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Discovery of 7-(3-(piperazin-1-yl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives as highly potent and selective PI3Kδ inhibitors

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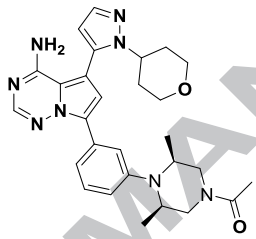

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ABSTRACT

Abstract: As demonstrated in preclinical animal models, the disruption of PI3Kδ expression or its activity leads to a decrease in inflammatory and immune responses. Therefore, inhibition of PI3Kδ may provide an alternative treatment for autoimmune diseases, such as RA, SLE, and respiratory ailments. Herein, we disclose the identification of 7-(3-(piperazin-1-yl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives as highly potent, selective and orally bioavailable PI3Kδ inhibitors. The lead compound demonstrated efficacy in an *in vivo* mouse KLH model.

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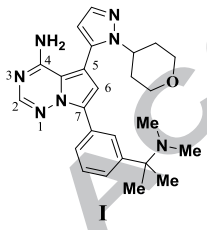
Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that phosphorylate the 3-hydroxyl position of the inositol ring of phosphatidylinositol (PI) substrate within the plasma membrane and intracellular compartments. Phosphoinositide 3-kinases are divided into two classes: class IA and class IB. PI3K class IA includes PI3Kα, PI3Kβ and PI3Kδ, and PI3K class IB includes PI3Kγ. PI3Kα and PI3Kβ are both involved in insulin signaling. PI3Kα also protects the heart against myocardial infarction-induced heart failure and PI3Kβ functions in platelet activation. PI3Kδ is involved in early signaling events of leukocytes responding to a wide variety of stimuli. Its expression is mainly in leukocytes, and its signaling function is via the production of phosphoinositide 3,4,5-triphosphate at the proximity of activated receptors for recruiting other signaling molecules.[1-3] PI3Kδ is the main PI3K isoform responsible for B cell development and activation. It is also responsible for T cell differentiation, activation and function. PI3Kγ takes over only some B cell functions in the absence of PI3Kδ.[3-5] Therefore, PI3Ks are preferentially studied to potentially provide new cures for various diseases mediated by one or more PI3K isoforms. Many non-specific PI3K inhibitors have been reported.[6-13] Recently, the search for selective inhibitors of PI3K isoforms has been increased. Mechanistically, PI3Kδ plays a critical role in mediating immune cell function that makes it a research priority in the search for treatments for autoimmune diseases and B-Cell malignacies.[14-18] Inhibition of PI3Kδ leads to a decrease of immune responses which has been validated in animal disease models for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[19-21] The study of PI3Kδ mRNA and protein expression levels in RA patients also provides solid evidence that selective inhibition of PI3Kδ may result in potential treatments for inflammatory diseases.[22] However, recent articles also describe situations where inhibition of PI3Kδ can activate the immune system.[23] There are some reports about relatively potent and selective PI3Kδ inhibitors,[24-31] but it still remains a significant challenge to identify a PI3Kδ inhibitor that is both highly potent and selective against all other PI3K isoforms. Described herein is our efforts to identify a potent and selective PI3Kδ inhibitor.

In our previous report, compound **I** (**Figure 1**) was efficacious at 30 mg/kg in a mouse collagen induced arthritis model.[32] However, the compound showed acute toxicity in an exploratory tox study in mice at 300 mg/kg/day dose. Therefore, finding a replacement of **I** became our mission.



I

PI3Kδ (IC_{50}) = 2 nM
Selectivity:
δ/α = 665; δ/γ = 130; δ/β = 800
CD86 WB (IC_{50}) = 118 nM
hERG (Patch clamp) = 65% @ 10 μM
Na^+(Patch clamp) = 17% @ 10 μM (1Hz)
Microsomal stability in mouse:
58% remaining @ 0.5μM 10 min. incubation

Figure 1. Profile of Compound I

Computational modeling of our HTS hit in PI3Kδ (**Figure 2**), suggested two important binding interactions, one between C4-NH_2 and Glu826 on the hinge, and the other between N-3 of the triazine ring and Val828. When bound in this manner, the cyclohexyl ring sits next to the gatekeeper residue, Ile825.

