponding carboxylic acid (**62**) was performed via palladium-catalyzed carbonylation using carbon monoxide gas and Xantphos as ligand [14], followed by hydrolysis of the intermediate methyl ester. In the next step, the Weinreb-amide **63** was generated by activation of the carboxylic acid using carbonyldiimidazol (CDI) and subsequent reaction with *N*,*O*-dimethylhydroxylamine hydrochloride [15]. For the ketone synthesis, the amino function of 2,4-difluoroaniline was masked with trimethylsilyl (TMS) and the aromatic ring was lithiated with

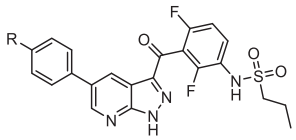
Table 5
Binding affinities for derivatives substituted with electron withdrawing groups.



No.	R =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
40		39	100	98	**57**	100	44
41		68	85	76	**29**	100	75
42		29	77	93	**15**	95	52
43		25	79	61	**4.2**	100	23
44		0.45	63	14	**1.5**	100	21
45		0.9	32	100	**0.25**	98	91

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

Table 6
Comparison of binding affinities of **28** and **45** on MKK4 at different concentrations.



No.	R =	MKK4[a] [100 nM]	MKK4[a] [10 nM]
28		0.1	3.7
45		0.25	5.1

[a] Binding affinities from KINOMEscan assay. Values are shown as POC determined in duplicate.

n-butyllithium (*n*-BuLi) to generate the nucleophile in a modified literature procedure [16]. **62** was converted to the corresponding sodium salt using sodium hydride. Reaction of both components and acidic deprotection of the TMS groups yielded the ketone **64**. The conversion to the corresponding sulfonamides **65a** − **d** was carried out by heating **64** in pyridine with the appropriate sulfonyl chloride and catalytic amounts of 4-dimethylaminopyridine (4-DMAP). For most of the final compounds the Suzuki coupling was performed as the last step under microwave irradiation at 100−120 °C, while **54** and **55** were prepared from **67** and corresponding aryl bromides. For the synthesis of **67**, tetrahydropyranyl (THP) protection of the core heterocycle of **65b** was performed in dichloromethane catalyzed with *para*-toluenesulfonic acid yielding **66** which was converted to the borylated species **67** under classical Suzuki-Miyaura-borylation conditions [17]. Preparations of aryl bromide and boronic acids/pinacol ester that were not commercially available are described in the supporting information.

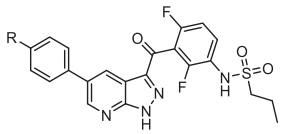
3. Conclusion

In this work we reported the development of novel compounds selectively addressing MKK4, derived from the approved $BRAF^{V600E}$ inhibitor **8**, by variation of the core heterocycle from 1*H*-pyrrolo[2,3-*b*]pyridine to 1*H*-pyrazolo[2,3-*b*]pyridine and further iterative modifications. With compound **58** we were able to dramatically shift selectivity from BRAF to MKK4 with a high affinity for MKK4 in the low one-digit nanomolar range and high kinome selectivity. We developed distinct structure-activity relationships (SARs) in the multiparameter optimization process. The crucial off- and anti-targets in the MKK4 inhibition pathway that might limit the regeneration of hepatocytes were not addressed either. To the best of our knowledge, this work is the first report of 1*H*-pyrazolo[2,3-*b*]pyridine-based MKK4 inhibitors having such a selectivity profile.

4. Experimental section

General. All commercially available reagents and solvents were

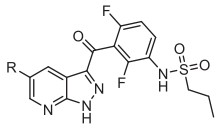
Table 7
Derivatives of **45** with different hydrogen bond/acceptor properties and pK_a values.

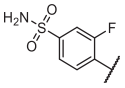
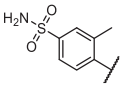
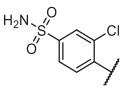


No.	R =	BRAF[a] [100 nM]	JNK1[a] [100 nM]	MAP4K5[a] [100 nM]	MKK4[a] [100 nM]	MKK4[a] [10 nM]	MKK7[a] [100 nM]	ZAK[a] [100 nM]
46		0.5	74	17	**1.2**	**14**	100	33
47		0.4	59	26	**3**	**41**	100	32
48		0	47	67	**0.35**	**0.5**	71	38
49		8.2	59	1.1	**0.85**	**16**	100	4.3
50		1.4	38	81	**0.15**	**1.1**	64	20
51		1.2	28	75	**0.1**	**0.2**	27	7.5
52		0.65	48	10	**0.15**	**4**	99	8.1

[a] Binding affinities from KINOMEscan assay. Values are shown as POC determined in duplicate.

Table 8
Ortho substitution of the sulfamoylphenyl residue.

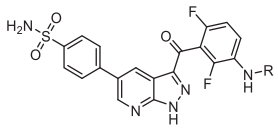


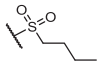
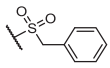
No.	R =	BRAF[a] [100 nM]	JNK1[a] [100 nM]	MAP4K5[a] [100 nM]	MKK4[a] [100 nM]	MKK4[a] [10 nM]	MKK7[a] [100 nM]	ZAK[a] [100 nM]
53		2.2	100	77	**1**	**9.4**	100	100
54		16	100	n.d.	**3.1**	**24**	100	94
55		21	100	n.d.	**3.4**	**23**	100	100

[a] Binding affinities from KINOMEscan assay. Values are shown as POC determined in duplicate.

used as received. Reactions sensitive to air or moisture were performed under an atmosphere of argon and/or in anhydrous solvents. Anhydrous solvents were purchased from Acros Organics (AcroSeal). Unless stated otherwise, extracts were dried over sodium sulfate prior to filtration. Thin layer chromatography was performed on TLC Silica Gel 60 F_{254} aluminum sheets provided by Merck, detection at $\lambda = 254$ nm und 366 nm. Flash chromatography was carried out on Interchim PuriFlash XS420 flash-chromatography system and Grace Davison Davisil LC60A 20–45 μm silica. Purity of the compounds was determined by HPLC analysis on Agilent 1100 Series Liquid Chromatograph using a Phenomenex Luna C8 150 × 4.6 mm, 5-μm column with gradient elution (MeOH/0.01 M KH_2PO_4 buffer, pH 2.3, flow rate 1.5 mL/min) and detection at $\lambda = 230$ and 254 nm. All final compounds were determined with >95% purity if not stated otherwise. Mass spectra were recorded 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/min N_2), elution of the spots with MeOH. High resolution mass spectra (ESI) of the final compounds were obtained from the Mass Spectrometry Department, Eberhard Karls Universitaet Tuebingen. NMR-spectra were measured on Bruker Avance 200 or 400 NMR

Table 9
Variations of the sulfonamide sidechain derived from **45**.



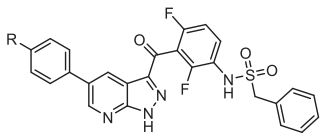
No.	R =	BRAF[a] [100 nM]	JNK1[a] [100 nM]	MAP4K5[a] [100 nM]	MKK4[a] [100 nM]	MKK4[a] [10 nM]	MKK7[a] [100 nM]	ZAK[a] [100 nM]
56		16	42	99	**0.6**	**12**	99	100
57		2.1	58	100	**0.25**	**6.9**	100	100
58		76	86	96	**0.4**	**10**	99	100

[a] Binding affinities from KINOMEscan assay. Values are shown as POC determined in duplicate.

spectrometers. The spectra were calibrated on the deuterated solvents and chemical shifts (δ) are stated relative to tetramethylsilane in ppm. Prepared intermediate reagents that are listed in the supporting information are named **R** with consecutive numbering.

5-Bromo-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (61). To a stirred mixture of 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (6.81 g, 34.4 mmol) and KOH (6.75 g, 120.4 mmol) in DMF (45 mL) iodine was added (9.60 g, 37.8 mmol) in one portion at room temperature. After a short induction period the exothermic reaction began. After 1 h about 1 g of iodine was added and the mixture stirred at 45 °C for 1 h. The mixture was poured into a dilute solution of Na_2SO_3 and then acidified with 2N HCl. The solids were collected by suction filtration, washed with water and dried in an oven at 110 °C. Yield: 10.92 g (92%). ^{1}H NMR (200 MHz, DMSO) δ 14.29 (s, 1H), 8.62 (s, 1H), 8.17 (s, 1H); 13C NMR (50 MHz, DMSO) δ 150.53, 150.17, 131.86, 120.58, 112.43, 91.95; $[M\text{-}H]^-$ = 322.0/324.0.

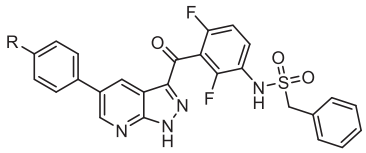
Table 10
Comparison of benzylsulfonamide compounds **58** and **59**.



No.	R =	BRAF[a] [100 nM]	JNK1[a] [100 nM]	MAP4K5[a] [100 nM]	MKK4[a] [100 nM]	MKK4[a] [10 nM]	MKK7[a] [100 nM]	ZAK[a] [100 nM]
58		76	86	96	**0.4**	**10**	99	100
59		75	49	1.4	**0.1**	**11**	100	1.8

[a] Binding affinities from KINOMEscan assay. Values are shown as POC determined in duplicate.

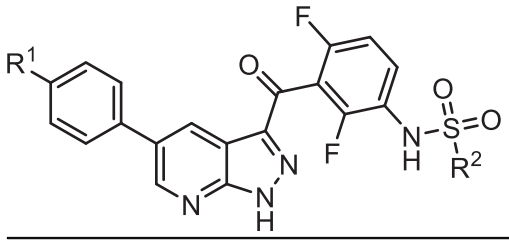
Table 11
Determination of Kd-values.

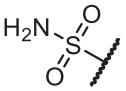
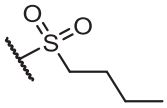
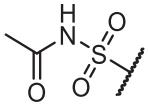
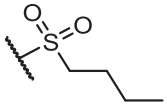
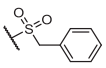


No.	R =	BRAF[a]	JNK1[a]	MAP4K5[a]	MKK4[a]	MKK7[a]	ZAK[a]
58		450	210	1100	**1.7**	5000	5000
59		610	140	5.8	**1.5**	5000	9.5

[a] Kd-values (nM) determined with KINOMEscan assay in duplicates.

Table 12
Determination of inhibitory activity.

