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Discovery and in Vivo Evaluation of Dual PI3Kβ/δ Inhibitors

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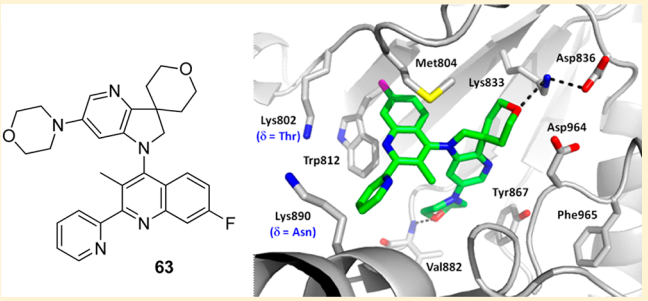
Supporting Information

ABSTRACT: Structure-based rational design led to the synthesis of a novel series of potent PI3K inhibitors. The optimized pyrrolopyridine analogue **63** was a potent and selective PI3Kβ/δ dual inhibitor that displayed suitable physicochemical properties and pharmacokinetic profile for animal studies. Analogue **63** was found to be efficacious in animal models of inflammation including a keyhole limpet hemocyanin (KLH) study and a collagen-induced arthritis (CIA) disease model of rheumatoid arthritis. These studies highlight the potential therapeutic value of inhibiting both the PI3Kβ and δ isoforms in the treatment of a number of inflammatory diseases.



INTRODUCTION

Class I phosphoinositide 3-kinases (PI3Ks) are lipid kinases that have emerged as attractive targets for the treatment of a number of diseases in both inflammation and oncology therapeutic areas.[1] All class I PI3Ks have the ability to catalyze the in vivo conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which induces Akt phosphorylation and acts as a secondary messenger in the control of a wide number of cellular functions including metabolism, cell growth and motility.[2] Class IA PI3Ks are composed of PI3Kα, β and δ, and these enzymes primarily respond to stimuli from receptor protein tyrosine kinases[3] whereas the sole representative of class IB, PI3Kγ, mainly responds to stimuli from GPCRs.[4] In terms of tissue distribution, PI3Kα and β are ubiquitously expressed whereas PI3Kγ and δ are mainly expressed in leukocytes. This expression pattern, in conjunction with mouse genetic studies, has established PI3Kα and β as promising targets for the treatment of human cancer[5] and, the central role of PI3Kγ and δ in leukocyte biology, suggested that inhibition of these two enzymes might also be a viable approach for the treatment of a variety of inflammatory diseases.[6] These findings have prompted the development of small molecule inhibitors targeting different PI3K isoforms,[1] and among these, the PI3Kδ inhibitor CAL-101[7] has shown promise for the potential treatment of cancer patients suffering from chronic lymphocytic leukemia (CLL)[8] or non-Hodgkin's lymphoma (NHL).[9]

To gain a better understanding of the in vivo pharmacology associated with inhibition of one or more of the PI3K isoforms, we embarked on a program to identify novel PI3K inhibitors that could ultimately become useful therapeutics for the treatment of a variety of oncology and/or inflammatory human diseases. This effort has resulted in the identification of a number of both dual PI3Kα/mTOR and selective PI3Kδ inhibitors which are in different phases of clinical development.[10,11] In this communication we report our progress toward the design and synthesis of inhibitors that target both the PI3Kβ and δ isoforms and describe our preclinical studies in animal models of inflammation.[12,13]

RESULTS AND DISCUSSION

As part of our research effort to identify novel PI3K inhibitors, lead compound **1** was designed by combining an indoline ring derived from our NF-κ-B-inducing kinase (NIK) program[14] with a quinoline core. The latter was conceived as a structural modification of a cinnoline ring identified as part of our internal p38 inhibitor program.[15] At the outset, it was hypothesized that compound **1** would be an ATP competitive inhibitor of PI3K with a binding mode in which the morpholine ring would interact with the hinge binder region of the enzyme, the geminal dimethyl group of the indoline would occupy the affinity pocket region and one of the methyl groups of the quinoline ring would partially reach into the ribose pocket (Figure 1). When compound **1** was synthesized and tested in an in vitro ATP loss assay,[16]

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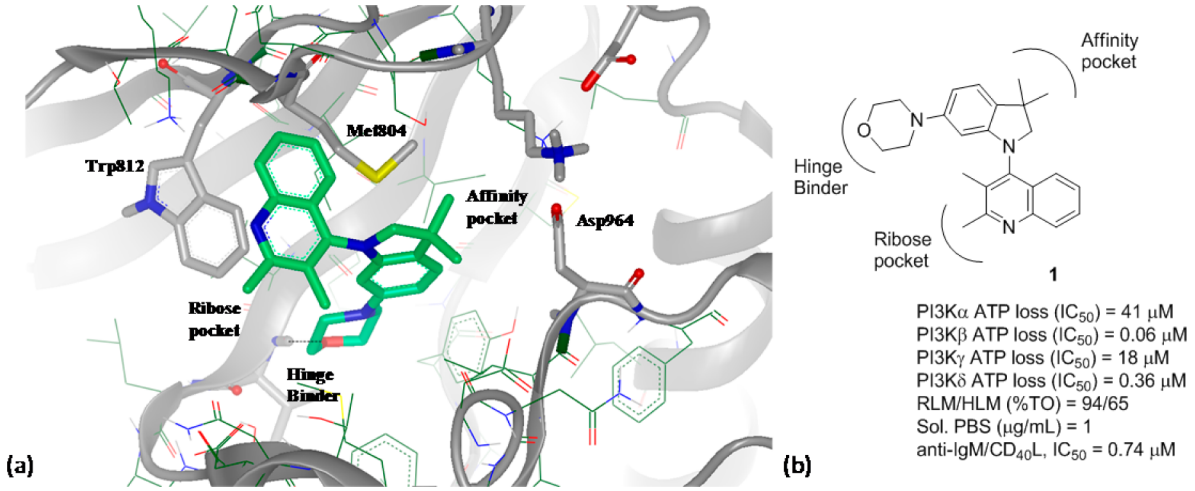
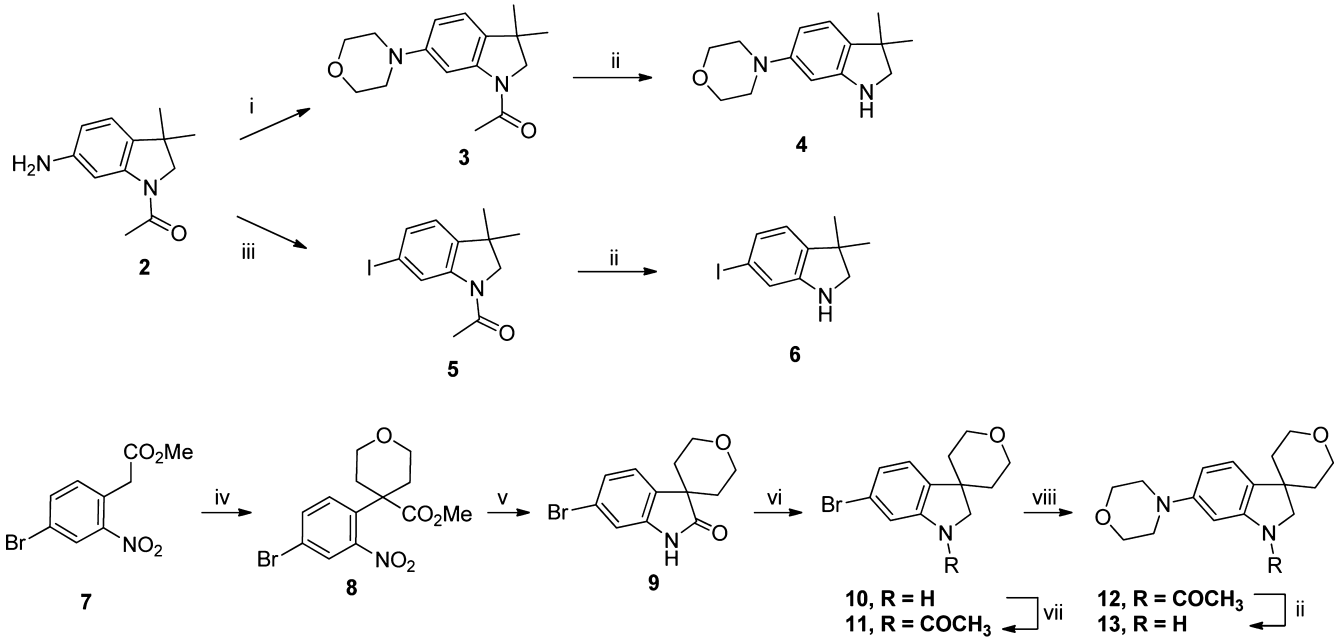


Figure 1. (a) Proposed binding mode of compound **1** with PI3Kδ. Dashed lines indicate hydrogen bond. Amino acid labels correspond to the PI3Kγ isoform. (b) Profile of lead analogue **1**.

Scheme 1[a]



[a]Reagents and conditions: (i) bis(2-bromoethyl) ether, 150 °C, 67%; (ii) HCl, 84−86%; (iii) $NaNO_2$, KI, 65%; (iv) NaH, bis(2-bromoethyl) ether, 36%; (v) Fe/AcOH, 72%; (vi) Red-Al, 64%; (vii) Ac_2O, DMAP, 86%; (viii) Pd_2dba_3, morpholine, XPhos, 72%.

we observed that it was a potent PI3Kβ inhibitor (IC_{50} = 60 nM) but exhibited moderate PI3Kδ potency (IC_{50} = 362 nM) and poor activity in an in vitro B-cell proliferation assay (anti-IgM/CD40L, IC_{50} = 745 nM).[17] This analogue also displayed poor physicochemical properties as illustrated by its poor microsomal stability and solubility.[18] To elucidate the pharmacological implications of inhibiting both PI3Kβ and δ isoforms, a systematic medicinal chemistry effort to optimize compound **1** was initiated. The specific goal of the program was to identify a potent PI3Kβ/δ dual inhibitor with suitable physicochemical properties (good microsomal stability, low potential for CYP inhibition, satisfactory PXR profile and good solubility) and pharmacokinetic (PK) profile for in vivo efficacy and tolerability studies. Notably, recent studies in chimeric mice prepared with bone marrow lacking both PI3Kβ and PI3Kδ activity have suggested that combined pharmacological inhibition of PI3Kβ and δ might be a viable strategy for the treatment of inflammatory diseases such as rheumatoid arthritis (RA).[19] To test this hypothesis, our optimized PI3Kβ/δ dual inhibitors were evaluated in animal models of inflammation.

Chemistry. The general synthetic route that provided access to these analogues is described in Scheme 3 and involved the coupling of indolines **4**, **6**, **10** or **13** (Scheme 1) with quinoline fragments **23a−f** (Scheme 2). The synthesis of indoline **4** started with available 1-(6-amino-3,3-dimethylindolin-1-yl)ethanone **2**,[20] which was transformed into the corresponding morpholino intermediate **3** by an alkylation reaction with bis(2-bromoethyl) ether. Subsequent deprotection with HCl afforded indoline **4**. Iodoindoline **6** was synthesized starting from aminoindoline **2**, via a diazotization−iodination reaction sequence and subsequent deprotection of the acetyl group in **5**. The synthesis of indolines **10** and **13** started with nitro compound **7**, which was deprotonated with NaH in DMF and alkylated with bis(2-bromoethyl) ether to provide