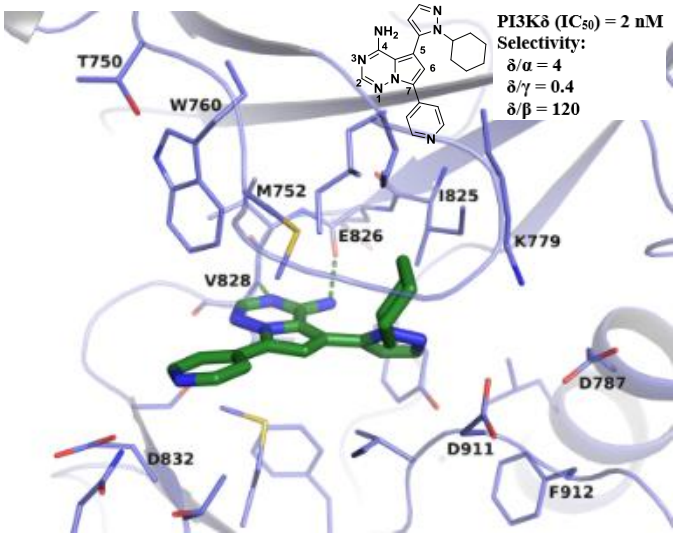
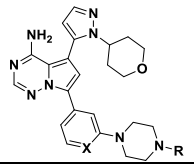


Figure 2. The computational model of HTS hit in PI3Kδ

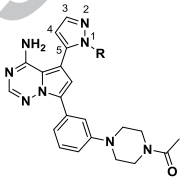
Table 1. Initial optimization



	R	X	PI3K δ IC50 (nM)[a]	selectivity		
				δ vs. α	δ vs. γ	δ vs. β
1	H	N	1.8	47	6	338
4		N	4.7	39	10	184
5		N	0.8	72	6	1323
6		N	5.2	46	10	1778
2	H	C	5.0	70	23	129
7		C	2.0	197	35	1001
8		C	0.9	252	55	1984
9		C	2.4	73	22	1247

[a] All PI3K isoform assays were performed in ADP Glo format

There is a selectivity pocket between Trp760 and Thr750, and the model suggested substitutions on the pyridine ring that project into this pocket might improve selectivity against other PI3K isoforms. Furthermore, the lack of hydrogen bonding between the nitrogen of the pyridine ring and PI3Kδ suggested that the pyridine could be replaced by a phenyl ring. Additional analysis of the model indicated that the pyridine ring was in the same plane as the pyrrolotriazine. Therefore, an ortho substituent on the pyridine which forced the aminopyrrolotriazine and pyridine rings to rotate out of plane would likely interfere with the binding of C4-NH_2 and N-3 with the hinge residues. In contrast, the para position was directed into an open space where a substituent might have a more limited impact on selectivity. Based on these observations, optimization of the substituent at the meta position on the C-7 aryl group was initiated. In preliminary SAR studies, replacement of the cyclohexyl ring with an isosteric 4-tetrahydropyran at N-1 of the C-5 pyrazole resulted in both improved selectivity against other PI3K isoforms and improved metabolic stability.[32] Based on these results, continued C-7 optimization was conducted with 4-tetrahydropyran on the C-5 pyrazole. Compared to the HTS hit, compounds **1 and 4-6** (**Table 1**), which incorporated a piperazinyl moiety at the meta position on the pyridine ring, exhibited better δ activity and improved selectivity against the other PI3K isoforms. In addition, when the pyridine moiety was replaced by a phenyl ring (**2** and **7-9**), the resultant compounds were equipotent (<5 nM) with the pyridine derivatives (**1** and **4-6**), but were more selective against the α and γ isoforms. As indicated in **Table 1**, PI3Kβ selectivity was generally not an issue for this chemotype. Substitution on N-1 of the C-5 pyrazole ring was then investigated (**Table 2**). Here, the data suggested that the steric and electronic effects of the R group did not have a significant impact on PI3Kδ enzyme potency and selectivity, although the 4-tetrahydropyran (**9**) provided better cellular potency than the other R groups that were studied.