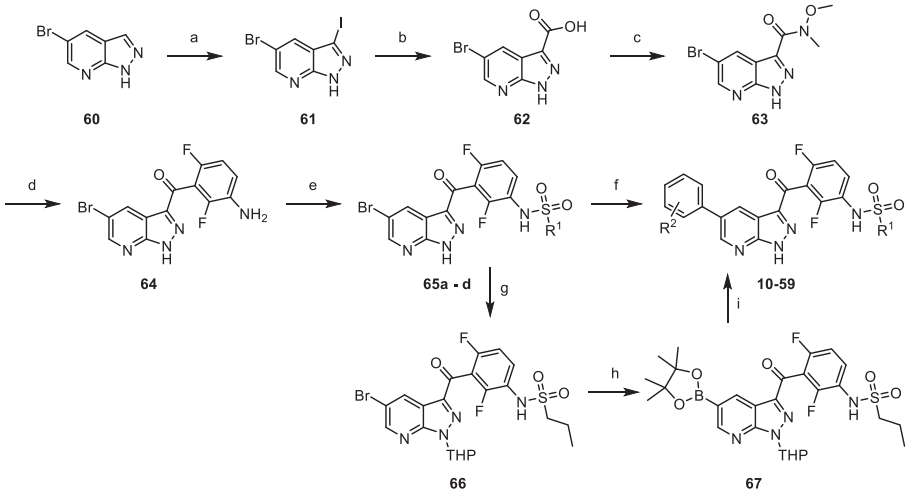


No.	R^1 =	R^2 =	IC_{50} MKK4 [nM][a]
45			89
48			29
58			146

[a] IC_{50}-values (nM) determined with ^{33}PanQinase assay.

5-Bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylic acid (62). 5-Bromo-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (**61**) (10.44 g, 32.2 mmol) was dissolved in DMF, MeOH and triethylamine (75 mL each). The vessel was evacuated and backfilled with argon (4x). XantPhos (1.12 g, 1.93 mmol) and $Pd(OAc)_2$ (270 mg, 0.97 mmol) were added and carbon monoxide (generated from formic acid and sulfuric acid) was bubbled through the solution while heating to 60 °C. The mixture was stirred under an atmosphere of carbon monoxide (balloon) for 8 h. Every 1.5 h carbon monoxide was bubbled through the solution for 5 min. The mixture was concentrated under reduced pressure, and the residue was triturated with 2N HCl. The solids were heated at 95 °C in about 100 mL 1N NaOH overnight. After cooling to room temperature, the mixture was acidified with conc. HCl, and the precipitate collected by suction filtration and washed with water (note: since the precipitate is very voluminous, a large suction funnel has to be used). The solids were dried in an oven at 110 °C. After complete drying, the product was sonicated in 100 mL of toluene for 5 min and stirred for 30 min. The product was filtered, washed with an additional 20 mL of toluene and dried at 110 °C. Yield: 7.92 g (quant.). ^{1}H NMR (200 MHz, DMSO) δ 8.64 (d, J = 7.9 Hz, 2H), 5.69 (bs, 1H); ^{13}C NMR (50 MHz, DMSO) δ 163.27, 150.97, 149.67, 136.69, 132.65, 115.73, 113.6; $[M-H]^-$ = 239.9/241.9.

5-Bromo-N-methoxy-N-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (63). 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylic acid (**62**) (7.91 g, 32.7 mmol) and 1,1′-carbonyldiimidazole (5.83 g, 35.9 mmol) were stirred in 200 mL of DMF at 60 °C for 45 min. *N*,*O*-dimethylhydroxylamine hydrochloride



Scheme 1. Synthesis of the pyrazolopyridine compounds.[a].

(3.51 g, 35.9 mmol) was added to the resulting suspension, and the mixture was stirred for 4 h at 65 °C. Most of the solvent was removed under vacuum, and half sat. $NaHCO_3$-solution was added to the residue. The solids were collected by suction filtration, washed with water and dried at 110 °C. Yield: 7.94 g (85%). 1H NMR (200 MHz, DMSO) δ 14.46 (s, 1H), 8.62 (d, J = 20.4 Hz, 2H), 3.76 (s, 3H), 3.44 (s, 3H), $[M-H]^-$ = 283.0/285.0.

(3-Amino-2,6-difluorophenyl) (5-bromo-1*H*-pyrazolo[3,4-*b*] pyridin-3-yl)methanone (64).

To a solution of 2,4-difluoroaniline (7.99 g, 61.9 mmol, 2.2 equiv.) in THF (55 mL), 2N *n*-BuLi in *n*-hexane (24.8 mL, 61.9 mmol, 2.2 equiv.) was added dropwise at −78 °C, followed by the dropwise addition of trimethylsilylchloride (7.85 mL, 61.9 mmol) in THF (10 mL). The mixture was warmed to −50 °C and stirred for 10 min. After cooling to −78 °C, 2N *n*-BuLi in *n*-hexane (24.8 mL, 61.9 mmol, 2.2 equiv.) and trimethylsilylchloride (7.85 mL, 61.9 mmol) in THF (10 mL) were added consecutively dropwise, and the reaction was stirred for 30 min at room temperature. The mixture was cooled to −78 °C, 2N *n*-BuLi in *n*-hexane (24.8 mL, 61.9 mmol, 2.2 equiv.) was added dropwise, and the mixture was stirred for 30 min. This is considered reaction solution A. In a separate flask, 60% NaH in mineral oil (1.24 g, 30.9 mmol, 1.05 equiv.) was added in portions to a suspension of **62** in THF (55 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. This is considered reaction solution B. Reaction solution B was added to reaction solution A, warmed to −15 °C and stirred for 15 min. Conc. HCl (12 mL) was carefully added, and the mixture stirred for 5 min at room temperature. Saturated $NaHCO_3$-solution was slowly added until phase separation occurred. The phases were separated, the aqueous phase extracted with THF, and the extracts were dried and filtered. *i*-PrOH (150 mL) was added to the extract, and the extract was concentrated to a volume of about 100 mL. The product was collected by suction filtration, washed with *i*-PrOH and dried. Yield:7.14 g (70%). 1H NMR (200 MHz, DMSO) δ 14.91 (s, 1H), 8.77 (dd, J = 5.4, 2.1 Hz, 2H), 7.18−6.59 (m, 2H), 5.25 (s, 2H); 13C NMR (50 MHz, DMSO) δ 183.95, 151.04, 150.79, 150.27 (dd, J = 161.0, 6.8 Hz), 145.50 (dd, J = 167.3, 6.8 Hz), 141.34, 133.35 (dd, J = 12.8, 2.6 Hz), 132.28, 117.45 (dd, J = 8.4, 6.5 Hz), 116.24 (dd, J = 22.7, 19.1 Hz), 115.55, 114.81, 111.26 (dd, J = 21.7, 3.5 Hz); $[M-H]^-$ = 351.1/353.1.

***N*-[3-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,6-difluorophenyl]methanesulfonamide (65a).** (3-amino-2,6-difluorophenyl)-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methanone (**64**) (350 mg, 0.991 mmol) and 4-DMAP (6.05 mg, 0.0496 mmol, 5%) were dissolved in pyridine (2 mL) and heated to 65 °C. Methanesulfonyl chloride (0.36 mL, 1.49 mmol, 1.5 equiv.) was added, and the mixture stirred for 2 h. The mixture was poured into aqueous 2N HCl and extracted with EtOAc. The organic phase was washed with 2N HCl and brine, dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (DCM + EtOAc) 0%−30% and triturated with *n*-hexane. Yield: 164 mg, 0,38 mmol (38%). 1H NMR (200 MHz, DMSO) δ 15.07 (s, 1H), 9.82 (s, 1H), 8.80 (dd, J = 4.8, 2.1 Hz, 2H), 7.65 (td, J = 9.0, 5.9 Hz, 1H), 7.32 (td, J = 8.9, 1.5 Hz, 1H), 3.07 (s, 3H); 13C NMR (101 MHz, DMSO) δ 182.3, 156.4 (dd, J = 248.8, 6.6 Hz), 152.92 (dd, J = 251.8, 8.1 Hz), 151.0, 150.9, 141.0, 132.2, 130.1, 130.0, 121.80 (dd, J = 13.2, 3.7 Hz), 116.84 (dd, J = 23.0, 20.9 Hz), 115.7, 114.7, 112.16 (dd, J = 22.4, 3.7 Hz), 40.4; $[M-1]^-$ = 428.7.

***N*-(3-(5-Bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (65b).** (3-amino-2,6-difluorophenyl) (5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methanone (**64**) (2.00 g, 5.66 mmol) and 4-DMAP (35 mg, 0.28 mmol, 5%) were heated in 9 mL pyridine to 65 °C and 1-propanesulfonyl chloride (1.21 g, 0.96 mL, 8.50 mmol) was added. After 2 h another 0.19 mL of 1-propanesulfonyl chloride were added. The warm solution was added to about 80 mL 2N HCl, the solids collected and washed with water. The solids were taken up in EtOAc and washed with 2N HCl and brine, dried over sodium sulfate and evaporated. The product was purified by flash chromatography (SiO_2, DCM/EtOAc 0%−20%) and triturated with *n*-hexane. Yield: 1.68 g (65%). 1H NMR (200 MHz, DMSO) δ 9.86 (s, 1H), 8.79 (dd, J = 5.3, 2.0 Hz, 3H), 7.64 (td, J = 9.0, 6.0 Hz, 1H), 7.30 (t, J = 8.9 Hz, 1H), 3.17−2.96 (m, 3H), 1.87−1.62 (m, 2H), 0.96 (t, J = 7.4 Hz, 4H); 13C NMR (50 MHz, DMSO) δ 182.75, 157.39 (dd, J = 177.1, 7.4 Hz), 152.42 (dd, J = 180.3, 7.3 Hz), 151.56, 151.34, 141.39, 132.59, 130.78−130.05 (m), 122.20 (dd, J = 13.5, 3.6 Hz), 117.19 (dd, J = 23.0, 20.9 Hz), 116.14, 115.18, 112.59 (dd, J = 22.2, 3.8 Hz), 54.14, 17.22 12.97; $[M-H]^-$ = 457.1/459.1.

***N*-[3-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl]butane-1-sulfonamide (65c).** (3-amino-2,6-difluorophenyl)-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methanone (**64**) (350 mg, 0.991 mmol) and 4-DMAP (6.05 mg, 0.0496 mmol) were dissolved in pyridine (2 mL) and heated to 65 °C. Butane-1-sulfonyl chloride (0.36 mL, 1.49 mmol, 1.5 equiv.) was added, and the mixture stirred overnight. 0.25 equiv. butane-1-sulfonyl chloride were added, and stirring continued for 2h at 65 °C. The mixture was poured into aqueous 2N HCl and extracted with EtOAc. The organic phase was washed with 2N HCl and brine, dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/EtOAc) 10%−50% and triturated with *n*-hexane. Yield: 180 mg (38%) 1H NMR (200 MHz, DMSO) δ 15.03 (s, 1H), 9.83 (s, 1H), 9.02−8.62 (m, 2H), 3.21−3.03 (m, 2H), 1.70 (dt, J = 15.0, 7.5 Hz, 2H), 1.37 (dq, J = 14.5, 7.3 Hz, 2H), 0.84 (t, J = 7.2 Hz, 3H); 13C NMR (50 MHz, DMSO) δ 182.4, 151.1, 151.0, 141.1, 132.3, 115.8, 114.8, 51.8, 25.1, 20.7, 13.4; $[M-1]^-$ = 470.8.