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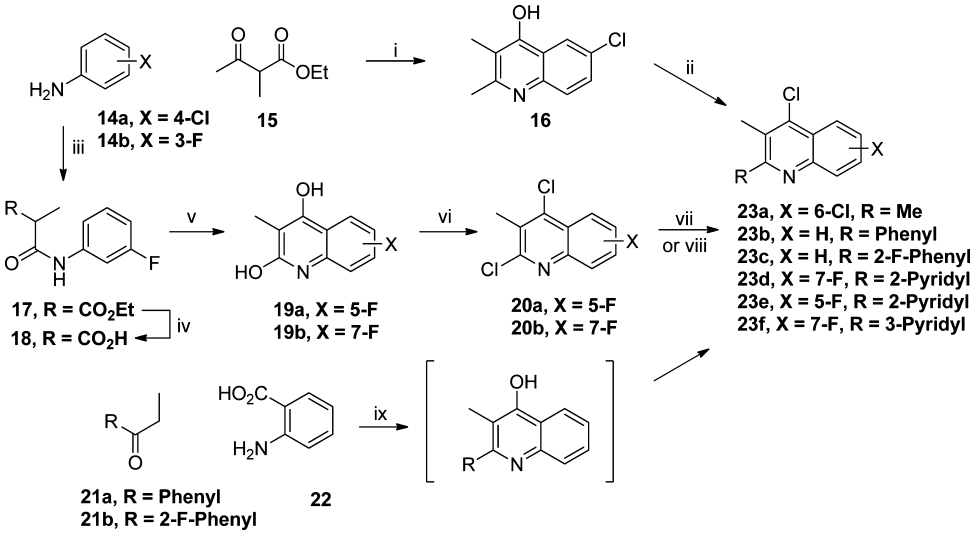
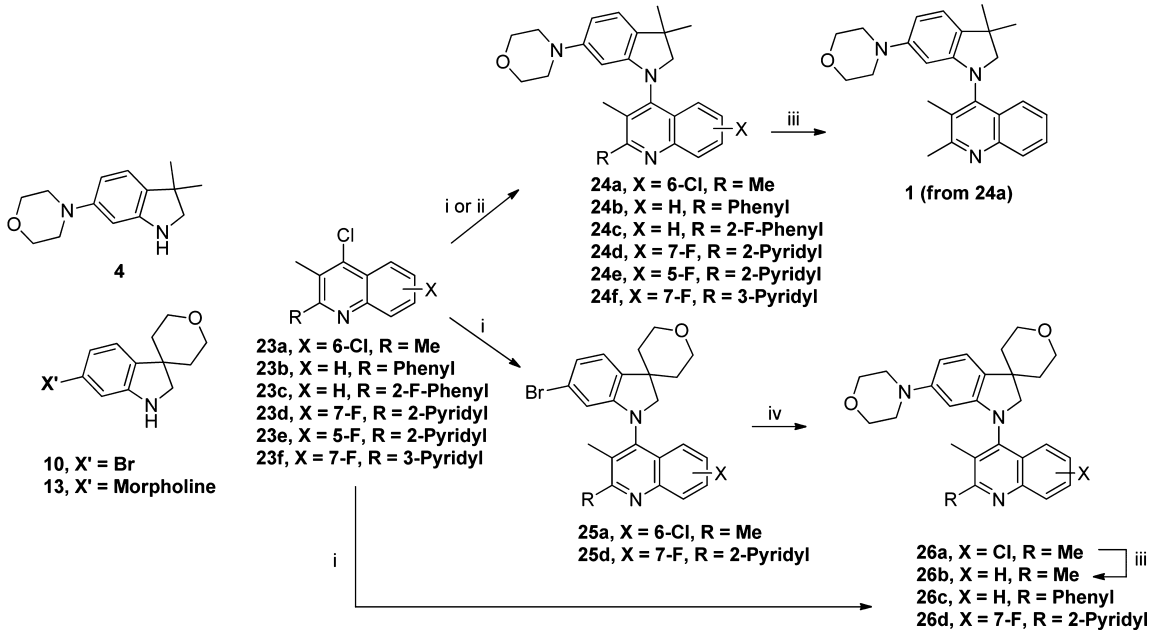
Scheme 2[a]



[a]Reagents and conditions: (i) PPA, 170 °C, 70%; (ii) $POCl_3$, reflux, 83%; (iii) diethyl methylmalonate, 130 °C, 49%; (iv) NaOH, 89%; (v) PPA, 130 °C, 81%; (vi) $POCl_3$, 100 °C, 45%; (vii) $Pd(PPh_3)_4$, 2-tributylstannylpyridine, 55%; (viii) $Pd(PPh_3)_4$, 3-tributylstannylpyridine, 55%; (ix) $POCl_3$, 90 °C.

Scheme 3[a]



[a]Reagents and conditions: (i) NaH, dimethylformamide, 2−51%; (ii) Pd_2dba_3, BINAP, Cs_2CO_3, 29−62%; (iii) H_2, Pd/C, 31−38%; (iv) CuI, K_2CO_3, L-proline, 13−23%.

tetrahydropyran **8**. Subsequent reduction of the nitro group with Fe/AcOH provided indolinone **9**, which was reduced with Red-Al to provide indoline fragment **10**. The synthesis of **13** was achieved in a three step sequence involving protection of the indoline nitrogen in **10** with an acetyl group, Pd-mediated coupling of **11** with morpholine and final acid mediated deprotection of **12**. Chloroquinolines **23a−f** were synthesized following three different synthetic routes (Scheme 2). The first approach started with chloroaniline **14a** which was reacted with ethyl 2-methyl-3-oxobutanoate in hot PPA and subsequently chlorodehydrated with $POCl_3$ to provide **23a**. Quinolines **23b,c** were synthesized by reaction of ketones **21a,b** with anthranilic acid in hot $POCl_3$ (Scheme 2, bottom). Lastly the synthesis of quinolines **23d−f** was carried out in a four step sequence involving reaction of 3-fluoroaniline (**14b**) with diethyl methyl malonate, basic ester hydrolysis of **17**, quinoline formation with PPA, chlorination with $POCl_3$ and final Stille reaction of chloro intermediates **20a,b** with $Pd(PPh_3)_4$ and 2(or 3)-tributylstannylpyridine.

Coupling of indoline **4** with chloroquinolines **23a,c** was carried out following a Pd-catalyzed protocol to provide analogues **24a,c**. Deprotonation of indoline **4** with NaH and subsequent S_NAr with chloroquinoline fragments **23b,d,e** afforded analogues **24b,d,e** (Scheme 3). The synthesis of **1** was achieved by hydrogenation of **24a** with Pd/C. Analogues **26a,d** were synthesized in a two step

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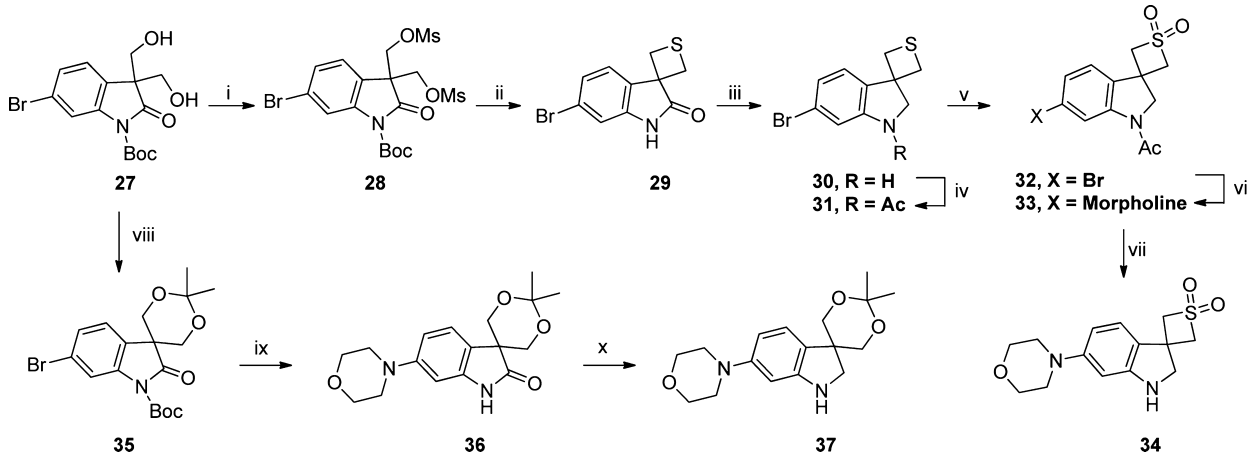
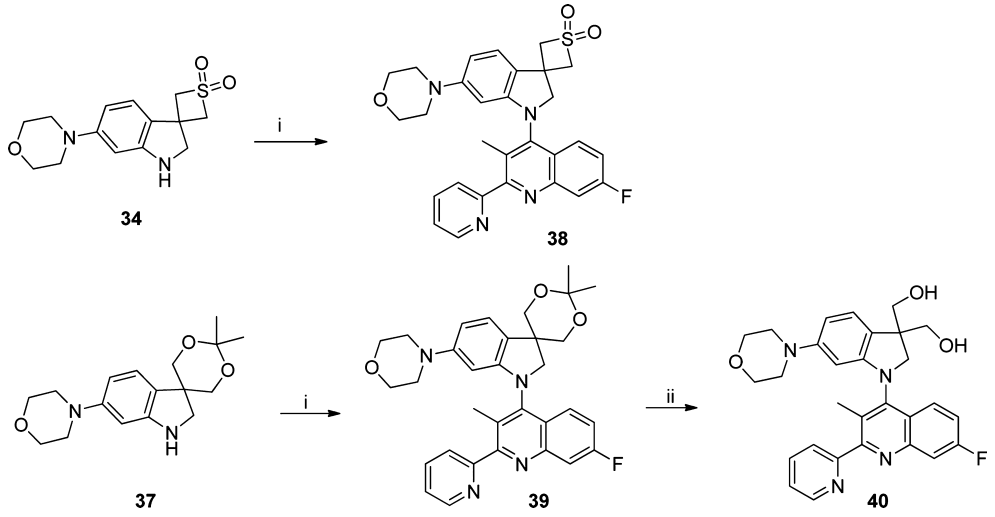
Scheme 4[a]



[a]Reagents and conditions: (i) MsCl, Et_3N, 56%; (ii) $Na_2S{\cdot}9H_2O$, 13%; (iii) Red-Al; (iv) AcCl; (v) Oxone, 24% (from **29**); (vi) Pd_2dba_3, XPhos, morpholine, 59%; (vii) HCl, 65%; (viii) 2,2-dimethoxypropane, 47%; (ix) Pd_2dba_3, XPhos, morpholine, 35%; (x) Red-Al, 53%.

Scheme 5[a]



[a]Reagents and conditions: (i) Pd_2dba_3, RuPhos, 26−57%, **23d**; (ii) HCl, 51%.

sequence employing a base-mediated coupling of quinolines **23a,d** with indoline **10** and final Cu-mediated coupling with morpholine. Hydrogenation of **26a** under catalytic Pd/C conditions afforded analogue **26b**. Analogue **26c** was synthesized via the base mediated coupling described before between indoline **13** and chloroquinoline **23b**.

A different set of analogues targeting the affinity pocket region of the PI3K enzyme were synthesized following the sequence described in Scheme 4. Diol **27**[21] was first reacted with mesyl chloride and then treated with sodium sulfide to afford 6-bromospiro[indoline-3,3′-thietan]-2-one (**29**). Subsequent Red-Al reduction of indolinone **29** provided indoline **30**, which was protected with acetyl chloride to afford intermediate **31**. Oxone oxidation of the cyclic sulfide in **31** provided sulfone intermediate **32**. Coupling of the morpholine ring in **32** was carried out with Pd_2dba_3 and XPhos, and final acid-catalyzed deprotection of the acetyl group provided indoline **34**. Alternatively, diol **27** was protected with 2,2-dimethoxypropane, and a Pd-mediated coupling with XPhos and morpholine gave intermediate **36**. Indolinone **36** was subsequently reduced with Red-Al to afford indoline **37**.

With indolines **34** and **37** in hand, Pd-mediated coupling with chloroquinoline **23d** provided analogue **38** and intermediate **39**, respectively. Subsequent acid-mediated deprotection of the ketal group in **39** led to the desired diol analogue **40** (Scheme 5).

The synthesis of a different set of analogues in which the morpholine hinge binder was replaced by a number of heterocycles is described in Scheme 6. Indoline **6** was coupled with 4-pyridylboronic acid in the presence of $Pd(PPh_3)_4$ to provide intermediate **41**. Coupling of indoline **41** with quinoline **23d** was carried out under Pd-catalyzed conditions to give analogue **44a**. An acid mediated coupling of indoline **6** with chloroquinoline **23d** provided iodo intermediate **42**, which was converted to the pinacol boronic ester **43** by reaction with $Pd(PCy_3)_2$ and bis-(pinacolato)diboron. This intermediate was transformed into analogues **44b** and **44c** via a Pd-catalyzed reaction with 4-chloro-2-aminopyrimidine and 4-chloro-6-methylpyrimidin-2-amine, respectively.

