Table S1. Comparison of analogs 1,2 and control compound D-073.

	PI3K Biochemical Potency IC_{50} (μM)				PI3Kδ Cellular potency IC_{50} (μM)		Other properties				
Analog	δ	α	β	γ	B cell	pAKT	Sol.[a]	CYP 3A4/2D6[b]	Perm-eability[c]	Mouse IV CL[d]	Mouse PO %F[e]
2	0.12	65	7.9	2.6	0.075	-					
D-073	0.025	10	1.8	0.14	0.011	-	0.014	77/14	36	4.4	38
1	0.018	33	2.7	0.85	0.0086	0.0015	>200	<10/<10	30	0.54	45

[a]μg/mL. [b](%Inh.). [c]Papp x 10^{-6} cm/s. [d]dose iv. 0.5 mg/kg. 100% DMSO. [e]dose po 2.0 mg/kg, 1% Tween 80, 1% methyl cellulose, 98% water.

Preparation of Methyl, 3-(1,3-dioxoindolin-2-yl)-2-oxobutanoate

To a flask connected to an ozonator was added 4-(1,3-dioxoisoindolin-2-yl)-3-oxo-2-(triphenylphosphoranylidene)pentanenitrile (50.4 g, 100 mmol) in DCM (1 L) and MeOH (1 L). The mixture was stirred at -78 °C and ozone slowly sparged through the vessel. After 2.5 h the solution turned blue, and the reaction conditions maintained for an additional 4 h. The ozone was removed and reaction vessel was purged with N_2 overnight as it gradually warmed to rt. The solvents were removed under reduced pressure and the crude material was dissolved in EtOAc. This was set aside until the appearance of crystals of triphenyl phosphine oxide, which were filtered. The filtrate was concentrated and dissolved into a minimum DCM which was subjected to chromatography. 330 g silica redisep column 40-100% EtOAc in Hexane gradient (40% for 20 minutes) yield 56% (14.6 g, 55.8 mmol) Mass Spectrum (ESI)¬ m/e = 261.9 (M+1). The isolated product is a mixture of several undetermined isomers that did not affect the next step.

Preparation of 4-(1,3-dioxoisoindolin-2-yl)-3-oxo-2-(triphenylphosphoranylidene)pentanenitrile

(cyanomethyl)triphenylphosphonium chloride (60.0 g, 178 mmol) was dissolved in water (375 mL) and DCM (375 mL). NaOH (18.1 g, 452 mmol) in water (75 mL) was added slowly. After 1 h, the layers were separated and the organic layer washed with brine and dried over $MgSO_4$. This solution was added to a solution of phthaloyl-dl-alanine (22.0 g, 100 mmol), DMAP (1.48 g, 12.1 mmol), and EDCI (21.5 g, 112 mmol) in DCM (745 mL) at rt and stirred overnight. At this time water (1.9 L) was added, and the layers separated. The organic layer was washed with brine and dried over $MgSO_4$ and concentrated to dryness. Chromatography: redisep silica column (330 g and 120 g) 30-100% EtOAc in Hexane. yield 58% (51.7 g, 102.9 mmol) ^{1}H NMR (400 MHz, [D_6]DMSO) δ ppm 7.86 - 7.91 (2 H, m), 7.81 - 7.86 (2 H, m), 7.70 - 7.76 (3 H, m), 7.55 - 7.65 (12 H, m), 5.10 - 5.16 (1 H, m), 1.54 (3 H, d, *J* = 7.0 Hz) Mass Spectrum (ESI)¬ m/e = 502.9 (M+1).

Table S2. Data collection and refinement statistics

	PI3Kγ + **1**[†]	PI3Kγ + **16**[†]	PI3Kγ + **27**[†]
Data Collection			
Space group	C2	C2	C2
Cell dimensions			
a, b, c (Å)	143.9, 68.2, 106.7	145.9, 68.2, 107.4	143.0, 67.6, 106.0
α, β, γ (°)	90, 94.8, 90	90, 95.4, 90	90, 95.3, 90
Resolution (Å)	30 – 2.70 (2.80 – 2.70)	30 – 2.30 (2.38 – 2.30)	30 – 2.40 (2.49 – 2.40)
Total reflections	64610	177033	148533
Unique reflections	27232	46753	39103
Completeness (%)	95.3 (96.4)	99.7 (100)	98.6 (96.5)
R_{merge}	0.076 (0.399)	0.048 (0.678)	0.057 (0.667)
I/σ(I)	15.1 (2.3)	23.2 (2.2)	22.1 (2.1)
Refinement			
Reflections used	25280	44330	37119
R_{work}/R_{free}	0.216/0.291	0.219/0.274	0.211/0.252
Average B-value (Å^2)			
Protein	84	81	82
Ligand	65	66	60
Number of atoms			
Protein	6729	6594	6649
Ligand	29	30	30
Solvent	49	108	114
R.m.s. deviations			
Bond lengths (Å)	0.008	0.008	0.007
Bond angles (°)	1.14	1.14	1.13
PDB ID code	4WWN	4WWO	4WWP

[†] Values in parentheses are for the highest resolution shell.