***N*-[3-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl]-1-phenylmethanesulfonamide (65d).** (3-amino-2,6-difluorophenyl)-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl) methanone (**64**) (350 mg, 0.99 mmol) and 4-DMAP (6.05 mg, 0.05 mmol) were dissolved in pyridine (2 mL) and heated to 65 °C. Phenylmethanesulfonyl chloride (283 mg, 1.49 mmol, 1.5 equiv.) was added, and the mixture stirred for 2h. The mixture was poured into aqueous 2N HCl and extracted with EtOAc. The organic phase was washed with 2N HCl and brine, dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane + EtOAc) 0%−50% and triturated with *n*-hexane. Yield: 315 mg (63%). 1H NMR (200 MHz, $CDCl_3$) δ 14.22 (s, 1H), 8.96 (s, 1H), 8.79 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 2.1 Hz, 1H), 7.52−7.25 (m, 6H), 6.87 (td, J = 9.1, 1.6 Hz, 1H), 4.32 (s, 2H); 13C NMR (101 MHz, $CDCl_3$) δ 182.7, 156.6 (dd, J = 251, 6.8 Hz), 153.03 (d, J = 7.7 Hz), 151.2, 150.6, 150.5, 141.6, 132.9, 130.8, 127.75 (dd, J = 151.3, 7.9 Hz), 126.9, 121.87 (dd, J = 13.1, 3.9 Hz), 117.12 (dd, J = 22.8, 20.7 Hz), 115.7, 115.5, 111.61 (dd, J = 22.5, 3.8 Hz), 58.8. $[M-1]^-$ = 504.7.

***N*-[3-[5-bromo-1-(oxan-2-yl)pyrazolo[3,4-*b*]pyridine-3-carbonyl]-2,4-difluorophenyl]propane-1-sulfonamide. (66).** To a suspensions of *N*-[3-(5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl]propane-1-sulfonamide (**65b**) (0.33 g, 0.73 mmol) in dichloromethane (3 mL) dihydropyran (0.13 mL, 1.45 mmol, 2equiv.) and *p*-toluenesulfonic acid monohydrate (27 mg, 0.145 mmol, 0.2 equiv.) were added, and the mixture was heated to reflux temperature for 45 min. After cooling, the mixture was washed with sat. $NaHCO_3$-solution, dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in a minimum amount of DCM and added dropwise to *n*-hexane with stirring. After 5 min the solids were collected by suction filtration and dried. Yield: 297 mg (75%), used without further purification. 1H NMR (200 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.65 (s, 1H), 7.70 (dd, J = 13.6,

8.1 Hz, 1H), 7.02 (d, $J = 9.6$ Hz, 2H), 6.14 (d, $J = 9.2$ Hz, 1H), 4.14−3.64 (m, 2H), 3.22−2.90 (m, 2H), 2.61−2.31 (m, 1H), 2.15−1.16 (m, 10H); 13C NMR (50 MHz, $CDCl_3$) δ 182.4, 151.0, 149.7, 140.7, 133.7, 127.33 (d, $J = 8.6$ Hz), 121.36 (dd, $J = 13.1$, 3.8 Hz), 116.8, 116.6, 112.44 (dd, $J = 22.6$, 3.7 Hz), 83.3, 77.2, 68.2, 54.1, 28.9, 24.8, 22.4, 17.3, 12.9; $[M-1]^- = 540.7$.

***N*-[2,4-difluoro-3-[1-(oxan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[3,4-*b*]pyridine-3-carbonyl] phenyl]propane-1-sulfonamide (67).** A vessel was charged with *N*-[3-[5-bromo-1-(oxan-2-yl)pyrazolo[3,4-*b*]pyridine-3-carbonyl]-2,4-difluorophenyl]propane-1-sulfonamide (**66**) (271 mg, 0.499 mmol), bis(pinacolato)diboron (139 mg, 0.55 mmol, 1.1 equiv.) and anhydrous potassium acetate (147 mg, 1.50 mmol, 3 equiv.). Degassed, dry 1,4-dioxane (5 mL) was added, and the vessel was evacuated and refilled with argon (3x). $Pd(dppf)Cl_2$ (9.12 mg, 0.0125 mmol) was added, and the mixture stirred at 85 °C overnight. After cooling to room temperature, the mixture was diluted with EtOAc, filtered over celite, and the solvent was removed. The residue was dissolved in DCM, petrol ether (60/90) was added, and DCM removed under reduced pressure. After cooling for 1 h at 4 °C the solids were collected by suction filtration and dried. Yield: 267 mg (91%), which was used without further purification. 1H NMR (200 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.94 (s, 1H), 7.68 (d, $J = 5.9$ Hz, 1H), 7.12−6.83 (m, 2H), 6.22 (d, $J = 9.0$ Hz, 1H), 4.19−3.60 (m, 2H), 3.07 (s, 2H), 2.57−1.11 (m, 23H); 13C NMR (50 MHz, $CDCl_3$) δ 182.5, 155.5, 152.4, 141.9, 139.3, 127.3 (d, $J = 9.0$ Hz), 121.23 (dd, $J = 13.1$, 4.0 Hz), 114.9, 112.33 (dd, $J = 23.2$, 2.9 Hz), 84.4, 82.8, 77.2, 68.1, 54.1, 29.0, 24.9, 22.5, 17.2, 12.9; $[M-1]^- = 588.9$.

Suzuki-coupling reaction under microwave irradiation (General procedure A). A microwave vessel is charged with a magnetic stir bar, corresponding 5-bromo-1*H*-pyrazolo[3,4-*b*]pyridine (**65a-d**), appropriate boronic acid or pinacol boronate, catalyst, and purged with argon. Degassed 1,4-dioxane and degassed aqueous 1.5 M K_2CO_3 are added, and the mixture is heated to the stated temperature (100−120 °C) under microwave irradiation until complete conversion (usually 30 min). After cooling, the mixture is diluted with EtOAc and neutralized with sat. NH_4Cl solution. The aqueous phase is removed, the organic phase is concentrated, and the product isolated by flash chromatography and triturated if necessary.

***N*-(3-(5-(4-Chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (10).** Compound **10** was prepared according to **general procedure A** using **65b** (77 mg, 0.17 mmol), 4-chlorophenylboronic acid (29 mg, 0.18 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (10 mg, 5%) and 1.5 M K_2CO_3 (0.39 mL, 0.59 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/diethyl ether 5−35%). Yield: 46 mg (56%). HPLC-purity: 99%. 1H NMR (200 MHz, DMSO) δ 9.04 (s, 1H), 8.78 (s, 1H), 7.89 (d, $J = 8.5$ Hz, 2H), 7.71−7.54 (m, 3H), 7.31 (t, $J = 8.7$ Hz, 1H), 3.19−3.05 (m, 2H), 1.75 (dd, $J = 14.8$, 7.6 Hz, 2H), 0.97 (t, $J = 7.2$ Hz, 3H); 13C NMR (50 MHz, DMSO) δ 182.9, 152.8, 150.0, 142.3, 136.4, 133.5, 132.0, 130.3 (dd, $J = 10$, 2 Hz), 129.7, 129.6, 128.1, 122.2 (dd, $J = 14$, 4 Hz), 117.5 (dd, $J = 23$, 21 Hz), 113.9, 112.6 (dd, $J = 22$, 4 Hz), 54.1, 17.2, 13.0; ESI-HRMS: $m/z = 489.06149$, calcd for $C_{22}H_{17}ClF_2N_4O_3S$ $m/z = 489.06052$ $[M-H]^-$. IR (ATR) [cm^{-1}] 1673, 1486, 1432, 1140, 895, 825, 500.

***N*-(2,4-Difluoro-3-(5-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (11).** Compound **11** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), phenylboronic acid (15 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.59 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0−35%) and trituration with *n*-hexane. Yield: 27 mg (56%). HPLC-purity: 97%.1H NMR (200 MHz, DMSO) δ 7.84 (d, $J = 7.2$ Hz, 2H), 7.71−7.40 (m, 4H), 7.31 (t, $J = 8.7$ Hz, 1H), 3.18−3.04 (m, 2H), 1.87−1.63 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); 13C NMR (101 MHz, DMSO) δ 182.6, 152.3, 149.8, 141.9, 137.2, 133.0, 129.9, 129.8, 129.3, 128.4, 128.1, 127.6, 127.5, 126.7, 113.6, 53.9, 16.8, 12.6; ESI-HRMS: $m/z = 455.10002$, calcd for $C_{22}H_{18}F_2N_4O_3S$ $m/z = 455.09949$ $[M-H]^-$. IR (ATR) [cm^{-1}] 1486, 1145, 974, 791, 700, 558, 408.

***N*-(3-(5-(2-Chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (12).** Compound **12** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2-chlorophenylboronic acid (22 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0−30%) and trituration with DCM and *n*-hexane. Yield: 23 mg (43%). HPLC-purity: 99%. 1H NMR (200 MHz, DMSO) δ 15.00 (s, 1H), 9.82 (s, 1H), 8.79 (d, $J = 2.1$ Hz, 1H), 8.62 (d, $J = 2.1$ Hz, 1H), 7.73−7.44 (m, 5H), 7.31 (td, $J = 9.0$, 1.6 Hz, 1H), 3.19−2.94 (m, 2H), 1.87−1.61 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H). ESI-HRMS: $m/z = 489.06052$, calcd for $C_{22}H_{17}ClF_2N_4O_3S$ $m/z = 489.06052$ $[M-H]^-$. IR (ATR) [cm^{-1}] 1686, 1478, 1436, 1328, 1240, 1132, 987, 916, 762, 789, 621, 500.

***N*-(3-(5-(3-Chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (13).** Compound **13** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-chlorophenylboronic acid (19 mg, 0.14 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.59 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0−35%). Yield: 30 mg (56%). HPLC-purity: 99%. 1H NMR (200 MHz, DMSO) δ 9.05 (s, 1H), 8.80 (s, 1H), 8.06−7.19 (m, 6H), 3.18−3.03 (m, 2H), 1.91−1.61 (m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H); 13C NMR (101 MHz, DMSO) δ 182.5, 152.4, 149.8, 142.0, 139.4, 133.9, 131.5, 130.9, 129.9, 129.8, 128.1, 127.9, 127.2, 126.2, 121.8 (dd, $J = 13.0$, 3.1 Hz), 113.4, 112.1 (dd, $J = 22.8$, 3.4 Hz), 53.8, 16.8, 12.5; ESI-HRMS: $m/z = 489.006115$, calcd for $C_{22}H_{17}ClF_2N_4O_3S$ $m/z = 489.06052$ $[M-H]^-$.IR (ATR) [cm^{-1}] 1686, 1495, 1432, 1149, 979, 816, 558, 508.