An alternative series of compounds was synthesized by replacing the indoline in the previous analogues with a pyrrolopyridine ring. The synthesis of the new pyrrolopyridine fragments started with the S_NAr of pyridine **45** with dimethyl malonate followed by

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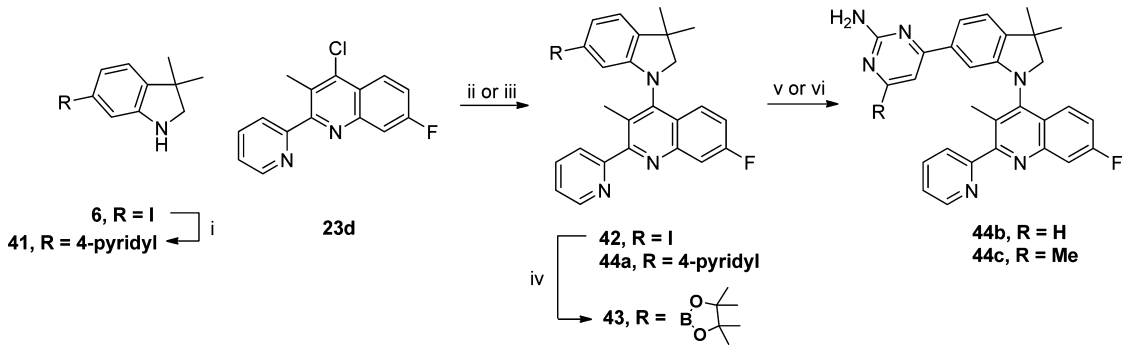
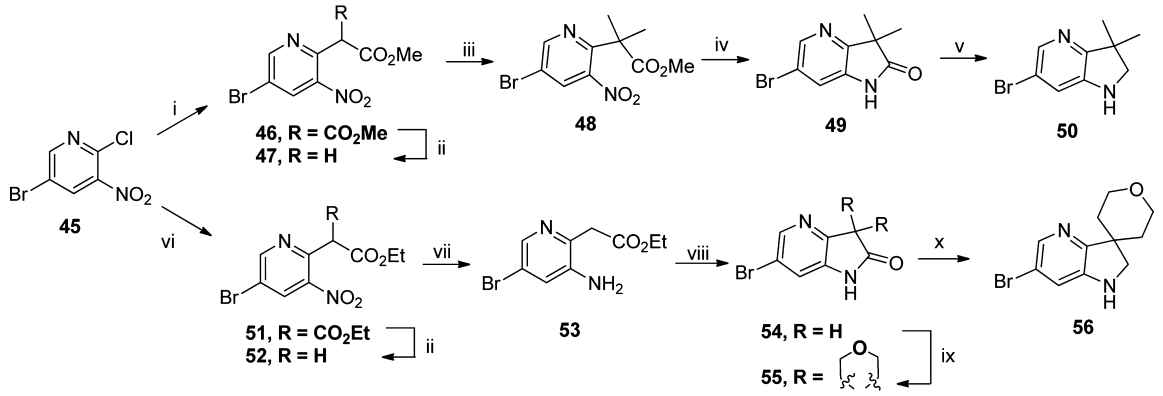
Scheme 6[a]



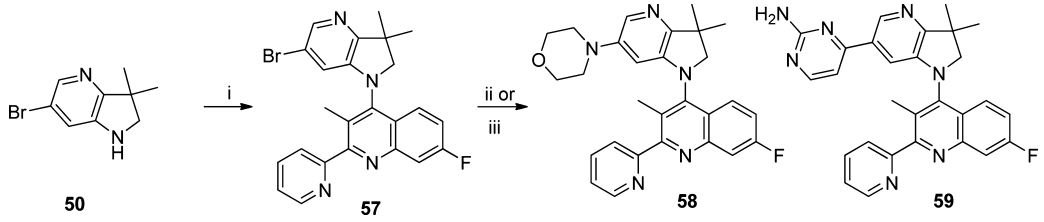
[a]Reagents and conditions: (i) $Pd(PPh_3)_4$, 4-pyridylboronic acid, 32%; (ii) **6**, **23d**, HCl, 130 °C, 55%; (iii) **41**, **23d**, Pd_2dba_3, BINAP, 8%; (iv) $Pd(PCy_3)_2$, bis(pinacolato)diboron, 42%; (v) $PdCl_2(PPh_3)_2$, 4-chloro-2-aminopyrimidine, 26%; (vi) 4-chloro-6-methylpyrimidin-2-amine, $PdCl_2(PPh_3)_2$, 42%.

Scheme 7[a]



[a]Reagents and conditions: (i) dimethyl malonate, K_2CO_3, 97%; (ii) NaCl, DMSO, 150 °C, 75%; (iii) NaH, iodomethane, 88%; (iv) Fe, AcOH, reflux, 83%; (v) Red-Al, 85%; (vi) diethyl malonate, K_2CO_3; (vii) Raney-Ni, 73% from **45**; (viii) AcOH, 93%; (ix) NaH, bis(2-chloroethyl) ether, 14%; (x) Red-Al, 71%.

Scheme 8[a]



[a]Reagents and conditions: (i) **23d**, HCl, 150 °C, 45%; (ii) morpholine, Pd_2dba_3, XPhos, 46%; (iii) (a) $Pd(PCy_3)_2$, bis(pinacolato)diboron, (b) $PdCl_2(PPh_3)_2$, 4-chloro-2-aminopyrimidine, 37% from **57**.

a decarboxylation reaction to provide **47**. This intermediate was alkylated using NaH and iodomethane to give **48**, which was subsequently cyclized to the pyrrolopyridinone **49** in hot Fe/AcOH. Final Red-Al reduction provided the desired pyrrolopyridine **50**. The synthesis of **56** proceeded through the nitro intermediate **52**, which was reduced to the corresponding aminopyridine **53** using Raney-Ni. Cyclization in hot toluene/AcOH provided **54**, which was subsequently alkylated with bis(2-chloroethyl) ether to give the desired tetrahydropyran **55**. Reduction with Red-Al provided the pyrrolopyridine building block **56** (Scheme 7).

With pyrrolopyridine **50** in hand, acid mediated coupling with chloroquinoline **23d** afforded intermediate **57**, which was converted into analogues **58** and **59** using the previously described Pd-mediated conditions (Scheme 8).

The synthesis of pyrrolopyridine **61** was carried out by a Pd mediated coupling of the Boc-protected intermediate **60** with morpholine. Deprotection of the Boc group in **61** provided intermediate **62**, which was coupled with **23d** under Pd-catalyzed conditions to provide multigram quantities of **63** (Scheme 9).

Kinase and Cellular Inhibitory Activities. The initial SAR of analogues **24a–f** and **26b–d** revealed that introduction of a phenyl group at the 2-position of the quinoline ring significantly improved the potency of these analogues against the PI3Kδ isoform (see analogues **1**/**24b** and **26b**/**26c**, Table 1). The gain in potency of these analogues was consistent with the proposed

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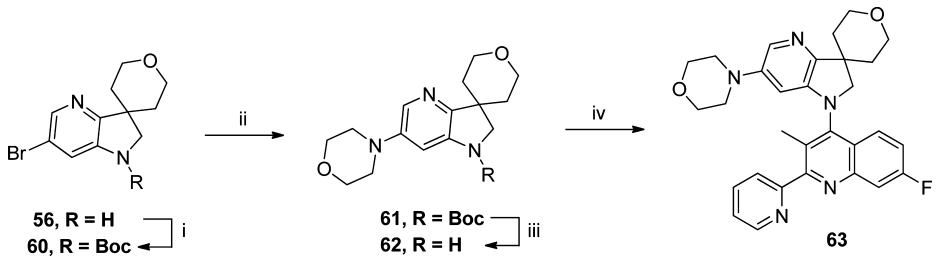
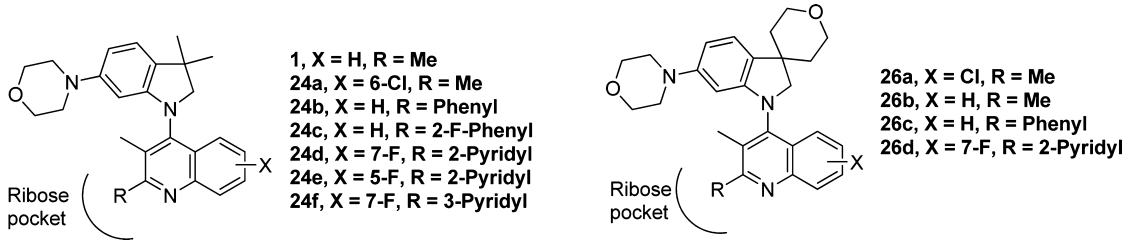
Scheme 9[a]



[a]Reagents and conditions: (i) Boc_2O, 88%; (ii) Pd_2dba_3, XPhos, morpholine, 68%; (iii) TFA, 84%; (iv) **23d**, XPhos-precatalyst, 41%.

Table 1. Profile of Analogues 1, 24a–f and 26b–d



			IC_{50} (nM)						
			biochem potency[a]		cellular potency[b]	physicochemical properties			
analogue	R	X	PI3Kβ	PI3Kδ	cell (δ)	RLM/HLM % TO	CYP3A4/CYP2D6 % inh	hPXR[c] POC	Sol. (PBS) μg/mL
1	Me	H	60	362	745	94/65	25/13	14	1
24a	Me	6-Cl	60	626	886	84/54	24/12	17	1
24b	phenyl	H	59	85	91	57/42	<10/<10	197	2.4
24c	2-F-phenyl	H	35	47	509	52/47	83/10	162	1
24d	2-pyridyl	7-F	58	30	76	34/40	65/16	106	7.4
24e	2-pyridyl	5-F	720	72	263	49/52	66/16	104	5.2
24f	3-pyridyl	7-F	39	17	74	74/58	53/14	114	3.6
26b	Me	H	54	450		71/70	36/13	1	
26c	phenyl	H	105	91	64	46/62	84/14	103	3.2
26d	2-pyridyl	7-F	143	64	127	13/64	51/11	22	

[a]ATP loss assay. [b]Anti-IgM/CD40L Human B Cell proliferation assay. [c]At a 2 μM compound concentration (compared to 10 μM of rifampicin). IC_{50} values are reported as the mean from at least two independent experiments.

binding mode depicted in Figure 1 in which the phenyl ring would reach into the ribose pocket. Subsequent replacement of the phenyl group in **24b** and **26c** with a 2-pyridyl ring (analogues **24d**, **26d**) had the effect of improving both the solubility and PXR profile[22] of these compounds. Comparison between the 7-F and 5-F quinoline substitution patterns (analogues **24d**, **24e**, Table 1) indicated that the 7-F substitution provided analogues with improved in vitro potency and microsomal stability. In contrast the 6-Cl quinoline substitution pattern (analogue **24a**) was detrimental to potency against the PI3Kδ isoform. Based on this data the 2-pyridyl substituent and the 7-F quinoline substitution pattern were deemed optimal and were incorporated in subsequent analogues.

Analogues **38** and **40** that retained the optimized quinoline core and had different substitution at the 3-position of the indoline ring were subsequently tested. The data collected from these analogues showed that polar substituents in the affinity pocket region were tolerated, but these compounds displayed lower potency against all PI3K isoforms (Table 2).

In contrast, replacement of the morpholine hinge binder in **24d** with a number of different heterocycles (Table 3) led to the identification of the aminopyrimidine analogue **44b**, which exhibited increased potency over the PI3Kγ and δ isoforms relative to **24d**.

Despite the improvements in potency the overall profile of these analogues was still not suitable for advanced in vivo animal studies since these compounds showed poor solubility, low microsomal stability and unfavorable CYP inhibition profiles (Table 1). It was hypothesized that decreasing the lipophilicity of these analogues might mitigate some of these liabilities. Thus, compounds in which the indoline ring in **24d** was replaced with a pyrrolopyridine motif were synthesized. Notably when these analogues were tested in our in vitro assays, we observed that the pyrrolopyridine ring had the effect of improving both the overall physicochemical properties and biochemical potency of our inhibitors.[23] In particular analogue **63** had improved microsomal stability, CYP inhibition and PXR profile relative to **24d** as well as good cellular potency against both PI3Kβ[24] and PI3Kδ isoforms (Table 4).

Binding Mode and Protein Kinase Selectivity. In order to confirm the binding mode of our inhibitors, crystal structures of analogues **24f** and **63** in complex with PI3Kγ were obtained (Figure 1).[25] As predicted, these structures showed that the morpholine ring interacts with the hinge binder region of PI3Kγ,

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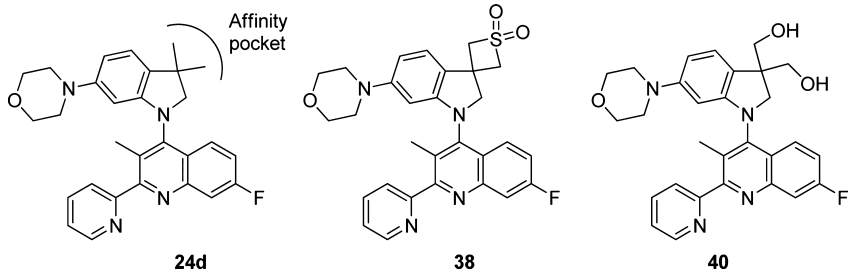
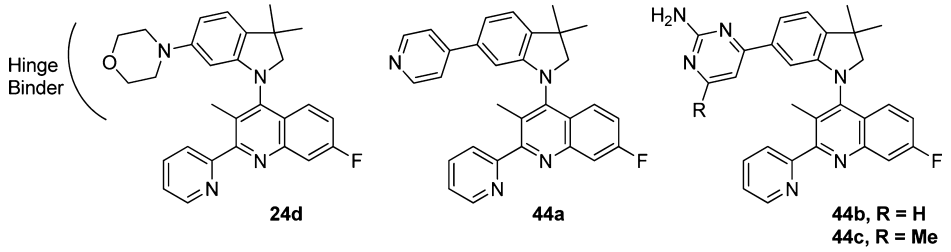
Table 2. Profile of Analogues 38, 40



analogue	PI3Kα (nM)	PI3Kβ (nM)	PI3Kγ (nM)	PI3Kδ (nM)
24d	3960[a]	58[a]	2010[a]	30[a]
38	>12500[b]	395[b]	7340[b]	80[b]
40	>125000[b]	269[b]	16000[b]	154[b]

[a]IC_{50}, ATP loss assay; [b]K_i. IC_{50} values are reported as the mean from at least two independent experiments.