	R	PI3Kδ IC50 (nM)	selectivity			B-cell prolif IC50 (nM)[a]	CD86/C69 WB IC50 (nM)[b]
			δ vs.α	δ vs.γ	δ vs.β		
10		2.5	66	37	1017	-	681/-
11		5.0	134	25	1001	26	422/-
12		6.6	136	27	755	-	-/1208
13		5.5	134	25	914	17	-/143
9		2.4	73	22	1247	2.2	66/4.0

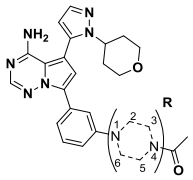
Table 2. SAR study of the R group on N1 of the C5-pyrazole

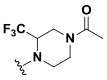
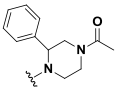
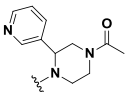
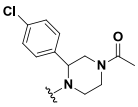
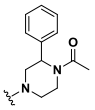
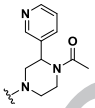
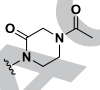
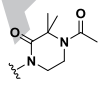
[a] Inhibition of human B-cell proliferation was measured by thymidine incorporation.
[b] Human whole blood assay measuring suppression of CD86 or CD69 expression

Compound **9** was highly active in the human B cell proliferation assay (IC_{50}: 2.2 nM), and in the human whole blood CD69 assay (IC_{50}: 3.5 nM), and was moderately active in the human whole blood CD86 assay (IC_{50}: 66 nM). Using **9**, an X-ray co-crystal structure was obtained with the kinase domain of PI3Kδ (**Figure 3**) that displayed similar hinge binding as the HTS hit (**Figure 2**). In addition, it was observed that the acyl piperazine of **9** stacks with Trp760 which allows the acyl oxygen to form a hydrogen bond with Thr750. In contrast, an X-ray co-crystal structure of **9** obtained with PI3Kα indicated that Arg770 moves to allow the acyl piperazine to stack with Trp780 (**Figure 4**) which provides no opportunity for the acyl oxygen to be involved in a similar hydrogen bond interaction with PI3Kα, and likely provides an explanation for the observed PI3Kα selectivity. Fixing C-5 as 4-tetrahydropyran-pyrazole, a SAR study of substitution of the piperazine attached to the C-7 phenyl was conducted (**Table 3**). New compounds **14-24** (**Table 3)** were all very potent in the

PI3Kδ enzyme assay, and selectivity against the other PI3K isoforms improved with the size of the R group. Although compound **18**,

Table 3. SAR study of piperazine moiety at the meta position of the C-7 phenyl



	R	PI3Kδ IC50 (nM)	selectivity δ vs. α	selectivity δ vs. γ	selectivity δ vs. β	B-cell Prolif. IC50 (nM)
9		2.4	73	22	1247	2.2
14		1.7	139	33	950	2.5
15		0.8	256	44	316	8.2
16		0.9	292	143	600	4.3
17		0.5	755	159	1359	1.7
18		1.3	75	34	70	---
19		1.3	611	44	1443	5.8
20		1.4	275	213	3000	50
21		4.3	69	6	95	36
22		1.2	117	20	598	24
23*		5.5	72	12	470	64
24*		0.3	251	93	2300	4.2

*Prepared via procedure *b* in Scheme 2.

(R=4-chlorophenyl) was still very potent against PI3Kδ, its selectivity against α and β dropped significantly. One explanation for these observed results could be that the hydrophobic substitution at 2 position of the piperazine enhances the stacking interaction between acyl piperazine and Trp760. However, when the substitution becomes too big, it collides with Trp760, which disrupts the stacking interaction and the hydrogen bond interaction between acyl oxygen and Thr750. Compounds **20-22**, which incorporated an R group at the 3 and/or 5 position of the piperazine ring were also very potent in the PI3Kδ enzyme assay, but lost ~10 fold potency in the B-cell proliferation assay, and were less selective compared to the corresponding 2 and/or 6 regio-isomers (**16, 17** and **19**). Compared to **9,** compound **23** exhibited similar δ