***N*-(2,4-Difluoro-3-(5-(2-fluorophenyl)-1*H*-pyrazolo[3,4-*b*] pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (14).** Compound **14** was prepared according to **general procedure A** using **65b** (60 mg, 0.17 mmol), 2-fluorophenylboronic acid (24 mg, 0.17 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (8 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0−30%). Yield: 38 mg (61%). HPLC-purity: 99%. 1H NMR (200 MHz, DMSO) δ 14.97 (s, 1H), 9.85 (s, 1H), 8.91 (t, $J = 1.9$ Hz, 1H), 8.77−8.61 (m, 1H), 7.80−7.25 (m, 6H), 3.18−3.02 (m, 2H), 1.86−1.64 (m, 2H), 0.97 (t, $J = 7.5$ Hz, 3H); ESI-HRMS: $m/z = 473.09043$, calcd for $C_{22}H_{17}F_3N_4O_3S$ $m/z = 473.09007$ $[M-H]^-$. IR (ATR) [cm^{-1}] 1682, 1599, 1482, 1253, 1145, 941, 804, 762, 712, 566, 500, 475.

***N*-(2,4-Difluor-3-(5-(3-Fluorphenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-carbonyl)phenyl)propan-1-sulfonamide (15).** Compound **15** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-fluorophenylboronic acid (17 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0−35%). Yield: 31 mg (60%). HPLC-purity: 100%. 1H NMR (400 MHz, DMSO) δ 14.96 (s, 1H), 9.82 (s, 1H), 9.06 (d, $J = 2.1$ Hz, 1H), 8.81 (d, $J = 2.1$ Hz, 1H), 7.79−7.53 (m, 4H), 7.37−7.24 (m, 2H), 3.16−3.07 (m, 2H), 1.82−1.68 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); 13C NMR (101 MHz, DMSO) δ 182.5, 163.9, 161.5, 152.3, 149.8, 142.0, 139.6, 139.5, 131.6, 131.6, 131.2, 131.1, 129.9, 129.8, 128.0, 123.6, 121.9, 121.8, 121.7, 121.7, 114.9, 114.7, 114.4, 114.2, 113.4, 112.2, 112.2, 112.0, 112.0, 53.8, 16.8, 12.5; ESI-HRMS: $m/z = 473.09063$, calcd for $C_{22}H_{17}F_3N_4O_3S$ $m/z = 473.09007$ $[M-H]^-$. IR (ATR) [cm^{-1}] 1682, 1490, 1320, 1153, 979, 900, 820, 778, 554, 504.

***N*-(2,4-Difluoro-3-(5-(4-fluorophenyl)-1*H*-pyrazolo[3,4-*b*]**

pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (16). Compound **16** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-fluorophenylboronic acid (17 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–35%). Yield: 33 mg (64%). HPLC-purity: 100%.^{1}H NMR (200 MHz, DMSO) δ 14.91 (s, 1H), 9.89 (s, 1H), 9.02 (d, J = 2.1 Hz, 1H), 8.74 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 8.6, 5.4 Hz, 2H), 7.64 (td, J = 9.0, 5.9 Hz, 1H), 7.45–7.21 (m, 3H), 3.21–3.02 (m, 2H), 1.87–1.61 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 163.5, 161.0, 157.5, 157.5, 155.1, 155.0, 154.0, 153.9, 152.1, 151.5, 151.5, 149.7, 141.9, 133.6, 133.6, 132.0, 129.8, 129.7, 129.6, 129.5, 127.6, 121.9, 121.8, 121.7, 121.7, 117.3, 117.3, 117.1, 117.1, 116.9, 116.9, 116.1, 115.9, 113.4, 112.2, 112.2, 112.0, 112.0, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 473.09057, calcd for $C_{22}H_{17}F_3N_4O_3S$ m/z = 473.09007 [M-H]$^-$. IR (ATR) [cm^{-1}] 1677, 1490, 1440, 1315, 1228, 1144, 974, 811, 537, 503.

***N*-(2,4-Difluoro-3-(5-(*o*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (17).** Compound **17** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2-methylphenylboronic acid (19 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2 mL) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%) and trituration with DCM and *n*-hexane. Yield: 32 mg (62%). HPLC-purity: 99%. ^{1}H NMR (200 MHz, DMSO) δ 8.75 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H), 7.67 (td, J = 9.0, 5.9 Hz, 1H), 7.48–7.23 (m, 5H), 3.24–3.00 (m, 2H), 2.31 (s, 3H), 1.89–1.65 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ESI-HRMS: m/z = 469.11528, calcd for $C_{23}H_{20}F_2N_4O_3S$ m/z = 469.11514 [M-H]$^-$. IR (ATR) [cm^{-1}] 1677, 1477, 1432, 1323, 1244, 1312, 982, 907, 757, 724, 636, 620, 503.

***N*-(2,4-Difluoro-3-(5-(*m*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (18).** Compound **18** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-methylphenylboronic acid (16 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 34 mg (66%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.92 (s, 1H), 9.86 (s, 1H), 9.05 (d, J = 2.1 Hz, 1H), 8.77 (d, J = 2.1 Hz, 1H), 7.74–7.56 (m, 3H), 7.55–7.23 (m, 3H), 3.22–3.00 (m, 2H), 2.45 (s, 3H), 1.92–1.58 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 152.2, 149.9, 141.9, 138.6, 137.1, 133.1, 129.2, 128.8, 128.1, 127.5, 124.6, 113.6, 53.8, 21.1, 16.9, 12.6; ESI-HRMS: m/z = 469.11596, calcd for $C_{23}H_{20}F_2N_4O_3S$ m/z = 469.11514 [M-H]$^-$. IR (ATR) [cm^{-1}] 1674, 1482, 1241, 1128, 766, 695, 646, 496.

***N*-(2,4-Difluoro-3-(5-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (19).** Compound **19** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-methylphenylboronic acid (16 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 37 mg (72%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.91 (s, 1H), 9.85 (s, 1H), 9.01 (d, J = 1.9 Hz, 2H), 8.72 (d, J = 2.0 Hz, 2H), 7.82–7.55 (m, 5H), 7.45–7.23 (m, 4H), 3.21–3.04 (m, 3H), 2.38 (s, 4H), 1.86–1.64 (m, 3H), 0.97 (t, J = 7.3 Hz, 4H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 152.1, 149.8, 141.8, 137.6, 134.3, 132.9, 129.9, 127.3, 127.1, 121.8 (dd, J = 13, 4 Hz), 113.6, 112.2 (dd, J = 22, 4 Hz), 53.8, 20.7, 16.9, 12.6; ESI-HRMS: m/z = 469.11596, calcd for $C_{23}H_{20}F_2N_4O_3S$ m/z = 469.11514 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1486, 1432, 1324, 1153, 970, 804, 554, 512.

***N*-(2,4-Difluoro-3-(5-(2-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (20).** Compound **20** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2-methoxyphenylboronic acid (18 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–40%). Yield: 46 mg (87%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.90 (s, 1H), 9.83 (s, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 7.63 (td, J = 9.0, 5.9 Hz, 1H), 7.45 (dd, J = 12.8, 4.6 Hz, 2H), 7.38–7.05 (m, 3H), 3.82 (s, 3H), 3.17–3.04 (m, 2H), 1.87–1.61 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 156.3, 151.6, 151.5, 141.7, 130.9, 130.7, 129.8, 129.8, 126.2, 121.1, 113.1, 111.9, 55.7, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 485.11061, calcd for $C_{23}H_{20}F_2N_4O_4S$ m/z = 485.11006 [M-H]$^-$. IR (ATR) [cm^{-1}] 1481, 1432, 1315, 1244, 1136, 753, 720, 503.

***N*-(2,4-Difluoro-3-(5-(3-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (21).** Compound **21** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-methoxyphenylboronic acid (18 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–40%). Yield: 33 mg (62%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.94 (s, 1H), 9.83 (s, 1H), 9.04 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 7.64 (td, J = 9.1, 6.0 Hz, 1H), 7.51–7.26 (m, 4H), 7.09–6.99 (m, 1H), 3.87 (s, 3H), 3.20–2.99 (m, 2H), 1.86–1.61 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 159.9, 152.3, 150.0, 141.9, 138.7, 132.9, 130.4, 127.7, 121.8 (dd, J = 13, 4 Hz), 119.8, 113.9, 113.5, 112.9, 55.3, 53.8, 16.9, 12.6; ESI-HRMS: m/z = 485.10872, calcd for $C_{23}H_{20}F_2N_4O_4S$ m/z = 485.11006 [M-H]$^-$. IR (ATR) [cm^{-1}] 1678, 1594, 1495, 1436, 1141, 783, 691, 558, 504.

***N*-(2,4-Difluoro-3-(5-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (22).** Compound **22** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-methoxyphenylboronic acid (18 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–40%). Yield: 33 mg (62%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.87 (s, 1H), 9.79 (s, 1H), 9.00 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.63 (td, J = 9.0, 5.9 Hz, 1H), 7.31 (td, J = 9.0, 1.3 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 3.83 (s, 1H), 3.22–3.03 (m, 1H), 1.86–1.63 (m, 1H), 0.97 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 159.5, 152.0, 149.6, 141.8, 132.8, 129.9, 129.4, 128.7, 126.7, 114.8, 113.7, 55.3, 53.9, 16.9, 12.6; ESI-HRMS: m/z = 485.11009, calcd for $C_{23}H_{20}F_2N_4O_4S$ m/z = 485.11006 [M-H]$^-$. IR (ATR) [cm^{-1}] 1503, 1253, 1137, 899, 837, 795, 708, 496.

***N*-(2,4-Difluoro-3-(5-(2-hydroxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (23).** Compound **23** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2-hydroxyphenylboronic acid (17 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–50%). Yield: 29 mg (56%). HPLC-purity: 94%. ^{1}H NMR (200 MHz, DMSO) δ 14.89 (s, 1H), 9.88 (s, 2H), 8.87 (d, J = 2.1 Hz, 1H), 8.71 (d, J = 2.1 Hz, 1H), 7.63 (td, J = 9.0, 6.0 Hz, 1H), 7.45 (dd, J = 7.3, 1.4 Hz, 1H), 7.38–7.21 (m, 2H), 7.10–6.89 (m, 2H), 3.20–3.02 (m, 2H), 1.86–1.64 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.7, 154.6, 151.6, 151.5, 141.7, 131.1, 130.8, 130.0 129.8, 129.7, 129.6, 124.2, 121.8 (dd, J = 13, 4 Hz), 119.9, 116.2, 113.2, 112.2 (dd, J = 23, 4 Hz), 53.8, 16.9, 12.6; ESI-HRMS: m/z = 471.09516, calcd for $C_{22}H_{18}F_2N_4O_4S$ m/z = 471.09441 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1436, 1253, 1141, 895, 755, 500.