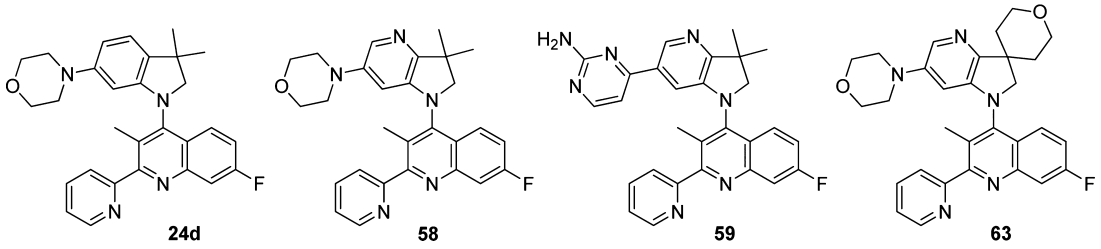
Table 3. Profile of Analogues 44a−c



analogue	PI3Kα (nM)	PI3Kβ (nM)	PI3Kγ (nM)	PI3Kδ (nM)
24d	3960[a]	58[a]	2010[a]	30[a]
44a	2320[a]	81[a]	1400[a]	198[a]
44b	3540[b]	54[b]	90[b]	10[b]
44c	>125000[b]	>125000[b]	364[b]	449[b]

[a]IC_{50}, ATP loss assay; [b]K_i. IC_{50} values are reported as the mean from at least two independent experiments

Table 4. Profile of Analogues 58, 59 and 63



	biochem potency (nM)				cellular potency: IC_{50} (nM)		physicochemical properties			
analogue	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	cell (δ)[c]	cell (β)[d]	RLM/HLM % TO	CYP3A4/CYP2D6 % inh	hPXR[e] POC	Sol. (PBS) μg/mL
24d	3960[a]	58[a]	2010[a]	30[a]	60	53	34/40	65/16	106	7.4
58	1720[b]	30[b]	92[b]	7[b]	6	51	28/47	17/<10	22	11
59	510[b]	18[b]	28[b]	3[b]	4	10	34/12	32/10	65	17
63	3250[b]	44[b]	509[b]	11[b]	9	36	21/35	12/<10	8	146

[a]IC_{50}, ATP loss assay. [b]K_i. [c]Anti-IgM/CD40L Human B Cell proliferation assay. [d]PI3Kβ counter screen assay in MDA-MB-468 cells. [e]At a 2 μM concentration (compared to 10 μM of rifampicin). IC_{50} values are reported as the mean from at least two independent experiments.

while the indoline, or pyrrolopyridine ring, occupies the affinity pocket and the quinoline ring sits in a hydrophobic pocket formed by movement of the Met804 side chain (Figure 2). The pyridine ring sits in the ribose pocket orthogonal to the quinoline ring. When bound to the protein, these molecules adopt a propeller-shape conformation in which the quinoline and indoline rings are at an angle of approximately 90°.[26] During the course of our studies toward the identification and development of selective PI3Kδ inhibitors, we and others found that this propeller-shaped conformation was critical for gaining selectivity over protein kinases.[27] Thus, we were pleased to discover that, when this analogue was tested in an Ambit kinase panel (440 kinases, 10 μM

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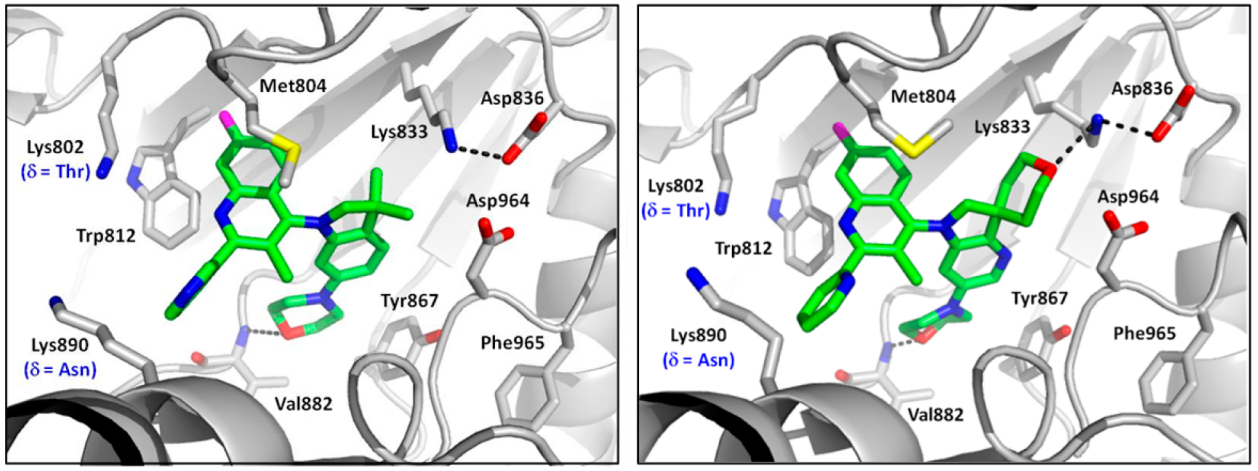
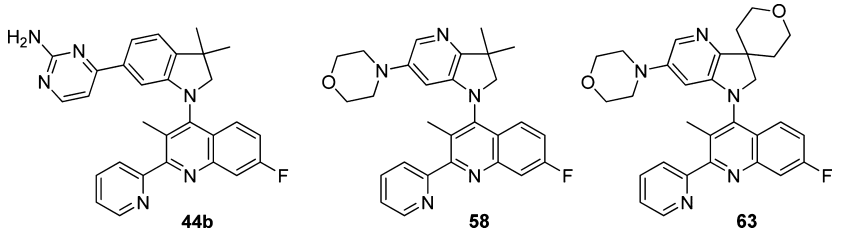


Figure 2. Crystal structures of PI3Kγ in complex with **24f** and **63** (PDB codes 4FJY and 4FJZ, respectively). Amino acid labels correspond to the PI3Kγ isoform; blue labels indicate the corresponding residue in PI3Kδ. Dashed lines indicate hydrogen bonds.

Table 5. Rat PK of Inhibitors 44b, 58 and 63



	iv (0.5 mg/kg)[a]			po (2.0 mg/kg)[b]		AUC (μM·h)	
analogue	Cl (L/h/kg)	Vss (L/kg)	$t_{1/2}$ (h)	AUC (μM·hr)	F (%)	po (3.0 mg/kg)[c]	po (10.0 mg/kg)[c]
44b	1.61	7.5	6.1				
58	0.97	5.0	6.2	2.0	47		
63	0.80	3.3	4.0	3.2	65	7.5	23.3

[a]100% DMSO. [b]0.5% methyl cellulose, 1% Tween80, 98.5% water. [c]5% EtOH, 12.5% HPBCD, 20% PEG400, 25% PG, 37.5% water.

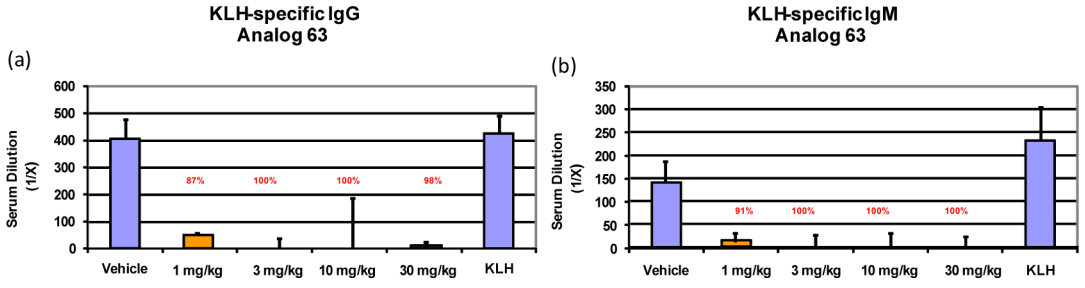


Figure 3. Inhibition of KLH-specific antibodies. Female Lewis rats were immunized with 60 μg/rat of KLH intravenously. Treatment with vehicle or **63** at 1, 3, 10, or 30 mg/kg qd for 10 days by oral gavage began 2 h before KLH immunization. Serum samples were collected on day 10. KLH-specific IgG and IgM levels were measured by ELISA. Data are represented as mean of the dilution factor, and the error bars represent SEM of data from 8 rats.

concentration of **63**), only two hits were detected at POC < 40% (ERBB3 and ANKK1, 30 and 34 POC respectively),[28] revealing the excellent kinase selectivity profile of this compound. In addition analogue **63** also tested negative in a hERG binding assay.[29]

In Vivo PK. Rat PK studies were carried out with analogues **44b**, **58** and **63** (Table 5). These compounds showed moderate to good PK profiles, and it was observed that replacement of the indoline ring in **44b** with the pyrrolopyridine motif in analogues **58** and **63** had the effect of improving their overall PK profile. The pyrrolopyridine analogue **63** had lower clearance and higher oral bioavailability than analogue **58**. Based on these data, inhibitor **63** was selected for dose escalation studies, and it was found that this compound also displayed good pharmacokinetic properties at 3 and 10 mg/kg doses (Table 5).

In Vivo Pharmacology. Based on the favorable potency, selectivity, and PK profile of **63**, this analogue was selected for further in vivo evaluation in animal models of inflammation. Thus, the first experiment that was performed was a KLH study in rats.[30] In this experiment, the animals were dosed orally once a day with vehicle or dual inhibitor **63** at 1, 3, 10, and 30 mg/kg for a period of 10 days.[31] Two hours after the first oral dose, the

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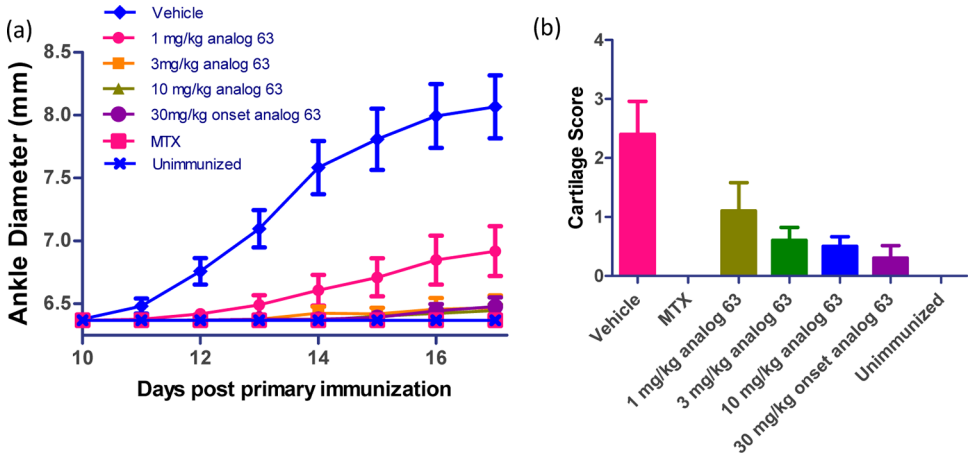

Figure 4. (a) CIA study with analogue **63**. Rats were administered with collagen by intradermal injection on day 1 and 6. Treatment with vehicle or **63** at 1, 3, or 10 mg/kg qd by oral gavage began on day 1 and continued for 17 days (prophylactic dose). A second group of immunized animals was treated with **63** at 30 mg/kg qd by oral gavage on days 11 through 16 (therapeutic dose). Progression of inflammation was assessed by measurement of hind paw diameters. Data are represented as mean ankle diameter size, and the error bars represent SEM of data from 8 animals. (b) Histopathological analysis. Ethanol fixed hind paws were processed for histopathology scoring (see Supporting Information). Data are represented as mean cartilage score, and the error bars represent SEM of data from 8 animals.

animals were administered KLH. After 10 days serum samples were collected and the KLH specific antibodies were measured by ELISA (Figure 3). Gratifyingly we observed that the compound was well tolerated at all doses and all the animals treated with analogue **63** showed significant reduction of IgG and IgM specific antibodies (Figure 3).