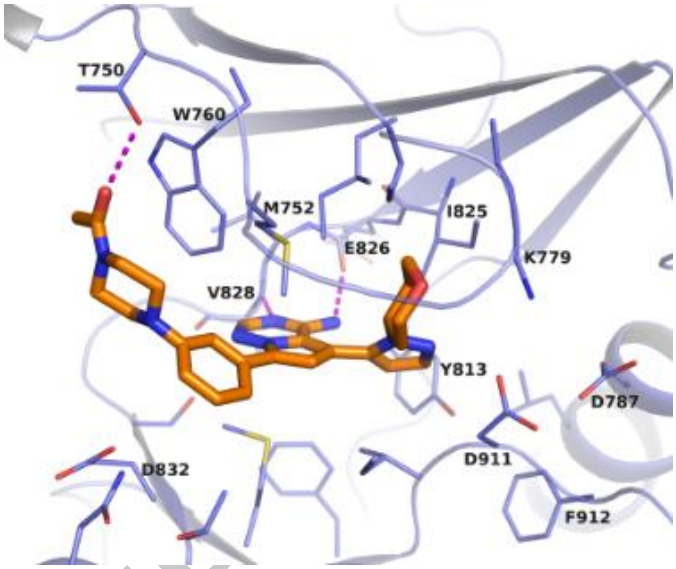


Figure 3. X-ray crystal structure of 9 in PI3Kδ (PDB code 5UBT)

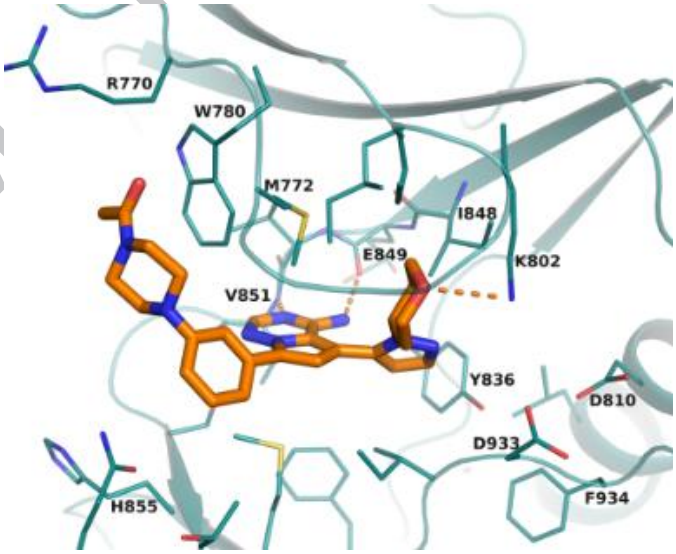
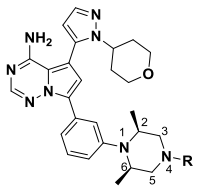


Figure 4. X-ray crystal structure of 9 in PI3Kα (PDB code 5UBR)

activity and selectivity against the other PI3K isoforms. Importantly, introduction of the carbonyl group in **23** improved metabolic stability. Furthermore, addition of a dimethyl group next to the carbonyl (**24**), significantly improved PI3Kδ activity and selectivity against α, β and γ. However, compound **24** showed poor permeability in Caco-2 assay. Next, the functional group attached to N-4 of the piperazine ring was studied (**Table 4**). Compounds in this series (**3**, **19** and **25-29**) were very potent in the PI3δ enzyme assay, and selectivity against PI3Kα increased with the size of the R group. In this set, **19** displayed the best human whole blood CD86 cellular potency which showed better correlations with further *in vivo* test results than other *in vitro* assay measurements. Keeping the 4-acyl-cis-2,6-dimethyl piperazinyl moiety at the meta position fixed, additional substitution on the C-7 aromatic ring was then investigated (**Table 5**). From this study, it was observed that substitution at the 5 position of the phenyl ring (**30** and **31**) or replacement of the phenyl with a 5-pyridine ring (**32**) improved selectivity against all of the other PI3K isoforms, but resulted in poor mouse liver microsomal stability. Based on the SAR outlined in **Tables 1-5**, compound **19** was selected for further characterization. Overall, **19** exhibited a favorable profile based on the results

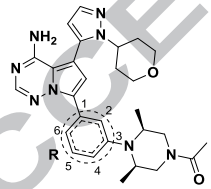
from *in vitro* liability assays (**Table 6**), and selectivity observed in both the enzyme and cellular PI3K assays. In mouse PK studies (**Table 7**), **19** exhibited sustained exposure that was equal to its IC_{50} in the CD86 whole blood assay (WB) at 3 mg/kg. Based on its favorable PK profile, **19** was then evaluated in a mouse KLH model to measure IgM antibody response. The compound was dosed twice a day (BID) and 250 µg of KLH was administered i.p. to BALB/c mice to induce an antibody response. In this study, compound **19** was efficacious at 3 mg/kg, reducing the IgM response by 63% (**Figure 5**). Compound **19** was then further evaluated in a 4-day exploratory toxicity study in mice at doses up to 300 mg/kg/day (QD), and found to be well tolerated at all doses (Day 4 AUC ≤ 520 µM●h; Cmax ≤ 55 µM). No morbidity/mortality was observed.