***N*-(2,4-Difluoro-3-(5-(3-hydroxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (24).** Compound **24** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-hydroxyphenylboronic acid (17 mg,

0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–50%) and trituration with DCM. Yield: 32 mg (62%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 15.21 (s, 1H), 10.04 (s, 2H), 9.32 (d, J = 2.1 Hz, 1H), 9.03 (d, J = 2.1 Hz, 1H), 7.98 (td, J = 9.1, 6.0 Hz, 1H), 7.76–7.43 (m, 4H), 7.29–7.14 (m, 1H), 3.54–3.34 (m, 2H), 2.19–1.96 (m, 2H), 1.31 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 158.0, 152.2, 149.6, 141.8, 138.4, 133.0, 130.3, 127.3, 118.1, 115.1, 114.1, 113.5, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 471.09437, calcd for $C_{22}H_{18}F_2N_4O_4S$ m/z = 471.09441 [M-H]$^-$. IR (ATR) [cm^{-1}] 1678, 1594, 1495, 1436, 1141, 783, 691, 558, 504.

***N*-(2,4-Difluoro-3-(5-4-hydroxyphenyl)-1*H*-pyrazolo[3,4-*b*] pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (25).** Compound **25** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-hydroxyphenylboronic acid (17 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G3 (6 mg) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–55%) and trituration with DCM. Yield: 33 mg (64%). HPLC-purity: 96%. ^{1}H NMR (200 MHz, DMSO) δ 14.86 (s, 1H), 9.82 (s, 1H), 9.73 (s, 1H), 8.97 (d, J = 2.1 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 7.72–7.52 (m, 3H), 7.30 (t, J = 8.8 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 3.19–3.00 (m, 2H), 1.85–1.63 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 157.7, 151.8, 149.5, 141.7, 133.1, 128.6, 127.7, 126.2, 116.1, 113.6, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 471.09510, calcd for $C_{22}H_{18}F_2N_4O_4S$ m/z = 471.09441 [M-H]$^-$. IR (ATR) [cm^{-1}] 1649, 1495, 1132, 833, 566, 504.

***N*-(3-(5-(2-Aminophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (26).** Compound **26** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2-aminophenylboronic acid (17 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–60%). Yield: 31 mg (60%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.85 (s, 1H), 9.87 (s, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 7.63 (td, J = 9.1, 6.0 Hz, 1H), 7.31 (t, J = 8.7 Hz, 1H), 7.20–7.03 (m, 2H), 6.82 (d, J = 7.8 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 5.02 (s, 2H), 3.18–3.03 (m, 2H), 1.85–1.58 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 151.8, 151.3, 145.9, 141.7, 132.4, 130.7, 129.8, 129.7, 129.0, 122.2, 116.9, 115.5, 113.6, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 470.11087, calcd for $C_{22}H_{19}F_2N_5O_3S$ m/z = 470.11039 [M-H]$^-$. IR (ATR) [cm^{-1}] 1675, 1618, 1487, 1336, 1136, 993, 899, 756, 653, 490.

***N*-(3-(5-(3-Aminophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (27).** Compound **27** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-aminophenylboronic acid (19 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2 mL) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–60%), trituration with DCM and *n*-hexane. Yield: 28 mg (54%). HPLC-purity: 98%. ^{1}H NMR (400 MHz, DMSO) δ 14.91 (s, 1H), 9.83 (s, 1H), 8.94 (s, 1H), 8.66 (s, 1H), 7.63 (s, 1H), 7.37–7.10 (m, 2H), 7.04–6.86 (m, 2H), 6.66 (d, J = 6.2 Hz, 1H), 5.30 (s, 2H), 3.12 (s, 2H), 1.75 (d, J = 5.9 Hz, 2H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 152.2, 149.5, 149.4, 141.7, 137.6, 133.7, 129.7, 126.9, 114.7, 113.7, 113.5, 112.5, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 470.11076, calcd for $C_{22}H_{19}F_2N_5O_3S$ m/z = 470.11039 [M-H]$^-$. IR (ATR) [cm^{-1}] 1594, 1486, 1432,1336, 1149, 987, 912, 870, 783, 566, 504.

***N*-(3-(5-(4-Aminophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (28).** Compound **27** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (26 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/(DCM/EtOAc (9 + 1) 0–60%). Yield: 28 mg (54%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 8.93 (s, 1H), 8.58 (s, 1H), 7.72–7.43 (m, 3H), 7.30 (t, J = 9.0 Hz, 1H), 6.72 (d, J = 7.9 Hz, 2H), 5.39 (s, 2H), 3.21–2.95 (m, 2H), 1.74 (dd, J = 13.9, 5.0 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H); ESI-HRMS: m/z = 470.11079, calcd for $C_{22}H_{19}F_2N_5O_3S$ m/z = 470.11039 [M-H]$^-$. IR (ATR) [cm^{-1}] 1490, 1440, 1324, 1278, 1253, 1149, 1008, 899, 816, 571, 504.

***N*-(3-(5-(3-(Dimethylamino)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (29).** Compound **29** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-dimethylaminophenylboronic acid (20 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–40%), trituration with DCM/*n*-hexane (2 + 1). Yield: 29 mg (53%). HPLC-purity: 97%. ^{1}H NMR (200 MHz, DMSO) δ 9.11–8.84 (m, 1H), 8.70 (d, J = 2.1 Hz, 1H), 7.64 (td, J = 9.0, 6.0 Hz, 1H), 7.32 (q, J = 8.1 Hz, 2H), 7.11–6.99 (m, 2H), 6.81 (dd, J = 8.1, 1.8 Hz, 1H), 3.18–3.04 (m, 2H), 2.99 (s, 6H), 1.87–1.63 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.3, 151.0, 150.0, 141.8, 137.9, 134.0, 129.7, 127.4, 115.3, 113.5, 112.2, 112.2, 112.1, 112.0, 112.0, 111.2, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 498.14204, calcd for $C_{24}H_{23}F_2N_5O_3S$ m/z = 498.14169 [M-H]$^-$. IR (ATR) [cm^{-1}] 1682, 1486, 1336, 1153, 991, 912, 762, 566.

***N*-(3-(5-(4-(Dimethylamino)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (30).** Compound **30** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), *N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (30 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G4 (4 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 115 °C for 45 min. Flash-chromatography (SiO_2, DCM/EtOAc 0–50%). Yield: 38 mg (70%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.83 (s, 1H), 9.82 (s, 1H), 8.98 (d, J = 2.2 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 7.73–7.54 (m, 3H), 7.31 (td, J = 8.9, 1.5 Hz, 1H), 6.87 (d, J = 8.9 Hz, 2H), 3.19–3.05 (m, 2H), 2.97 (s, 6H), 2.97 (s, 6H), 1.86–1.64 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 156.3 (dd, J = 249, 6 Hz), 152.7 (dd, J = 251, 9 Hz), 151.6, 150.2, 149.3, 141.6, 133.3, 129.7 (d, J = 9 Hz), 127.8, 125.3, 124.2, 121.74 (dd, J = 14, 3 Hz), 113.8, 112.8, 112.07 (dd, J = 23, 3 Hz), 53.8, 16.8, 12.5; ESI-HRMS: m/z = 498.14208, calcd for $C_{24}H_{23}F_2N_5O_3S$ m/z = 498.14169 [M-H]$^-$. IR (ATR) [cm^{-1}] 1599, 1490, 1432, 1366, 1316, 1141, 812, 558.

***N*-(3-(5-(2,4-Dichlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (31).** Compound **31** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 2,4-dichlorophenylboronic acid (27 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2 mL) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/(DCM/EtOAc (9 + 1) 0–60%). Yield: 28 mg (49%). HPLC-purity: 97%. ^{1}H NMR (200 MHz, DMSO) δ 15.03 (s, 1H), 9.83 (s, 1H), 8.78 (d, J = 2.1 Hz, 1H), 8.64 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 1.7 Hz, 1H), 7.71–7.55 (m, 3H), 7.35–7.22 (m, 1H), 3.17–3.05 (m, 2H), 1.86–1.58 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ESI-HRMS: m/z = 523.02184, calcd for $C_{22}H_{16}Cl_2F_2N_4O_3S$ m/z = 523.02155 [M-H]$^-$. IR (ATR) [cm^{-1}] 1682, 1482, 1328, 1323, 1124, 1053, 1020, 983, 920, 808, 708, 504.

***N*-(3-(5-(3,5-Dichlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (32).** Compound **32** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3,5-dichlorophenylboronic acid (23 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane

(0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 31 mg (54%). HPLC-purity: 95%. ^{1}H NMR (200 MHz, DMSO) δ 9.06 (d, J = 2.2 Hz, 1H), 8.86 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 1.8 Hz, 2H), 7.72–7.55 (m, 2H), 7.31 (td, J = 9.0, 1.5 Hz, 1H), 3.20–3.00 (m, 2H), 1.87–1.64 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.4, 152.7, 149.7, 142.1, 140.9, 134.8, 130.1, 128.7, 127.4, 126.3, 113.3, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 523.02155, calcd for $C_{22}H_{16}Cl_2F_2N_4O_3S$ m/z = 523.02155 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1590, 1486, 1141, 999, 904, 800, 558, 504.

***N*-(3-(5-(3,4-Dichlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (33).** Compound **33** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3,4-dichlorophenylboronic acid (27 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%), trituration with *n*-pentane. Yield: 34 mg (58%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 9.05 (s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 7.92–7.53 (m, 3H), 7.31 (t, J = 8.8 Hz, 1H), 3.26–2.91 (m, 2H), 1.90–1.58 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ESI-HRMS: m/z = 523.02171, calcd for $C_{22}H_{16}Cl_2F_2N_4O_3S$ m/z = 523.02155 [M-H]$^-$. IR (ATR) [cm^{-1}] 1678, 1590, 1482, 1424, 1316, 1257, 1124, 1024, 941, 895, 825, 704, 566, 487.