In a second in vivo experiment we aimed to test the efficacy of **63** in the context of an animal model of rheumatoid arthritis (RA). Specifically, for this experiment we used a collagen-induced arthritis (CIA) model in Lewis rats[32] in which the disease is induced via an injection of collagen (symptoms of arthritis, such as paw swelling, are typically observed 10 days after the collagen treatment). In this study the animals were administered with vehicle, or analogue **63** at 1, 3, and 10 mg/kg once a day for 17 days after the first collagen injection[33] (prophylactic doses). A second group of animals was left untreated for 10 days after the collagen treatment, and on days 11 through 16 they were administered with analogue **63** orally once a day at 30 mg/kg ("onset", therapeutic dose).[34] Progression of inflammation was assessed by measurement of hind paw diameters[35] and after 17 days PK samples were taken in all the animals. As in the KLH experiment, all the animals survived to the end of the study without significant signs of toxicity. Remarkably, in this experiment we observed a robust dose dependent reduction of paw swelling in all the animals treated with analogue **63** at both prophylactic (1, 3, and 10 mg/kg) and therapeutic doses (30 mg/kg, Figure 4).[36] After necropsy, histopathological analysis showed that analogue **63** had also provided protection against cartilage erosion in a dose-dependent manner (Figure 4).

Analysis of the PK data in this study confirmed that analogue **63** in vivo exposures after a dose of 3, 10, and 30 mg/kg had provided coverage for over 24 h, of the IC_{50} of both PI3Kβ and δ cellular assays after correcting for plasma protein binding (Figure 5).[37]

Notably, the in vivo efficacy results from these experiments are consistent with studies in chimeric mice lacking PI3Kβ and PI3Kδ activity recently reported in the literature using a serum transfer model of arthritis.[19]

CONCLUSION

On the basis of our understanding of the binding mode of our first generation PI3Kδ inhibitors we designed a novel series of potent and selective dual PI3Kβ/δ inhibitors by combining a quinoline pharmacophore with an indoline ring from our internal NIK program. Systematic SAR studies allowed us to identify a number of PI3Kβ/δ dual inhibitors with improved potency and PK profiles. Among these, analogue **63** displayed satisfactory properties for advanced in vivo efficacy studies. These experiments showed that analogue **63** was well tolerated and efficacious in an animal model of RA, providing further evidence that pharmacological inhibition of the PI3Kβ and δ isoforms might be a valuable approach for the treatment of human inflammatory diseases such as RA.

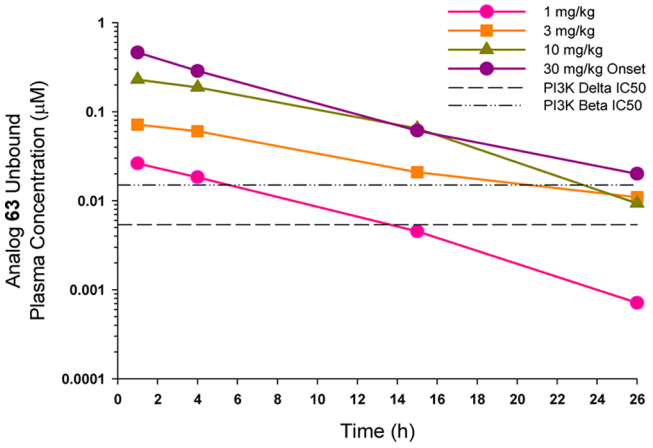

Figure 5. PK data of analogue **63** in CIA study.

EXPERIMENTAL SECTION

General Chemistry. All reactions were conducted under an inert gas atmosphere (nitrogen or argon) using a Teflon-coated magnetic stir bar at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Analytical thin layer chromatography (TLC) and flash chromatography were performed on Merck silica gel 60 (230–400 mesh). Removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 Torr. Microwave reactions were performed in a CEM Discover benchtop reactor. All yields reported are isolated yields.

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Preparative reversed-phase HPLC was performed using an Agilent 1100 system and Phenomenex Gemini C18 column (30 μm, 150 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elution [A, H_2O with 0.1% trifluoroacetic acid (TFA); B, CH_3CN with 0.1% TFA] with UV detection at 220 nm. All final compounds were purified to ≥95% purity as determined by an Agilent 1100 series HPLC with UV detection at 220 nm using the following method: Zorbax SB-C8 column (3.5 μm, 150 mm × 4.6 mm i.d.); mobile phase, A = H_2O with 0.1% TFA, B = CH_3CN with 0.1% TFA; gradient: 5−95% B (0.0−15.0 min); flow rate, 1.5 mL/min. Low-resolution mass spectral (MS) data were determined on an Agilent 1100 series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). ^{1}H NMR spectra were obtained on a Bruker Avance III 500 (500 MHz) or Bruker Avance 400 II (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = single; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad.

*1-(3,3-Dimethyl-6-morpholinoindolin-1-yl)ethanone, **3**.* A mixture of 1-(6-amino-3,3-dimethylindolin-1-yl)ethanone, **2** (10 g, 49 mmol), bis(2-bromoethyl) ether (12.5 mL, 49 mmol), and Na_2CO_3 (10.4 g, 97.9 mmol) in methanol (50 mL) was heated to 150 °C in a sealed tube. After 1 h, the mixture was cooled to room temperature and diluted with water (200 mL). The resulting solid was filtered, washed with water (300 mL), and dried in the air to give 1-(3,3-dimethyl-6-morpholinoindolin-1-yl)ethanone, **3** (9.07 g, 67% yield), as a gray solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 7.74 (1 H, s), 7.06 (1 H, d, J = 8.1 Hz), 6.61 (1 H, dd, J = 8.2, 2.1 Hz), 3.82 (2 H, s), 3.67 - 3.76 (4 H, m), 2.95 - 3.06 (4 H, m), 2.13 (3 H, s), 1.26 (6 H, s). Mass spectrum (ESI): m/e = 275.0 $[M + H]^+$.

*4-(3,3-Dimethylindolin-6-yl)morpholine, **4**.* 1-(3,3-Dimethyl-6-morpholinoindolin-1-yl)ethanone, **3** (9.07 g, 33.1 mmol), was dissolved in acetonitrile (100 mL) and treated with 5 N HCl (50 mL) at 95 °C. After 2 h, the mixture was cooled to room temperature. The reaction mixture was carefully neutralized with saturated $NaHCO_3$ solution to pH 10 and extracted with ethyl acetate (4 × 100 mL). The combined organics were washed with water, brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 1:0 to 0:1) to give 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (6.42 g, 84% yield), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.80 (1 H, d, J = 7.8 Hz), 6.14 (1 H, dd, J = 8.0, 2.2 Hz), 6.09 (1 H, d, J = 2.0 Hz), 5.28 (1 H, s), 3.65 - 3.73 (4 H, m), 3.13 (2 H, d, J = 2.0 Hz), 2.92 - 2.99 (4 H, m), 1.17 (6 H, s). Mass spectrum (ESI): m/e = 233.2 $[M + H]^+$.

*1-(6-Iodo-3,3-dimethylindolin-1-yl)ethanone, **5**.* In a 500 mL three-necked round-bottom flask equipped with an overhead stirrer was combined 1-(6-amino-3,3-dimethylindolin-1-yl)ethanone, **2** (6.98 g, 34.22 mmol), with 30 mL of ice/water. The solution was cooled in an ice bath before concentrated HCl (6.8 mL, 81.60 mmol) was added. A solution of $NaNO_2$ (2.48 g, 35.93 mmol) dissolved in 30 mL of water was added dropwise over a period of 10 min. After 30 min a solution of KI (11.36 g, 68.44 mmol) dissolved in $CHCl_3$ (70 mL) was added via an addition funnel over a period of 0.5 h. The resulting brownish solution was stirred at room temperature until gas evolution ceased. The reaction mixture was then transferred to a separation funnel, and the separated organic layer was washed with saturated $NaHCO_3$, followed by 5% $Na_2S_2O_3$. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica eluting with 20% hexane:CH_2Cl_2. The fractions containing the product were combined and concentrated under vacuum to give 1-(6-iodo-3,3-dimethylindolin-1-yl)ethanone, **5** (6.95 g, 65% yield), as a tan colored solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.39 (1 H, s), 7.37 (1 H, d, J = 7.8 Hz), 7.08 (1 H, d, J = 7.8 Hz), 3.85 (2 H, s), 2.16 (3 H, s), 1.29 (6 H, s) Mass Spectrum (ESI): m/e = 316.0 $[M + H]^+$.

*6-Iodo-3,3-dimethylindoline, **6**.* 1-(6-Iodo-3,3-dimethylindolin-1-yl)-ethanone, **5** (6.95 g, 22.08 mmol), was combined with methanol and concentrated HCl (25 mL, 300 mmol). The solution was heated at a gentle reflux for 1 h before it was cooled to room temperature. After cooling of the solution to 0 °C, a white solid was filtered off to give 6-iodo-3,3-dimethylindoline hydrochloride (5.96 g). The product was then dissolved in CH_2Cl_2 and washed with $NaHCO_3$ (saturated aqueous solution), dried over $MgSO_4$ and filtered and concentrated under vacuum to give 6-iodo-3,3-dimethylindoline (5.2 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.05 (1 H, dd, J = 7.8, 1.5 Hz), 6.95 (1 H, d, J = 1.7 Hz), 6.77 (1 H, d, J = 7.8 Hz), 3.75 (1 H, br s), 3.30 (2 H, s), 1.29 (6 H, m). Mass spectrum (ESI): m/e = 274.0 $[M + H]^+$.

*Methyl 4-(4-Bromo-2-nitrophenyl)tetrahydro-2H-pyran-4-carboxylate, **8**.* Sodium hydride (0.32 g, 8.03 mmol, 60% dispersion in oil) was added in portions at room temperature to a stirred solution of methyl 2-(4-bromo-2-nitrophenyl)acetate, **7** (1 g, 3.65 mmol), in DMSO (15 mL). After the mixture was stirred at room temperature for 30 min, sodium iodide (0.055 g, 0.365 mmol) and bis(2-bromoethyl) ether (1.27 g, 5.54 mmol) were added. The resultant mixture was stirred at 40 °C for 19 h. After this time the mixture was poured into brine with ice (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (3 × 80 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica (hexane:ethyl acetate, 1:0 to 0:1) to give methyl 4-(4-bromo-2-nitrophenyl)tetrahydro-2*H*-pyran-4-carboxylate, **8** (0.45 g, 36%), as an orange syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.89 (1 H, d, J = 2.2 Hz), 7.75 (1 H, dd, J = 8.6, 2.2 Hz), 7.50 (1 H, d, J = 8.8 Hz), 3.87−3.94 (2 H, m), 3.66−3.77 (5 H, m), 2.33 (2 H, dd, J = 14.1, 2.8 Hz), 1.99−2.05 (2 H, m). Mass spectrum (ESI): m/e = 344.0 $[(M + H)\ (^{79}Br)]^+$ and 346.0 $[(M + H)\ (^{81}Br)]^+$.

*6-Bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-2-one, **9**.* To a mixture of methyl 4-(4-bromo-2-nitrophenyl)tetrahydro-2H-pyran-4-carboxylate, **8** (6.67 g, 19.4 mmol), in AcOH (97 mL) was added Fe powder (5.42 g, 96.97 mmol), and the mixture was heated at 100 °C for 2 h. After this time the reaction mixture was cooled to room temperature and filtered over Celite. The Celite was washed with acetic acid, and the combined filtrates were evaporated in vacuo. The resulting residue was purified by column chromatography (hexane:ethyl acetate, 1:0 to 0:1) to give 6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-2-one, **9** (3.93, 72% yield), as an orange solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 10.53 (1 H, s), 7.47 (1 H, d, J = 7.8 Hz), 7.14 (1 H, dd, J = 8.1, 1.0 Hz), 6.98 (1 H, d, J = 1.0 Hz), 3.91−4.12 (2 H, m), 3.67−3.86 (2 H, m), 1.54−1.84 (4 H, m). Mass spectrum (ESI): m/e = 282.0 $[(M + H)\ (^{79}Br)]^+$ and 284.0 $[(M + H)\ (^{81}Br)]^+$.