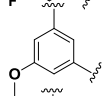
Table 4. SAR study of the R group on cis-2,6-dimethylpiperazine N-4



	R	PI3Kδ IC50 (nM)	selectivity δ vs.α	δ vs.γ	δ vs.β	B-cell Prolif. IC50 (nM)	CD86 WB IC50 (nM)
3	H	10.7	109	32	1053	-	314
25		6.4	108	40	1609	12	239
26		9.6	234	85	3140	39	193
19		1.3	611	44	1443	5.8	24
27		4.5	370	45	1115	-	81
28		1.5	390	64	1850	2.3	39
29		3.9	475	37	1269	28	291

Table 5. SAR study of the C-7 aryl group



	R	PI3Kδ IC50 (nM)	selectivity δ vs. α	δ vs. γ	δ vs. β	Mouse liver microsomal stability (% remaining)[a]
19		1.3	611	44	1443	54
30		0.9	628	56	2048	35
31		1.2	1244	190	2409	14
32		0.6	1036	148	1001	48

[a] Mouse liver microsomal stability assay at concentration of 0.5 µM for 10 min in a high throughput mode.

To support the SAR studies, a robust synthetic route was developed to efficiently access pyrrolo[2,1-f][1,2,4]triazine-4-amine derivatives (Scheme 1).[33,34] The route began with mono CBZ-protected hydrazine (**33**) which was reacted with

Table 6. Profile of compound 19

In vitro IC50		*Cellular assay IC50*	
δ (nM)	1.3	B cell prolif. (δ) (nM)	6
γ (nM)	57	CD86 WB (δ) (nM)	24
α (nM)	795	CD69 WB (δ) (nM)	13
β (nM)	1,876	CD86 Mo spleen (δ) (nM)	4
Met Stab (mouse)	54%		
Protein Binding (mouse, % free)	13.4		
hERG (patch clamp)	18% @ 10 µM		
Na^+ (patch clamp)	-2.6% @ 10 µM (1 Hz)		

Table 7. Exposures of 19 in Mouse KLH study (P.O.)

Time	0.6 mg/kg		3 mg/kg		15 mg/kg	
	C[a] (nM)	Ratio[b]	C[a] (nM)	Ratio[b]	C[a] (nM)	Ratio[b]
7h	<6.4	0.3	24.9		97.8	4
24 h	<5.6	0.2	<3.9	0.16	<7.0	0.3

[a] Concentration of compound **19** at noted time and dose
[b] Conc. of compound **19**/CD86 WB IC50

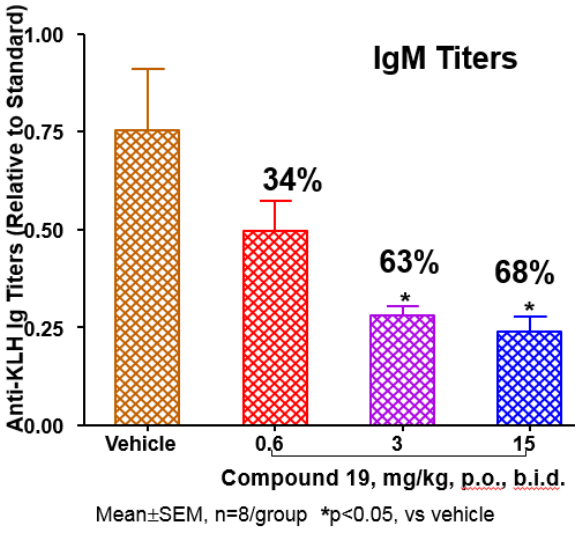
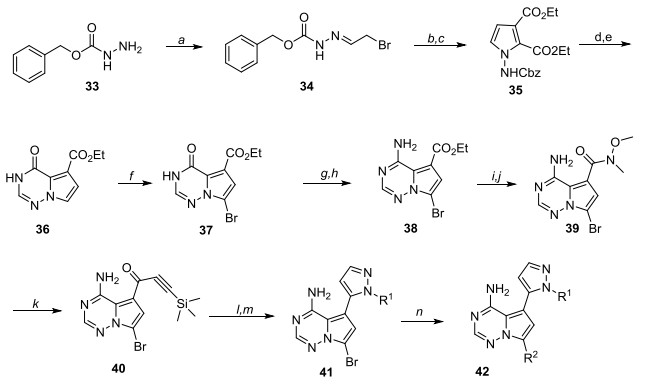