***N*-(3-(5-(3,4-Dimethylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (34).** Compound **34** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3,4-dimethylphenylboronic acid (18 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 34 mg (64%). HPLC-purity: 99%. ^{1}H NMR (200 MHz, DMSO) δ 14.44 (s, 1H), 9.37 (s, 1H), 8.54 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 2.1 Hz, 1H), 7.25–7.04 (m, 3H), 6.93–6.76 (m, 2H), 2.73–2.56 (m, 2H), 1.87 (s, 3H), 1.83 (s, 3H), 1.41–1.17 (m, 2H), 0.51 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.1, 149.7, 141.8, 137.1, 136.3, 134.5, 133.0, 130.3, 128.3, 126.9, 124.6, 113.5, 53.8, 19.3, 19.0, 16.8, 12.5; ESI-HRMS: m/z = 483.13124, calcd for $C_{24}H_{22}F_2N_4O_3S$ m/z = 483.13079 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1432, 1321, 1145, 971, 900, 814, 559, 508.

***N*-(3-(5-(4-Isopropylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (35).** Compound **35** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-isopropylphenylboronic acid (23 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2 mL) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 21 mg (39%). HPLC-purity: 97%. ^{1}H NMR (400 MHz, DMSO) δ 14.92 (s, 1H), 9.83 (s, 1H), 9.02 (s, 1H), 8.73 (s, 1H), 7.75 (d, J = 7.9 Hz, 2H), 7.69–7.59 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 8.8 Hz, 1H), 3.19–3.07 (m, 2H), 2.96 (dt, J = 13.6, 6.8 Hz, 1H), 1.82–1.67 (m, 2H), 1.25 (d, J = 6.9 Hz, 6H), 0.97 (t, J = 7.4 Hz, 3H); ESI-HRMS: m/z = 497.14710, calcd for $C_{25}H_{24}F_2N_4O_3S$ m/z = 497.14644 [M-H]$^-$. IR (ATR) [cm^{-1}] 1669, 1486, 1428, 1320, 1149, 1037, 970, 895, 812, 691, 558, 508.

***N*-(3-(5-(4-*tert*-Butylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (36).** Compound **36** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-*tert*-butylphenylboronic acid (21 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–25%). Yield: 41 mg (74%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.92 (s, 1H), 9.83 (s, 1H), 9.03 (d, J = 1.9 Hz, 1H), 8.73 (d, J = 1.7 Hz, 1H), 7.84–7.50 (m, 5H), 7.31 (t, J = 8.7 Hz, 1H), 3.22–3.01 (m, 2H), 1.85–1.63 (m, 2H), 1.34 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 156.3 (dd, J = 248, 7 Hz), 152.7 (dd, J = 251, 8 Hz), 152.1, 150.6, 149.7, 141.8, 134.2, 132.8, 127.1, 126.0, 121.8 (dd, J = 14, 3 Hz), 113.6, 112.1 (dd, J = 23, 4 Hz), 53.8, 39.5, 34.3, 31.0, 16.8, 12.5; ESI-HRMS: m/z = 511.16261, calcd for $C_{26}H_{26}F_2N_4O_3S$ m/z = 511.16209 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1495, 1432, 1149, 979, 816, 558, 508.

***N*-(3-(5-(4-Chloro-3-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (37).** Compound **37** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-chloro-3-trifluoromethylphenylboronic acid (21 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 110 °C for 1.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–25%). Yield: 31 mg (51%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 15.00 (s, 1H), 9.83 (s, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.33–8.10 (m, 2H), 7.89 (d, J = 8.3 Hz, 1H), 7.64 (td, J = 9.0, 6.0 Hz, 1H), 7.31 (td, J = 8.8, 1.2 Hz, 1H), 3.21–3.02 (m, 2H), 1.87–1.62 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.4, 149.8, 142.0, 136.9, 133.1, 132.3, 130.4, 128.6, 126.9, 126.8, 113.3, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 557.04836, calcd for $C_{23}H_{16}ClF_5N_4O_3S$ m/z = 557.04790 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1482, 1424, 1316, 1141, 974, 816, 554, 508.

***N*-(2,4-Difluoro-3-(5-(4-fluoro-2-methylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (38).** Compound **38** was prepared according to **general procedure A** using **65b** (62 mg, 0.13 mmol), 4-fluoro-2-methylphenylboronic acid (25 mg, 0.16 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (8 mg, 5%) and 1.5 M K_2CO_3 (0.31 mL, 0.47 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 49 mg (74%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.95 (s, 1H), 9.85 (s, 1H), 8.70 (d, J = 1.8 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H), 7.64 (td, J = 9.1, 6.0 Hz, 1H), 7.48–7.10 (m, 4H), 3.21–3.03 (m, 2H), 2.28 (s, 3H), 1.85–1.65 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 163.1, 160.6, 151.9, 151.1, 141.7, 138.5, 138.4, 134.0, 134.0, 132.7, 132.2, 132.1, 129.9, 129.8, 121.9, 121.7, 117.0, 116.8, 113.1, 113.0, 112.8, 112.2, 112.0, 53.8, 20.1, 16.8, 12.6; ESI-HRMS: m/z = 487.10665, calcd for $C_{23}H_{19}F_3N_4O_3S$ m/z = 487.10572 [M-H]$^-$. IR (ATR) [cm^{-1}] 1665, 1474, 1428, 1316, 1249, 1137, 916, 712, 500.

***N*-(2,4-Difluoro-3-(5-(3-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (39).** Compound **39** was prepared according to **general procedure A** using **65b** (53 mg, 0.12 mmol), 2-chloro-4-methoxyphenylboronic acid (22 mg, 0.14 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (7 mg, 5%) and 1.5 M K_2CO_3 (0.27 mL, 0.4 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–40%). Yield: 44 mg (73%). HPLC-purity: 97%. ^{1}H NMR (200 MHz, DMSO) δ 14.93 (s, 1H), 9.83 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 7.75–7.47 (m, 2H), 7.37–7.03 (m, 3H), 3.86 (s, 3H), 3.18–3.02 (m, 2H), 1.88–1.61 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 160.0, 151.9, 151.3, 141.8, 132.8, 132.5, 131.1, 130.4, 128.5, 121.9 (dd, J = 13, 4 Hz), 115.1, 114.0, 113.0, 55.8, 53.8, 16.9, 12.6; ESI-HRMS: m/z = 519.07206, calcd for $C_{23}H_{19}ClF_2N_4O_4S$ m/z = 519.07108 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1607, 1482, 1432, 1328, 1141, 1016, 720, 504.

***N*-(2,4-Difluoro-3-(5-(3-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (40).** Compound **40** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-trifluoromethylphenylboronic acid (27 mg, 0.14 mmol, 1.3 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.2 mL) in 1,4-dioxane (0.8 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–25%). Yield: 33 mg (58%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 14.99 (s, 1H), 9.83 (s, 1H), 9.10 (d, J = 2.2 Hz, 1H),

8.86 (d, J = 2.2 Hz, 1H), 8.26–8.02 (m, 2H), 7.87–7.54 (m, 3H), 7.32 (td, J = 8.7, 1.4 Hz, 1H), 3.18–2.99 (m, 2H), 1.86–1.54 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ESI-HRMS: m/z = 523.08771, calcd for $C_{23}H_{17}F_5N_4O_3S$ m/z = 523.08688 [M-H]$^-$. IR (ATR) [cm^{-1}] 1499, 1436, 1320, 1291, 1241, 1145, 1091, 904, 804, 700, 566, 500.

***N*-(2,4-Difluoro-3-(5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (41).** Compound **41** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-trifluoromethylphenylboronic acid (23 mg, 0.12 mmol, 1.1 equiv.), $Pd(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–30%). Yield: 29 mg (51%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 15.03 (s, 1H), 9.85 (s, 1H), 9.10 (d, J = 2.2 Hz, 1H), 8.86 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.64 (td, J = 9.0, 5.9 Hz, 1H), 7.32 (td, J = 8.9, 1.4 Hz, 1H), 3.24–2.96 (m, 2H), 1.89–1.60 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.5, 149.8, 142.0, 141.2, 131.4, 128.4, 128.3, 125.9, 125.9, 113.4, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 523.08726, calcd for $C_{23}H_{17}F_5N_4O_3S$ m/z = 523.08688 [M-H]$^-$. IR (ATR) [cm^{-1}] 1674, 1486, 1324, 1245, 1108, 837, 500.

***N*-(2,4-Difluoro-3-(5-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (42).** Compound **42** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 3-nitrophenylboronic acid (20 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G4 (6 mg) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–50%). Yield: 40 mg (73%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 14.99 (s, 1H), 9.84 (s, 1H), 9.13 (d, J = 2.2 Hz, 1H), 8.91 (d, J = 2.2 Hz, 1H), 8.64 (t, J = 1.9 Hz, 1H), 8.37–8.25 (m, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.64 (td, J = 9.0, 6.0 Hz, 1H), 7.32 (td, J = 9.0, 1.3 Hz, 1H), 3.21–3.04 (m, 1H), 1.88–1.61 (m, 1H), 0.97 (t, J = 7.4 Hz, 1H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 152.5, 149.9, 148.5, 142.1, 138.9, 134.2, 130.8, 130.7, 128.8, 122.8, 122.2, 113.4, 53.8, 16.9, 12.6; ESI-HRMS: m/z = 500.08487, calcd for $C_{22}H_{17}F_2N_5O_5S$ m/z = 500.08457 [M-H]$^-$. IR (ATR) [cm^{-1}] 1653, 1486, 1336, 1320, 1141, 987, 891, 841, 741, 616, 496.

***N*-(2,4-Difluoro-3-(5-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (43).** Compound **43** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-nitrophenylboronic acid (20 mg, 0.12 mmol, 1.1 equiv.), P(*t*-Bu)$_3$ Pd G4 (3 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 115 °C for 45 min. Flash-chromatography (SiO_2, DCM/EtOAc 0–50%). Yield: 21 mg (38%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 24.19 (s, 1H), 18.97 (s, 1H), 18.29 (d, J = 2.0 Hz, 1H), 18.06 (d, J = 2.1 Hz, 1H), 17.53 (d, J = 8.7 Hz, 2H), 17.32 (d, J = 8.7 Hz, 2H), 16.79 (td, J = 9.0, 5.8 Hz, 1H), 16.47 (t, J = 8.7 Hz, 1H), 12.35–12.17 (m, 2H), 11.01–10.78 (m, 2H), 10.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 159.7, 152.7, 149.9, 147.1, 143.8, 142.1, 130.7, 128.9, 128.8, 124.2, 113.4, 53.8, 16.9, 12.6; ESI-HRMS: m/z = 500.08512, calcd for $C_{22}H_{17}F_2N_5O_5S$ m/z = 500.08457 [M-H]$^-$. IR (ATR) [cm^{-1}] 1670, 1515, 1490, 1345, 1328, 1245, 1137, 991, 850, 492.