*6-Bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **10**.* A heterogeneous mixture of 6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-2-one, **9** (3.5 g, 12.4 mmol), in toluene (25 mL) was stirred at 80 °C. To the heated mixture was added a solution of Red-Al (65% in toluene, 11.6 mL, 37.2 mmol), and the mixture was stirred at 80 °C for 50 min. After this time the mixture was cooled to 0 °C and quenched with a 2 N solution of aqueous NaOH (31 mL, 62 mmol). The mixture was extracted with ethyl acetate (2 × 100 mL), and the combined extracts were washed with brine (3 × 100 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography (0 to 100% gradient of CH_2Cl_2:methanol:NH_4OH (89:9:1) in CH_2Cl_2) to give 6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **10**, as a yellow solid (2.13 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 6.91−6.99 (1 H, m), 6.66 (1 H, dd, J = 7.8, 1.7 Hz), 6.59 (1 H, d, J = 1.7 Hz), 5.85 (1 H, s), 3.70−3.87 (2 H, m), 3.36−3.51 (4 H, m), 1.65−1.84 (2 H, m), 1.39−1.57 (2 H, m). Mass spectrum (ESI): m/e 268.0 $[(M + H)\ (^{79}Br)]^+$ and 270.0 $[(M + H)\ (^{81}Br)]^+$.

*1-(6-Bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-1-yl)-ethanone, **11**.* 6-Bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **10** (3.07 g, 11 mmol), was dissolved in pyridine (10.0 mL, 124 mmol), and acetic anhydride (1.6 mL, 17 mmol) was added followed by DMAP (0.0576 g, 0.472 mmol). The reaction mixture was heated to 85 °C for 30 min. After this time the reaction mixture was cooled to room temperature. The resulting precipitate was collected by filtration, to give 1-(6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-1-yl)ethanone, **11** (3.07 g, 86% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.17−8.26 (1 H, m), 7.26 (1 H, d, J = 8.0 Hz), 7.17−7.23 (1 H, m), 4.10 (2 H, s), 3.79−3.91 (2 H, m), 3.44−3.59 (2 H, m), 2.22 (3 H, s), 1.79−1.92 (2 H, m), 1.47−1.61 (2 H, m). Mass spectrum (ESI): m/e 310.0 $[(M + H)\ (^{79}Br)]^+$ and 312.0 $[(M + H)\ (^{81}Br)]^+$.

*1-(6-Morpholino-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-1-yl)ethanone, **12**.* 1-(6-Bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-1-yl)ethanone, **11** (2.56 g, 8.25 mmol), was combined with

morpholine (1.08 mL, 12.4 mmol), dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-4-yl)phosphine (0.118 g, 0.248 mmol), Pd_2dba_3 (0.256 g, 0.248 mmol), and cesium carbonate (4.03 g, 12.4 mmol) in *tert*-butanol (30.0 mL, 314 mmol). The reaction mixture was purged with N_2, and it was heated at 110 °C for 4 h. After this time the reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was concentrated in vacuo. The crude material was triturated with ethyl acetate/hexane to give 1-(6-morpholino-2′,3′,5′,6′-tetrahydrospiro-[indoline-3,4′-pyran]-1-yl)ethanone, **12** (1.88 g, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.77 (1 H, dd, J = 2.0, 0.4 Hz), 7.11 (1 H, d, J = 8.2 Hz), 6.53−6.66 (1 H, m), 3.98−4.08 (2 H, m), 3.78−3.89 (2 H, m), 3.66−3.75 (4 H, m), 3.44−3.55 (2 H, m), 2.95−3.10 (4 H, m), 2.15−2.25 (3 H, m), 1.75−1.89 (2 H, m), 1.37−1.57 (2 H, m). Mass spectrum (ESI): m/e = 317.0 $[M + H]^+$.

*6-Morpholino-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **13**.* A mixture of 1-(6-morpholino-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran]-1-yl)ethanone, **12** (1.35 g, 4.27 mmol), in acetonitrile (30 mL) was treated with 2.0 M aqueous HCl (12 mL). The reaction mixture was stirred at room temperature overnight, and then it was heated to 120 °C for 36 h. After this time the reaction mixture was cooled to room temperature and quenched with aqueous NaOH. The mixture was partitioned between ethyl acetate (200 mL) and water (80 mL). The separated organic layer was washed with $NaHCO_3$ (saturated aqueous solution), and then it was dried over $MgSO_4$, filtered and evaporated in vacuo to give 6-morpholino-2′,3′,5′,6′-tetrahydrospiro-[indoline-3,4′-pyran], **13** (1.06 g, 90% yield), as a pale solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.00 (1 H, d, J = 8.0 Hz), 6.33 (1 H, dd, J = 8.2, 2.3 Hz), 6.27 (1 H, d, J = 2.3 Hz), 3.93−4.01 (2 H, m), 3.80−3.89 (4 H, m), 3.70−3.77 (1 H, m), 3.49−3.63 (4 H, m), 3.07−3.14 (4 H, m), 1.87−2.03 (2 H, m), 1.57−1.72 (2 H, m). Mass spectrum (ESI): m/e = 275.0 $[M + H]^+$.

*6-Chloro-2,3-dimethylquinolin-4-ol, **16**.* A stirred mixture of 4-chloroaniline, **14a** (2 g, 15.68 mmol), and ethyl 2-methyl-3-oxobutanoate, **15** (4.53 mL, 31.36 mol), in PPA (6.3 g) was heated at 170 °C for 2 h. After this time the mixture was cooled to room temperature and neutralized to pH 8 with 2 N aqueous NaOH. The resulting precipitate was collected by filtration, washed with water, and dried to give 6-chloro-2,3-dimethylquinolin-4-ol, **16** (2.3 g, 70% yield), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.61 (1 H, br s), 7.98 (1 H, d, J = 1.8 Hz), 7.56−7.63 (1 H, m), 7.48−7.55 (1 H, m), 2.37 (3 H, s), 1.97 (3 H, s). Mass spectrum (ESI): m/e = 208.0 $[M + H]^+$.

*4,6-Dichloro-2,3-dimethylquinoline, **23a**.* A mixture of 6-chloro-2,3-dimethylquinolin-4-ol, **16** (1 g, 4.82 mmol), and $POCl_3$ (5 mL, 48.2 mmol) was heated at reflux for 3 h. After this time the reaction mixture was concentrated under reduced pressure. The resulting residue was carefully treated with ice water, and the aqueous mixture was basified with NH_4OH. The resulting precipitate was collected by filtration, washed with water, and dried to give to give 4,6-dichloro-2,3-dimethylquinoline, **23a** (0.9 g, 83% yield), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.08 (1 H, d, J = 2.2 Hz), 7.98 (1 H, d, J = 8.8 Hz), 7.77 (1 H, dd, J = 9.0, 2.2 Hz), 2.68 (3 H, s), 2.52 (3 H, s). Mass spectrum (ESI): m/e = 226.0 $[M + H]^+$.

*Ethyl 3-(3-fluorophenylamino)-2-methyl-3-oxopropanoate, **17**.* A mixture of 3-fluoroaniline, **14b** (18 mL, 187 mmol), in pyridine (31 mL, 374 mmol) and diethyl methylmalonate (48 mL, 281 mmol) was heated at 130 °C for 24 h. After this time the reaction mixture was treated with an additional portion of diethyl methylmalonate (5 mL, 37.4 mmol) and heated at 130 °C for an additional 12 h. After this time the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was taken up in CH_2Cl_2 (100 mL), washed with $NaHCO_3$ (2 × 30 mL, saturated aqueous solution), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was dissolved in benzene and evaporated in vacuo. The resulting residue was purified by column chromatography (330 g of SiO_2, using a gradient of hexane:ethyl acetate, 1:0 to 3:1 as eluant) to provide ethyl 3-(3-fluorophenylamino)-2-methyl-3-oxopropanoate, **17** (22.1 g, 49% yield), as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.81 (1 H, br s), 7.49−7.61 (1 H, m), 7.24−7.31 (1 H, m), 7.15−7.20 (1 H, m), 6.76−6.91 (1 H, m), 4.26 (2 H, q, J = 7.2 Hz), 3.44 (1 H, q, J = 7.2 Hz), 1.56 (3 H, d, J = 7.0 Hz), 1.33 (3 H, t, J = 7.1 Hz). Mass spectrum (ESI): m/e = 240.1 $[M + H]^+$.

*3-(3-Fluorophenylamino)-2-methyl-3-oxopropanoic acid, **18**.* To a stirred solution of ethyl 3-(3-fluorophenylamino)-2-methyl-3-oxopropanoate, **17** (21.0 g, 87.8 mmol), in THF (80 mL) was added NaOH (4.21 g, 105 mmol) in water (20 mL). The reaction mixture was stirred at room temperature for 1 h. After this time the reaction mixture was acidified to pH 2 with concentrated HCl. The aqueous layer was extracted with ethyl acetate (2 × 150 mL), and the separated organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give 3-(3-fluorophenylamino)-2-methyl-3-oxopropanoic acid, **18** (16.5 g, 89% yield), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.34 (1 H, s), 7.59 (1 H, dt, J = 11.7, 2.2 Hz), 7.24−7.41 (2 H, m), 6.88 (1 H, tdd, J = 8.3, 8.3, 2.6, 1.4 Hz), 3.49 (1 H, q, J = 7.1 Hz), 1.27 (3 H, d, J = 7.0 Hz). Mass spectrum (ESI): m/e = 212.1 $[M + H]^+$.

*7-Fluoro-3-methylquinoline-2,4-diol and 5-Fluoro-3-methylquinoline-2,4-diol, **19a**, **19b**.* A stirred suspension of 3-(3-fluorophenylamino)-2-methyl-3-oxopropanoic acid, **18** (19 g, 90 mmol), in PPA (150 mL) was heated at 130 °C for 2 h. After this time the reaction mixture was cooled to room temperature and treated with 2 M aqueous NaOH until a precipitate formed. The precipitate was filtered and washed with 1 M aqueous NaOH (2 × 30 mL). The resulting white solid was dried under vacuum overnight to give 7-fluoro-3-methylquinoline-2,4-diol and 5-fluoro-3-methylquinoline-2,4-diol, **19a**, **19b** (14.1 g, 81% yield), as a 2.5:1 mixture of regioisomers. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm (major isomer) 11.48 (1 H, br s), 8.70 (1 H, br s), 7.95 (1 H, dd, J = 9.7, 6.2 Hz), 7.06 (2 H, td, J = 5.1, 2.3 Hz), 2.03 (3 H, s); (minor isomer) 11.48 (1 H, br s), 8.70 (1 H, br s), 7.33−7.55 (1 H, m), 7.14 (1 H, d, J = 8.2 Hz), 6.94 (1 H, dd, J = 12.6, 8.1 Hz), 2.03 (3 H, s). Mass spectrum (ESI): m/e = 194.1 $[M + H]^+$.

*2,4-Dichloro-7-fluoro-3-methylquinoline and 2,4-Dichloro-5-fluoro-3-methyl quinoline, **20a**, **20b**.* A stirred suspension of 7-fluoro-3-methylquinoline-2,4-diol and 5-fluoro-3-methylquinoline-2,4-diol, **19a**, **19b** (14.0 g, 72 mmol), and $POCl_3$ (68 mL, 725 mmol) was heated at 100 °C for 2 h. After this time the reaction mixture was allowed to cool to room temperature and the $POCl_3$ was evaporated in vacuo. The resulting dark brown residue was taken up in CH_2Cl_2 (300 mL) and washed with water (4 × 100 mL) to give the desired product as a white solid. The compound (∼11 g) was dissolved in CH_2Cl_2 (10 mL) and purified by column (330 g of SiO_2 using hexane:ethyl acetate (9:1) as eluant) to give a mixture of 2,4-dichloro-7-fluoro-3-methylquinoline and 2,4-dichloro-5-fluoro-3-methyl quinoline, **20a**, **20b** (7.5 g, 45% yield), in a 3.3:1 ratio of regioisomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm (major isomer) 8.52 (1 H, dd, J = 9.3, 5.1 Hz), 8.03 (1 H, dd, J = 7.9, 2.3 Hz), 7.59−7.81 (1 H, m), 2.78−2.88 (3 H, m); (minor isomer) 8.20 (1 H, d, J = 8.6 Hz), 8.10 (1 H, td, J = 8.4, 4.8 Hz), 7.65 (1 H, ddd, J = 11.7, 7.9, 0.9 Hz), 2.83 (3 H, s). Mass spectrum (ESI): m/e = 229.9 $[M + H]^+$.