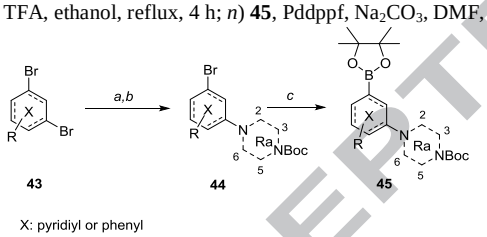
Figure 5. Compound 19 in KLH dependent antibody response

Bromoacetaldehyde dimethyl acetal to give **34**. Intermediate **34** was then reacted with the sodium salt of diethyl oxalacetate followed by cyclization in the presence of para-toluenesulfonic acid to give compound **35** in one pot. The CBZ group was

removed before treatment with formamidine gave **36**. Compound **36** was brominated with NBS to give **37**, which was then treated with thionyl chloride followed by displacement with ammonia to which was then treated with thionyl chloride followed by displacement with ammonia to provide **38**. Next, ester **38** was hydrolyzed, and converted to Weinreb amide **39**, which was treated with n-butyl lithium and TMS-acetylene to furnish **40**. Compound **40** was treated with dimethylamine, and then reacted with R^1-$NHNH_2$ to give **41** which was coupled with **45** to provide **42**. Finally, the Boc group was removed to furnish compounds **1-3**, or the free amine was further derivatized to give **4-32.** Incorporation of a piperazinyl moiety onto the C-7 aryl group was achieved via a Buchwald or Ullman coupling (**Scheme 2**). Intermediate **44** was converted to a pinacol boronic ester **45**, which was then used to synthesize the desired analogs as shown in **Scheme 1**.



Scheme 1 *a*) bromoacetaldehyde dimethyl acetal, H_3PO_4, H_2O, rt, 20 h; *b*) diethyl oxalacetate sodium salt, toluene, AcOH, rt, 20 h; *c*) p-TsOH, 50 °C 8 h; *d*) Pd/C, H_2 rt, 5 h; *e*) formamidine, AcOH, ethanol, 75 °C, 20 h; *f*) TFA, NBS, CH_2Cl_2, rt, 20 h; *g*) $SOCl_2$, DMF, reflux; *h*) conc. NH_4OH, dioxane, 0 °C, 30 min; *i*) NaOH, THF/H_2O (2:1), 70 °C, 4 h; *j*) N,O-dimethyl hydroxyl amine hydrochloride, T_3P, THF, 25 °C, 20 h; *k*) TMS-acetylene, *n*-butyl lithium, THF, -78 °C, 1 h; *l*) dimethylamine, THF, 25 °C, 20 h; *m*) R^1NHNH_2, TFA, ethanol, reflux, 4 h; *n*) **45**, Pddppf, Na_2CO_3, DMF, H_2O, 90 °C, 2 h



X: pyridiyl or phenyl

Scheme 2 *a*) a 4-Boc-piperazine moiety, BINAP, $Pd(OAc)_2$, Cs_2CO_3 or LiHMDS, toluene, 105 °C, 20 h; *b*) a 4-Boc-piperazine moiety, CuI, (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine, K_2CO_3, toluene, 105 °C, 20 h; *c*) bis(pinacolate)diboron, KOAc, $PdP(Ph_3)_4$, dioxane, 110 °C, microwave, 40 min

The identification and subsequent optimization of a novel class of 7-(3-(piperazin-1-yl)phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives as potent and selective PI3Kδ inhibitors have been described. Compound **19**, a highly potent and selective PI3Kδ inhibitor with improved hERG and ion channel profiles and an improved CD86 whole blood potency compared to compound **I**, showed efficacy in a mouse KLH model when dosed at 3 mg/kg BID. In a 4-day toxicity study in mice, no morbidity/mortality was observed, and compound **19** was well tolerated when dosed at 300 mg/kg (QD). Further evaluation and improvements in the physical and pharmacokinetic properties of compound **19** will be reported.

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