***N*-(2,4-Difluoro-3-(5-(4-(methylsulfony)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (44).** Compound **44** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-methylsulfonylphenylboronic acid (24 mg, 0.12 mmol, 1.1 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–50%). Yield: 34 mg (58%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 15.03 (s, 1H), 9.83 (s, 1H), 9.12 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.12 (q, J = 8.7 Hz, 4H), 7.72–7.55 (m, 1H), 7.32 (td, J = 9.0, 1.5 Hz, 1H), 3.30 (s, 3H), 3.21–3.03 (m, 2H), 1.85–1.64 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 182.6, 152.6, 150.0, 142.2, 142.1, 140.2, 131.3, 128.7, 128.5, 127.8, 121.8 (dd, J = 14, 4 Hz), 113.5, 53.8, 43.5, 16.9, 12.6; ESI-HRMS: m/z = 533.07774, calcd for $C_{23}H_{20}F_2N_4O_5S$ m/z = 533.07704 [M-H]$^-$. IR (ATR) [cm^{-1}] 1669, 1594, 1486, 1291, 1153, 895, 783, 533, 496.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzensulfonamide (45). Compound **45** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-sulfamoylphenylboronic acid (24 mg, 0.12 mmol, 1.1 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 10–60%). Yield: 39 mg (67%). HPLC-purity: 99%. ^{1}H NMR (200 MHz, DMSO) δ 14.53 (s, 1H), 9.37 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.28–7.06 (m, 2H), 7.02 (s, 2H), 6.86 (td, J = 8.8, 1.3 Hz, 1H), 2.76–2.53 (m, 2H), 1.40–1.18 (m, 2H), 0.51 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.4, 149.8, 143.5, 142.0, 140.3, 131.5, 131.5, 131.4, 128.7, 128.6, 128.2, 127.9, 126.4, 113.4, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 534.07295, calcd for $C_{22}H_{19}F_2N_5O_5S_2$ m/z = 534.07229 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1432, 1324, 1153, 891, 691, 554.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-*N*-methylbenzenesulfonamide (46). Compound **46** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), **R1** (26 mg, 0.12 mmol, 1.1 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 45 min. Flash-chromatography (SiO_2, DCM/EtOAc 20–60%), trituration with DCM. Yield: 33 mg (55%). HPLC-purity: 100%. ^{1}H NMR (400 MHz, DMSO) δ 15.01 (s, 1H), 9.83 (s, 1H), 9.11 (d, J = 2.1 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.64 (td, J = 9.0, 5.9 Hz, 1H), 7.58 (q, J = 5.0 Hz, 1H), 7.32 (t, J = 8.7 Hz, 1H), 3.19–3.02 (m, 2H), 1.80–1.70 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 152.5, 149.9, 142.0, 141.0, 138.8, 131.4, 128.4, 128.2, 127.5, 113.4, 53.8, 28.6, 16.8, 12.5; ESI-HRMS: m/z = 548.08842, calcd for $C_{23}H_{21}F_2N_5O_5S_2$ m/z = 548.28794 [M-H]$^-$. IR (ATR) [cm^{-1}] 1490, 1324, 1137, 899, 814, 566, 496.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-*N*-ethylbenzenesulfonamide (47). Compound **47** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), **R2** (25 mg, 0.11 mmol, 1.0 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 45 min. Flash-chromatography (SiO_2, DCM/EtOAc 10–50%), trituration with DCM. Yield: 33 mg (55%). HPLC-purity: 100%. ^{1}H NMR (400 MHz, DMSO) δ 14.97 (s, 1H), 9.82 (s, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 8.09 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H), 7.73–7.58 (m, 2H), 7.31 (t, J = 8.7 Hz, 1H), 3.16–3.06 (m, 2H), 2.89–2.80 (m, 2H), 1.81–1.69 (m, 2H), 1.05–0.94 (m, 6H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.5, 149.8, 142.0, 140.8, 140.0, 131.4, 128.3, 128.2, 127.3, 113.4, 53.8, 37.6, 16.8, 14.8, 12.5; ESI-HRMS: m/z = 562.10400, calcd for $C_{24}H_{23}F_2N_5O_5S_2$ m/z = 562.10359 [M-H]$^-$. IR (ATR) [cm^{-1}] 1499, 1328, 1149, 895, 695, 558, 496.

***N*-((4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)phenyl)sulfonyl)acetamide (48).** Compound **48** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), **R3** (46 mg, 0.14 mmol, 1.3 equiv.), XPhos Pd G3 (5 mg, 5%) and 1.5 M K_3PO_4 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.5 mL) at 120 °C for 30 min. Flash-chromatography (SiO_2, DCM/MeOH 5%). Yield: 27 mg (43%). HPLC-purity: 99%. ^{1}H NMR (400 MHz, DMSO) δ 15.01 (s, 1H), 12.21 (s, 1H), 9.83 (s, 1H), 9.11 (d, J = 2.1 Hz, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.12 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.64 (td, J = 9.0, 5.9 Hz, 1H), 7.32 (t, J = 8.5 Hz, 1H), 3.11 (dd, J = 5.7, 3.8 Hz, 2H), 1.96

(s, 3H), 1.83–1.69 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 168.9, 152.5, 149.9, 142.1, 138.8, 131.2, 128.6, 128.3, 128.1, 113.4, 53.8, 23.2, 16.8, 12.5; ESI-HRMS: m/z = 576.08346, calcd for $C_{24}H_{21}F_2N_5O_6S_2$ m/z = 576.08286 [M-H]$^-$. IR (ATR) [cm^{-1}] 1728, 1457, 1320, 1141, 866, 825, 537.

***N*-(2,4-Difluoro-3-(5-(4-(methylsulfonamido)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide (49).** Compound **49** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), **R4** (36 mg, 0.12 mmol, 1.1 equiv.), Pd(PPh$_3$)$_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 30 min. Flash-chromatography (SiO_2, DCM/MeOH 20–60%). Yield: 42 mg (69%). HPLC-purity: 99%. ^{1}H NMR (200 MHz, DMSO) δ 14.93 (s, 1H), 9.98 (s, 1H), 9.83 (s, 1H), 9.02 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.1 Hz, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.64 (td, J = 9.0, 6.1 Hz, 1H), 7.43–7.26 (m, 3H), 3.19–3.03 (m, 5H), 1.86–1.63 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.1, 149.6, 141.8, 138.5, 132.4, 128.3, 127.0, 120.0, 113.5, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 548.08820, calcd for $C_{23}H_{21}F_2N_5O_5S_2$ m/z = 548.08794 [M-H]$^-$. IR (ATR) [cm^{-1}] 1490, 1457, 1336, 1307, 1441, 887, 820, 500.

***N*-(3-(5-(4-(1*H*-Tetrazol-5-yl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorphenyl)propane-1-sulfonamide (50).** Compound **50** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-(1*H*-tetrazol-5-yl)phenylboronic acid (23 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G4 (5 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.3 mL) at 120 °C for 30 min. Flash-chromatography (SiO_2, DCM/MeOH (+1% formic acid) 5%). Yield: 45 mg (79%). HPLC-purity: 100%. ^{1}H NMR (200 MHz, DMSO) δ 14.99 (s, 1H), 9.83 (s, 1H), 9.14 (d, J = 2.1 Hz, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 19.9, 8.4 Hz, 4H), 7.65 (td, J = 9.0, 6.1 Hz, 1H), 7.32 (td, J = 9.0, 1.4 Hz, 1H), 3.20–3.05 (m, 2H), 1.90–1.59 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 156.29 (dd, J = 248.3, 6.4 Hz), 152.8 (dd, J = 251.2, 8.2 Hz),152.4, 149.8, 142.0, 139.7, 131.7, 129.9, 129.8, 128.3, 127.9, 127.7, 127.6, 123.8, 121.79 (dd, J = 13.4, 3.4 Hz), 117.1, 113.5, 112.12 (dd, J = 22.6, 4.3 Hz), 53.8, 16.8, 12.5; ESI-HRMS: m/z = 523.11225, calcd for $C_{23}H_{18}F_2N_8O_3S$ m/z = 523.11179 [M-H]$^-$. IR (ATR) [cm^{-1}] 1481, 1436, 1153, 899, 845, 749, 499.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzoic acid (51). Compound **51** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-carboxyphenylboronic acid (23 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G4 (5 mg, 5%) and 1.5 M K_2CO_3 (0.33 mL, 0.49 mmol, 4.5 equiv.) in 1,4-dioxane (0.4 mL) at 120 °C for 30 min. Flash-chromatography (SiO_2, DCM/MeOH (+1% formic acid) 5%). Yield: 41 mg (75%). HPLC-purity: 99%. ^{1}H NMR (200 MHz, DMSO) δ 14.99 (s, 1H), 13.14 (bs, 1H), 9.83 (s, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.84 (d, J = 2.2 Hz, 1H), 8.04 (dd, J = 22.3, 8.5 Hz, 4H), 7.64 (td, J = 9.0, 5.9 Hz, 1H), 7.31 (td, J = 8.9, 1.5 Hz, 1H), 3.21–3.03 (m, 2H), 1.86–1.61 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 167.0, 152.4, 149.8, 142.0, 141.3, 131.8, 130.2, 130.1, 128.1, 127.6, 113.5, 53.8, 16.8, 12.5; ESI-HRMS: m/z = 499.08935, calcd for $C_{23}H_{18}F_2N_4O_5S$ m/z = 499.08932 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1499, 1145, 895, 766, 571, 504.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzamide (52). Compound **52** was prepared according to **general procedure A** using **65b** (50 mg, 0.11 mmol), 4-carbamoylphenylboronic acid (20 mg, 0.12 mmol, 1.1 equiv.), XPhos Pd G4 (5 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) in 1,4-dioxane (0.4 mL) at 120 °C for 30 min. Flash-chromatography (SiO_2, DCM/MeOH 2–15%). Yield: 34 mg (60%). HPLC-purity: 96%. ^{1}H NMR (400 MHz, DMSO) δ 14.97 (s, 1H), 9.83 (s, 1H), 9.10 (d, J = 1.3 Hz, 1H), 8.83 (d, J = 1.3 Hz, 1H), 8.13–7.92 (m, 5H), 7.64 (td, J = 8.9, 6.2 Hz, 1H), 7.46 (s, 1H), 7.32 (t, J = 8.7 Hz, 1H), 3.18–3.06 (m, 2H), 1.83–1.68 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 167.4, 152.4, 149.8, 142.0, 139.8, 133.7, 132.0, 128.4, 127.9, 127.2, 113.5, 53.8, 16.8, 12.6; ESI-HRMS: m/z = 498.10575, calcd for $C_{23}H_{19}F_2N_5O_4S$ m/z = 498.10531 [M-H]$^-$. IR (ATR) [cm^{-1}] 1686, 1490, 1411, 1324, 1141, 895, 500.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-fluorobenzenesulfonamide (53). Compound **53** was prepared according to **general procedure A** using **65b** (89 mg, 0.19 mmol), **R5** (233 mg, 0.78 mmol, 4.1 equiv.), XPhos Pd G4 (17 mg, 5%) and 1.5 M K_2CO_3 (0.78 mL, 0.16 mmol, 3.5 equiv.) in 1,4-dioxane (1 mL) at 130 °C for 20 min. Flash-chromatography (SiO_2, DCM/MeOH 3–10%), trituration with DCM. Yield: 27 mg (24%). HPLC-purity: 94%. ^{1}H NMR (200 MHz, DMSO) δ 15.06 (s, 1H), 9.83 (s, 1H), 8.95 (s, 1H), 8.81 (s, 1H), 7.99 (t, J = 8.0 Hz, 1H), 7.88–7.74 (m, 2H), 7.73–7.55 (m, 3H), 7.40–7.23 (m, 1H), 3.22–2.98 (m, 2H), 1.88–1.59 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ESI-HRMS: m/z = 552.06320, calcd for $C_{22}H_{18}F_3N_5O_5S_2$ m/z = 552.06287 [M-H]$^-$. IR (ATR) [cm^{-1}] 1490, 1320, 1153, 895, 587, 492.