*4-Chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline and 4-Chloro-5-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d**, **23e**.* To a stirred solution of 2,4-dichloro-7-fluoro-3-methylquinoline and 2,4-dichloro-5-fluoro-3-methyl quinoline, **20a**, **20b** (5.0 g, 21.73 mmol), and 2-tri-*n*-butylstannylpyridine (8.0 mL, 21.73 mmol) in toluene (100 mL) was added $Pd(PPh_3)_4$ (1.25 g, 1.09 mmol). The reaction mixture was heated at reflux overnight. After this time the reaction mixture was cooled to room temperature and evaporated in vacuo. The resulting brown solid was triturated with hexane (100 mL) and filtered. The resulting brown solid was dissolved in CH_2Cl_2 and purified by column chromatography (220 g of SiO_2, hexane:ethyl acetate, 3:1) to give, in order of elution, 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (2.5 g, 42% yield) {^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.71−8.77 (1 H, m), 8.26 (1 H, dd, J = 9.2, 5.9 Hz), 7.86−7.95 (1 H, m), 7.72−7.83 (2 H, m), 7.36−7.46 (2 H, m), 2.62 (3 H, s). Mass spectrum (ESI): m/e = 273.0 $[M + H]^+$}, and 4-chloro-5-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23e** (0.8 g, 13% yield) {^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.67−8.82 (1 H, m), 7.95 (1 H, dt, J = 8.5, 1.1 Hz), 7.90 (1 H, td, J = 7.7, 1.8 Hz), 7.80 (1 H, dt, J = 7.8, 1.2 Hz), 7.62 (1 H, td, J = 8.2, 5.2 Hz), 7.37−7.42 (1 H, m), 7.26−7.33 (1 H, m), 2.57−2.64 (3 H, m). Mass spectrum (ESI): m/e = 273.0 $[M + H]^+$}.

*4-Chloro-7-fluoro-3-methyl-2-(pyridin-3-yl)quinoline, **23f**.* To a stirred solution of 2,4-dichloro-7-fluoro-3-methylquinoline, **20a** (1.0 g,

4.35 mmol), and 3-tri-*n*-butylstannylpyridine (1.6 mL, 4.35 mmol) in toluene (10 mL) was added $Pd(PPh_3)_4$ (251 mg, 0.22 mmol), and the reaction mixture was heated at reflux overnight. The resulting brown solid was triturated with hexane (20 mL) and filtered. The resulting brown solid was dissolved in CH_2Cl_2 and purified by column chromatography (40 g of SiO_2, hexane:ethyl acetate, 3:1) to give 4-chloro-7-fluoro-3-methyl-2-(pyridin-3-yl)quinoline, **23f** (650 mg, 55% yield), as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.83−8.90 (1 H, m), 8.74 (1 H, dd, J = 4.9, 1.8 Hz), 8.28 (1 H, dd, J = 9.2, 5.9 Hz), 7.93 (1 H, dt, J = 7.8, 2.0 Hz), 7.76 (1 H, dd, J = 9.6, 2.5 Hz), 7.41−7.50 (2 H, m), 2.56 (3 H, s). Mass spectrum (ESI): m/e = 273.0 $[M + H]^+$.

General Quinoline Synthesis Procedure A. To a mixture of substituted anthranilic acid (1.5 equiv) and substituted propiophenone (1.0 equiv) was added $POCl_3$ (25 mL). The mixture was heated at 90 °C for 2 h. After this time the reaction mixture was cooled to room temperature and the excess $POCl_3$ was removed in vacuo. The reaction mixture was carefully quenched with ice cold K_2CO_3 solution, and the aqueous layer was extracted with ethyl acetate, dried and concentrated in vacuo. The crude product obtained was chromatographed using silica gel, eluting with 3% ethyl acetate in hexane.

*4-Chloro-3-methyl-2-phenylquinoline, **23b**.* 4-Chloro-3-methyl-2-phenylquinoline, **23b**, was prepared according to quinoline synthesis procedure A. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.26 (1 H, dd, J = 8.4, 1.0 Hz), 8.12−8.17 (1 H, m), 7.73 (1 H, ddd, J = 8.4, 6.9, 1.4 Hz), 7.61−7.68 (1 H, m), 7.55−7.59 (2 H, m), 7.43−7.53 (3 H, m), 2.54 (3 H, s). Mass spectrum (ESI): m/e = 254.2 $[M + H]^+$.

*4-Chloro-2-(2-fluorophenyl)-3-methylquinoline, **23c**.* 4-Chloro-2-(2-fluorophenyl)-3-methylquinoline, **23c**, was prepared according to quinoline synthesis procedure A. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.28 (1 H, dd, J = 8.4, 1.0 Hz), 8.11−8.16 (1 H, m), 7.71−7.77 (1 H, m), 7.63−7.69 (1 H, m), 7.43−7.55 (2 H, m), 7.29−7.34 (1 H, m), 7.20 (1 H, ddd, J = 9.6, 8.4, 1.0 Hz), 2.47 (3 H, d, J = 2.0 Hz). Mass spectrum (ESI): m/e = 272.1 $[M + H]^+$.

General Coupling Procedure B. A mixture of indoline (1 equiv), quinoline (2 equiv), cesium carbonate (2 equiv), $Pd_2(dba)_3$ (0.1 equiv) and (±) BINAP (0.15 equiv) was dissolved in 1,4-dioxane (0.4M). The resulting mixture was purged with argon and subjected to microwave heating at 140 °C for 3 h. The crude residue was purified by chromatography (SiO_2, hexane:ethyl acetate) to give the desired morpholino−quinoline product.

General Coupling Procedure C. To a stirred solution of the halodimethylindoline (or the halodimethylpyrrolopyridine) (1 equiv) in dimethylformamide (0.03M) was added NaH (60% dispersion in oil, 1.5 equiv). The reaction mixture was stirred at room temperature for 20 min. After this time the substituted dichloroquinoline (1 equiv) in dimethylformamide (0.03M) was added. The resulting mixture was heated at 130 °C for 12 h. After this time the reaction mixture was allowed to cool to room temperature and quenched with Na_2CO_3 (10% aqueous solution). The reaction mixture was then treated with ethyl acetate and water. The separated organic layer was washed with LiCl (5% aqueous solution), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude residue was purified by chromatography (SiO_2, hexane:ethyl acetate) to give the desired bromoquinolines.

*6-Chloro-4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-2,3-dimethylquinoline, **24a**.* General coupling procedure B using 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (0.15 g, 0.65 mmol), and 4,6-dichloro-2,3-dimethylquinoline, **23a** (0.292 g, 1.29 mmol), gave 6-chloro-4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-2,3-dimethylquinoline, **24a** (80 mg, 29% yield). ^{1}H NMR (500 MHz, DMSO-d_6), TFA salt, δ ppm 8.09 (1 H, d, J = 9.0 Hz), 7.84−7.97 (2 H, m), 7.15 (1 H, d, J = 8.1 Hz), 6.48 (1 H, d, J = 8.1 Hz), 5.84 (1 H, s), 3.98 (1 H, d, J = 9.0 Hz), 3.78 (1 H, d, J = 9.0 Hz), 3.57−3.67 (4 H, m), 2.87−2.98 (4 H, m), 2.79 (3 H, s), 2.20 (3 H, s), 1.43 (3 H, s), 1.37 (3 H, s). HRMS (ESI): m/z 422.2009 $[M + H]^+$ ($C_{25}H_{28}ClN_3O$ requires 422.2000).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-2,3-dimethylquinoline, **1**.* A solution of 6-chloro-4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-2,3-dimethylquinoline, **24a** (10 mg, 0.024 mmol), in methanol (3 mL) was purged with N_2. After the mixture was purged, a catalytic amount of triethylamine and 10% Pd/C (0.003 g, 0.002 mmol) were added. The resulting mixture was stirred at room temperature for 2 h under a hydrogen atmosphere. After this time the reaction mixture was filtered through a pad of Celite and the solvent was evaporated in vacuo to give 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-2,3-dimethylquinoline, **1** (2.9 mg, 31% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.12 (1 H, d, J = 8.1 Hz), 7.80 (1 H, d, J = 8.1 Hz), 7.65 (1 H, t, J = 7.5 Hz), 7.38−7.43 (1 H, m), 7.06 (1 H, d, J = 7.6 Hz), 6.30 (1 H, d, J = 7.1 Hz), 5.52 (1 H, s), 3.63−3.78 (6 H, m), 2.88−2.97 (4 H, m), 2.73−2.81 (3 H, m), 2.26−2.32 (3 H, m), 1.42−1.53 (6 H, m). HRMS (ESI): m/z 388.2398 $[M + H]^+$ ($C_{25}H_{29}N_3O$ requires 388.2390).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-3-methyl-2-phenylquinoline, **24b**.* General coupling procedure C using 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (0.100 g, 0.430 mmol), and 4-chloro-3-methyl-2-phenylquinoline, **23b** (0.218 g, 0.861 mmol), gave 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-3-methyl-2-phenylquinoline, **24b** (0.045 g, 23%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.35 (1 H, d, J = 8.2 Hz), 8.17 (1 H, d, J = 8.2 Hz), 8.01 (1 H, t, J = 7.4 Hz), 7.81−7.90 (2 H, m), 7.77 (1 H, t, J = 7.6 Hz), 7.68 (3 H, br s), 7.31 (1 H, d, J = 8.0 Hz), 6.92 (1 H, br s), 6.56 (1 H, br s), 4.29 (1 H, d, J = 9.6 Hz), 3.97 (1 H, d, J = 9.2 Hz), 3.82 (4 H, br s), 3.19 (4 H, br s), 2.10 (3 H, s), 1.48 (3 H, s), 1.31−1.39 (3 H, m). HRMS (ESI): m/z 450.2549 $[M + H]^+$ ($C_{30}H_{31}N_3O$ requires 450.2547).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-2-(2-fluorophenyl)-3-methylquinoline, **24c**.* **24c** was prepared according to general coupling procedure B using 4-(3,3-dimethylindolin-6-yl)-morpholine, **4** (0.043 g, 0.184 mmol), and 4-chloro-2-(2-fluorophenyl)-3-methylquinoline, **23c** (0.050 g, 0.184 mmol). After purification by HPLC, 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-2-(2-fluorophenyl)-3-methylquinoline, **24c** (0.053 g, 62% yield), was obtained. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.00 (1 H, d, J = 7.8 Hz), 7.82 (1 H, d, J = 8.2 Hz), 7.69 (1 H, t, J = 7.6 Hz), 7.52 (3 H, m), 7.30 (2 H, m), 6.98 (1 H, d, J = 8.2 Hz), 6.20 (1 H, dd, J = 8.2, 2.0 Hz), 5.46 (1 H, d, J = 2.0 Hz), 3.75 (1 H, d, J = 9.0 Hz), 3.60 (1 H, d, J = 9.4 Hz), 3.51 (4 H, m), 2.77 (4 H, m), 1.99 (3 H, s), 1.39 (3 H, s), 1.30 (3 H, s). HRMS (ESI): m/z 468.2450 $[M + H]^+$ ($C_{30}H_{30}FN_3O$ requires 468.2452).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-7-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **24d**.* **24d** was prepared according to general coupling procedure C using 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (85 mg, 0.367 mmol), and 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (100 mg, 367 μmol). After purification, 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-7-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **24d** (10 mg, 6% yield), was obtained as a yellow film. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.73−8.76 (1 H, m), 7.80−7.94 (4 H, m), 7.40 (1 H, ddd, J = 7.6, 4.9, 1.5 Hz), 7.20−7.27 (1 H, m), 7.08 (1 H, d, J = 8.3 Hz), 6.31 (1 H, dd, J = 8.1, 2.2 Hz), 5.59 (1 H, d, J = 2.4 Hz), 3.69−3.81 (6 H, m), 2.89−3.03 (4 H, m), 2.37 (3 H, s), 1.51 (3 H, s), 1.46 (3 H, s). HRMS (ESI): m/z 469.2412 $[M + H]^+$ ($C_{29}H_{29}FN_4O$ requires 469.2405).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-5-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **24e**.* **24e** was prepared according to general coupling procedure C using 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (348 mg, 1496 μmol), and 4-chloro-5-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23e** (340 mg, 1247 μmol). After purification, 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-5-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **24e** (13 mg, 2% yield), was obtained as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.76 (1 H, dd, J = 3.5, 1.2 Hz), 8.02 (1 H, d, J = 8.2 Hz), 7.83−7.96 (2 H, m), 7.60 (1 H, td, J = 8.1, 5.3 Hz), 7.40 (1 H, ddd, J = 7.0, 5.1, 2.0 Hz), 7.08−7.17 (1 H, m), 7.04 (1 H, d, J = 8.2 Hz), 6.26 (1 H, dd, J = 8.0, 2.2 Hz), 5.50 (1 H, d, J = 2.3 Hz), 3.76−3.85 (1 H, m), 3.60−3.76 (5 H, m), 2.86−3.02 (4 H, m), 2.42 (3 H, s), 1.50 (3 H, s), 1.44 (3 H, s). HRMS (ESI): m/z 469.2405 $[M + H]^+$ ($C_{29}H_{29}FN_4O$ requires 469.2405).