4-(3-(2,6-Difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)-3-methylbenzenesulfonamide (54). A vessel was charged with **67** (75 mg, 0.13 mmol), **R6** (35 mg, 0.14 mmol, 1.1 equiv.), XPhos Pd G3 (3 mg, 2.5%) and purged with argon. Degassed 1,4-Dioxan (0.4 mL) and degassed 1.5 M K_2CO_3 (0.25 mL, 0.38 mmol, 3.5 equiv.) were added and the reaction was stirred at 55 °C for 1.5 h. The reaction was diluted with *i*-PrOH, strongly acidified with conc. HCl and stirred at 70 °C over night. The reaction was neutralized with $NaHCO_3$-solution and extracted with EtOAc. After removal of the solvent, the product was isolated by flash-chromatography (SiO_2, DCM/EtOAc 10–50%) and triturated with DCM. Yield: 41 mg (58%). HPLC-purity: 99%. ^{1}H NMR (400 MHz, DMSO) δ 15.00 (s, 1H), 9.82 (s, 1H), 8.76 (d, J = 2.0 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 7.84 (s, 1H), 7.78 (dd, J = 8.0, 1.3 Hz, 1H), 7.67–7.56 (m, 2H), 7.44 (s, 2H), 7.31 (t, J = 8.7 Hz, 1H), 3.16–3.07 (m, 2H), 1.80–1.69 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 152.0, 150.7, 143.7, 141.8, 141.0, 136.6, 132.4, 130.9, 129.9, 127.3, 123.3, 113.0, 53.8, 20.1, 16.8, 12.5; ESI-HRMS: m/z = 548.08844, calcd for $C_{23}H_{21}F_2N_5O_5S_2$ m/z = 548.08794 [M-H]$^-$. IR (ATR) [cm^{-1}] 1495, 1320, 1128, 899, 583, 504.

3-Chloro-4-(3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzensulfonamide (55). A vessel was charged with **67** (71 mg, 0.12 mmol), **R7** (39 mg, 0.14 mmol, 1.1 equiv.), Pd(PPh$_3$)$_4$ (7 mg, 5%) and purged with argon. Degassed 1,4-Dioxan (0.4 mL) and degassed 1.5 M K_2CO_3 (0.24 mL, 0.38 mmol, 3.5 equiv.) were added and the reaction was stirred at 55 °C for 1 h. The reaction was diluted with *i*-PrOH, strongly acidified with conc. HCl and stirred at 70 °C over night. The reaction was neutralized with $NaHCO_3$-solution and extracted with EtOAc. After removal of the solvent, the product was isolated by flash-chromatography (SiO_2, DCM/EtOAc 20–60%). Yield: 23 mg (31%). HPLC-purity: 94%. ^{1}H NMR (200 MHz, DMSO) δ 8.82 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H), 7.96–7.81 (m, 2H), 7.74–7.55 (m, 3H), 7.31 (t, J = 8.7 Hz, 1H), 3.19–3.05 (m, 3H), 1.87–1.62 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 183.1, 152.7, 151.3, 145.9, 142.5, 140.2, 133.4, 132.9, 131.2, 130.6, 127.3, 125.2, 122.4, 113.3, 54.4, 17.3, 13.1; ESI-HRMS: m/z = 568.03364, calcd for $C_{22}H_{18}F_2N_5O_5S_2$ m/z = 568.03332 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1324, 1141, 1095, 899, 492.

4-(3-(2,6-Difluoro-3-(methylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzenesulfonamide (56) Compound **56** was prepared according to **general procedure A** using **65a** (50 mg, 0.12 mmol), 4-sulfamoylphenylboronic acid (26 mg, 0.13 mmol, 1.1 equiv.), P(PPh$_3$)$_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.27 mL, 0.41 mmol, 3.5 equiv.) in 1,4-dioxane (0.4 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 50–100%),

trituration with DCM. Yield: 37 mg (62%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 14.99 (s, 1H), 9.85 (s, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.86 (d, J = 2.1 Hz, 1H), 8.03 (dd, J = 20.8, 8.4 Hz, 4H), 7.65 (td, J = 9.1, 6.1 Hz, 1H), 7.48 (s, 2H), 7.33 (t, J = 8.8 Hz, 1H), 3.08 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 156.40 (dd, J = 248.5, 6.7 Hz), 153.0 (dd, J = 251.5, 8.0 Hz), 152.4, 149.8, 143.5, 142.0, 140.3, 131.5, 130.0, 129.9, 128.2, 127.9, 126.4, 121.8 (dd, J = 13.3, 3.5 Hz), 117.13 (dd, J = 23.0, 21.5 Hz), 113.4, 112.15 (dd, J = 22.1, 3.1 Hz), 40.4; ESI-HRMS: m/z = 506.04162, calcd for $C_{20}H_{15}F_2N_5O_5S_2$ m/z = 506.04099 [M-H]$^-$.IR (ATR) [cm^{-1}] 1686, 1499, 1424, 1332, 1311, 1145, 904, 546, 500.

4-(3-(2,6-Difluoro-3-(butylsulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzenesulfonamide (57). Compound **57** was prepared according to **general procedure A** using **65c** (50 mg, 0.11 mmol), 4-sulfamoylphenylboronic acid (23 mg, 0.12 mmol, 1.1 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.25 mL, 0.37 mmol, 3.5 equiv.) in 1,4-dioxane (0.4 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 20–60%), trituration with DCM. Yield: 37 mg (62%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 15.00 (s, 1H), 9.82 (s, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.13–7.93 (m, 4H), 7.64 (td, J = 9.0, 6.2 Hz, 1H), 7.48 (s, 2H), 7.32 (td, J = 8.9, 1.2 Hz, 1H), 3.21–3.07 (m, 2H), 1.82–1.61 (m, 2H), 1.50–1.27 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 182.5, 156.3 (dd, J = 248, 6 Hz), 152.7 (dd, J = 251, 9 Hz), 152.4, 149.8, 143.5, 142.0, 140.3, 131.5, 129.9, 129.8, 128.2, 127.9, 127.5, 126.4, 126.3, 121.8 (dd, J = 13, 4 Hz), 117.1 (dd, J = 23, 21 Hz), 113.4, 112.2, 112.2, 112.0, 51.8, 25.1, 20.7, 13.4. ESI-HRMS: m/z = 548.08853, calcd for $C_{23}H_{21}F_2N_5O_5S_2$ m/z = 548.08794 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1323, 1161, 1132, 890, 695, 545.

4-(3-(2,6-Difluoro-3-((phenylmethyl)sulfonamido)benzoyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-yl)benzenesulfonamide (58). Compound **58** was prepared according to **general procedure A** using **65d** (50 mg, 0.10 mmol), 4-sulfamoylphenylboronic acid (22 mg, 0.11 mmol, 1.1 equiv.), $P(PPh_3)_4$ (6 mg, 5%) and 1.5 M K_2CO_3 (0.23 mL, 0.35 mmol, 3.5 equiv.) in 1,4-dioxane (0.4 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 20–60%), trituration with DCM. Yield: 30 mg (49%). HPLC-purity: 98%. ^{1}H NMR (200 MHz, DMSO) δ 15.01 (s, 1H), 9.89 (s, 1H), 9.11 (d, J = 1.7 Hz, 1H), 8.87 (d, J = 1.7 Hz, 1H), 8.17–7.81 (m, 4H), 7.70–7.14 (m, 9H), 4.54 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 182.6, 156.0 (dd, J = 248, 6 Hz), 152.4, 152.1 (dd, J = 251, 7 Hz), 149.8, 143.5, 142.0, 140.4, 132.0, 131.9, 131.5, 131.5, 131.4, 130.9, 129.2, 128.7, 128.6, 128.3, 128.3, 127.9, 127.5, 126.4, 126.3, 122.10 (dd, J = 13, 4 Hz), 117.2, 117.0, 113.4, 111.9 (dd, J = 22, 4 Hz) 58.5; ESI-HRMS: m/z = 582.07248, calcd for $C_{26}H_{19}F_2N_5O_5S_2$ m/z = 582.07229 [M-H]$^-$. IR (ATR) [cm^{-1}] 1486, 1336, 1153, 899, 691, 537, 487.

***N*-(3-(5-(4-Aminophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)-1-phenylmethanesulfonamide (59).** Compound **59** was prepared according to **general procedure A** using **65d** (155 mg, 0.31 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (70 mg, 0.32 mmol, 1.05 equiv.), $P(PPh_3)_4$ (11 mg, 5%) and 1.5 M K_2CO_3 (0.61 mL, 0.92 mmol, 3 equiv.) in 1,4-dioxane (1 mL) at 120 °C for 0.5 h. Flash-chromatography (SiO_2, DCM/EtOAc 0–60%), trituration with DCM. Yield: 64 mg (40%). HPLC-purity: 100%. 1H NMR (200 MHz, DMSO) δ 14.80 (s, 1H), 9.84 (s, 1H), 8.94 (d, J = 1.6 Hz, 1H), 8.60 (d, J = 1.5 Hz, 1H), 7.65–7.14 (m, 9H), 6.72 (d, J = 8.3 Hz, 2H), 5.40 (s, 2H), 4.53 (s, 2H); ESI-HRMS: m/z = 518.11101, calcd for $C_{26}H_{19}F_2N_5O_3S$ m/z = 518.10984 [M-H]$^-$.

Author contributions

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Declaration of competing interest

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113371.

Supporting information

Experimental procedures for the synthesis of intermediates **R1** – **R12**, results from scanEDGE kinase profiling for **58**, representative NMR spectra for compounds **61**–**67** and **58**.

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