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-indol-1-yl)-7-fluoro-3-methyl-2-(3-pyridinyl)quinoline, **24f**.* **24f** was prepared according to general coupling procedure C using 4-(3,3-dimethylindolin-6-yl)morpholine, **4** (213 mg, 0.92 mmol), and 4-chloro-7-fluoro-3-methyl-2-(pyridin-3-yl)quinoline (250 mg, 0.92 mmol), **23f**. After purification, 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-indol-1-yl)-7-fluoro-3-ethyl-2-(3-pyridinyl)quinoline, **24f** (50 mg, 12% yield), was obtained as

a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.90 (1 H, br s), 8.66−8.81 (1 H, m), 8.00 (1 H, dt, J = 7.8, 2.0 Hz), 7.89 (1 H, dd, J = 9.4, 5.9 Hz), 7.81 (1 H, dd, J = 10.0, 2.5 Hz), 7.48 (1 H, dd, J = 7.8, 4.7 Hz), 7.23−7.30 (1 H, m), 7.09 (1 H, d, J = 8.2 Hz), 6.34 (1 H, dd, J = 8.2, 2.3 Hz), 5.61 (1 H, d, J = 2.3 Hz), 3.68−3.81 (6 H, m), 2.90−3.02 (4 H, m), 2.30 (3 H, s), 1.52 (3 H, s), 1.47 (3 H, s). HRMS (ESI): m/z 469.2398 $[M + H]^+$ ($C_{29}H_{29}FN_4O$ requires 469.2405).

6-Bromo-1-(6-chloro-2,3-dimethylquinolin-4-yl)-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], ***25a.*** General coupling procedure C using 6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **10** (0.3 g, 1.12 mmol), and 4,6-dichloro-2,3-dimethylquinoline, **23a** (0.2783 g, 1.23 mmol), gave 6-bromo-1-(6-chloro-2,3-dimethylquinolin-4-yl)-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **25a** (0.264 g, 51% yield), as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.03 (1 H, d, J = 9.0 Hz), 7.71 (1 H, dd, J = 8.9, 2.3 Hz), 7.65 (1 H, d, J = 2.2 Hz), 7.22 (1 H, d, J = 7.8 Hz), 6.83 (1 H, dd, J = 7.8, 1.5 Hz), 5.94 (1 H, d, J = 1.5 Hz), 4.04 (1 H, d, J = 9.8 Hz), 3.80−3.93 (3 H, m), 3.39−3.54 (2 H, m), 2.68 (3 H, s), 2.22 (3 H, s), 1.94−2.06 (2 H, m), 1.85 (1 H, d, J = 13.4 Hz), 1.73 (1 H, dd, J = 13.4, 1.5 Hz). Mass spectrum (ESI): m/e = 457.1 $[(M + H)\ (^{79}Br)]^+$ and 459.1 $[(M + H)\ (^{81}Br)]^+$.

1-(6-Chloro-2,3-dimethyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], ***26a.*** A suspension of 6-bromo-1-(6-chloro-2,3-dimethylquinolin-4-yl)-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **25a** (230 mg, 0.50 mmol) and morpholine (87 μL, 1 mmol) was degassed with argon for 20 min. To the suspension were added CuI (19 mg, 0.1 mmol), K_2CO_3 (207 mg, 1.5 mmol), and L-proline (23 mg, 0.2 mmol), and the mixture was stirred at 120 °C. After 24 h the mixture was cooled to room temperature. To the mixture was added water (30 mL), and the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified by column chromatography on a silica gel column using 0% to 100% gradient of ethyl acetate in hexane as eluent to give 1-(6-chloro-2,3-dimethyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **26a** (0.055 g, 23.4% yield), as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 7.97−8.03 (1 H, m), 7.67 (2 H, dd, J = 4.5, 2.1 Hz), 7.10 (1 H, d, J = 8.1 Hz), 6.26 (1 H, dd, J = 8.1, 1.5 Hz), 5.46 (1 H, d, J = 1.5 Hz), 3.94 (1 H, d, J = 9.5 Hz), 3.82−3.91 (2 H, m), 3.78 (1 H, d, J = 9.8 Hz), 3.54−3.59 (4 H, m), 3.40−3.52 (2 H, m), 2.80−2.87 (4 H, m), 2.68 (3 H, s), 2.21 (3 H, s), 1.92−2.02 (2 H, m), 1.78 (1 H, d, J = 13.2 Hz), 1.68 (1 H, d, J = 12.5 Hz). Mass spectrum (ESI): m/e = 464.2 $[M + H]^+$.

1-(2,3-Dimethyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], ***26b.*** A mixture of 1-(6-chloro-2,3-dimethyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **26a** (0.027 g, 0.058 mmol), triethylamine (0.008 mL, 0.058 mmol), and 10% Pd/C (0.02 g, 0.0188 mmol) in methanol−ethyl acetate (2:1, 3 mL) was stirred under hydrogen at room temperature. After 3 h, the mixture was filtered through a Celite pad and the pad was washed with methanol and ethyl acetate to give a tan solid. The tan solid was purified by column chromatography on a silica gel column using 0 to 100% gradient of ethyl acetate in hexane as eluent to give 1-(2,3-dimethyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **26b** (9.5 mg, 38% yield), as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 7.97 (1 H, d, J = 8.3 Hz), 7.71 (1 H, d, J = 8.1 Hz), 7.62−7.68 (1 H, m), 7.42−7.49 (1 H, m), 7.08 (1 H, d, J = 8.3 Hz), 6.23 (1 H, dd, J = 8.2, 2.1 Hz), 5.41 (1 H, d, J = 2.2 Hz), 3.77−3.96 (4 H, m), 3.52−3.59 (4 H, m), 3.41−3.51 (2 H, m), 2.81 (4 H, dd, J = 5.4, 2.9 Hz), 2.68 (3 H, s), 2.22 (3 H, s), 1.91−2.03 (2 H, m), 1.78−1.85 (1 H, m), 1.65−1.72 (1 H, m). HRMS (ESI): m/z 430.2505 $[M + H]^+$ ($C_{27}H_{31}N_3O_2$ requires 430.2496).

1-(3-Methyl-2-phenyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], ***26c.*** **26c** was prepared according to general procedure C using 6-morpholino-2′,3′,5′,6′-tetrahydrospiro-[indoline-3,4′-pyran], **13** (0.216 g, 0.788 mmol), and 4-chloro-3-methyl-2-phenylquinoline, **23b** (0.100 g, 0.394 mmol). After purification, 1-(3-methyl-2-phenyl-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **26c** (0.071 g, 37% yield), was obtained. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.06−8.10 (1 H, m), 7.80−7.84 (1 H, m), 7.74 (1 H, ddd, J = 8.4, 6.8, 1.5 Hz), 7.64−7.69 (2 H, m), 7.48−7.59 (4 H, m), 7.11 (1 H, d, J = 8.3 Hz), 6.27 (1 H, dd, J = 8.3, 2.2 Hz), 5.58 (1 H, d, J = 2.2 Hz), 4.01 (1 H, d, J = 9.8 Hz), 3.83−3.97 (3 H, m), 3.56−3.63 (4 H, m), 3.48 (2 H, tt, J = 12.0, 2.1 Hz), 2.82−2.91 (4 H, m), 2.22 (3 H, s), 1.93−2.05 (2 H, m), 1.82−1.88 (1 H, m), 1.65−1.73 (1 H, m). HRMS (ESI): m/z 492.2644 $[M + H]^+$ ($C_{32}H_{33}N_3O_2$ requires 492.2652).

6-Bromo-1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], ***25d.*** **25d** was prepared according to general coupling procedure C using 6-bromo-2′,3′,5′,6′-tetrahydrospiro[indoline-3,4′-pyran], **10** (98 mg, 367 μmol), and 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (100 mg, 367 μmol). After purification, 6-bromo-1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **25d** (55 mg, 30% yield), was obtained as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.74 (1 H, d, J = 5.1 Hz), 7.89−7.98 (2 H, m), 7.85 (1 H, dd, J = 10.0, 2.5 Hz), 7.75 (1 H, dd, J = 9.2, 6.1 Hz), 7.41 (1 H, ddd, J = 6.7, 4.5, 2.5 Hz), 7.28−7.33 (1 H, m), 7.07 (1 H, d, J = 7.8 Hz), 6.89 (1 H, dd, J = 7.8, 2.0 Hz), 6.11 (1 H, d, J = 2.0 Hz), 3.93−4.10 (4 H, m), 3.45−3.60 (2 H, m), 2.38 (3 H, s), 2.08−2.25 (2 H, m), 1.91 (1 H, dd, J = 13.9, 2.5 Hz), 1.81 (1 H, dd, J = 13.7, 2.3 Hz). Mass spectrum (ESI): m/e 504 $[(M + H)\ (^{79}Br)]^+$ and 506 $[(M + H)\ (^{81}Br)]^+$.

1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], ***26d.*** A suspension of 6-bromo-1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-1,2,2′,3′,5′,6′-hexahydrospiro[indole-3,4′-pyran], **25d** (100 mg, 0.198 mmol), morpholine (35 μL, 397 μmol) and DMSO (2.5 mL) was degassed with argon for 15 min in a Schlenk tube. To the mixture were added copper(I) iodide (8 mg, 40 μmol), L-proline (9 mg, 79 μmol) and potassium carbonate (82 mg, 595 μmol), and the mixture was heated at 120 °C overnight. After this time the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (100 mL) and water (40 mL). The separated organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Column chromatography (hexane:ethyl acetate, 1:0 to 0:1) gave the desired product as a yellow oil. The product was further purified by reverse phase HPLC to give 1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-1,2,2′,3′,5′,6′-hexahydrospiro-[indole-3,4′-pyran], **26d** (13 mg, 13% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.76 (1 H, dd, J = 3.7, 1.0 Hz), 7.75−8.00 (4 H, m), 7.41 (1 H, ddd, J = 7.1, 5.0, 1.6 Hz), 7.21−7.27 (1 H, m), 7.13 (1 H, d, J = 8.2 Hz), 6.35 (1 H, dd, J = 8.2, 2.3 Hz), 5.61 (1 H, d, J = 2.3 Hz), 3.96−4.09 (3 H, m), 3.89−3.96 (1 H, m), 3.70−3.79 (4 H, m), 3.49−3.60 (2 H, m, J = 12.2, 12.2, 2.9, 2.7 Hz), 2.91−3.04 (4 H, m), 2.38 (3 H, s), 2.09−2.22 (2 H, m), 1.76−1.93 (2 H, m). HRMS (ESI): m/z 511.2504 $[M + H]^+$ ($C_{31}H_{31}FN_4O_2$ requires 511.2510).

tert-Butyl 6-Bromo-3,3-bis((methylsulfonyloxy)methyl)-2-oxoindoline-1-carboxylate, ***28.*** To an ice-cooled solution of *tert*-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxoindoline-1-carboxylate, **27** (5.27 g, 14.16 mmol), in CH_2Cl_2 (94 mL) was added triethylamine (7.89 mL, 56.6 mmol) followed by methanesulfonyl chloride (2.21 mL, 28.3 mmol). The solution was stirred for 1 h, and then it was concentrated under reduced pressure. Purification by column chromatography (eluting with a gradient of 10−60% ethyl acetate in hexane) gave *tert*-butyl 6-bromo-3,3-bis((methylsulfonyloxy)methyl)-2-oxoindoline-1-carboxylate, **28** (4.21 g, 56%), as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.15 (1 H, d, J = 1.6 Hz), 7.43 (1 H, m, J = 8.1, 1.7 Hz), 7.33 (1 H, d, J = 8.0 Hz), 4.58 (2 H, d, J = 10.2 Hz), 4.46 (2 H, d, J = 10.4 Hz), 2.98 (6 H, s), 1.67 (9 H, s). Mass spectrum (ESI): m/e = 550.0 $[(M+ Na)\ (^{79}Br)]^+$ and 552.0 $[(M+ Na)\ (^{81}Br)]^+$.

6-Bromospiro[indoline-3,3′-thietan]-2-one, ***29.*** To a solution of *tert*-butyl 6-bromo-3,3-bis((methylsulfonyloxy)methyl)-2-oxoindoline-1-carboxylate, **28** (3.70 g, 7.0 mmol), in anhydrous dimethylformamide (33 mL, deoxygenated with argon for 10 min) was added sodium sulfide nonahydrate (1.01 g, 4.20 mmol) under an argon atmosphere. The solution was stirred at 110 °C for 3 h, poured into saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography (eluting with a gradient of 10−50% ethyl acetate in hexane) gave 6-bromospiro[indoline-3,3′-thietan]-2-one, **29** (0.248 g, 13%), as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78−7.98 (2 H, m), 7.31 (1 H, dd, J = 7.9, 1.7 Hz),

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7.07 (1 H, d, J = 1.6 Hz), 3.89 (2 H, d, J = 9.59 Hz), 3.12 (2 H, d, J = 9.6 Hz). Mass spectrum (ESI): m/e =270.0 [(M + H) (^{79}Br)]$^+$ and 271.9 [(M + H) (^{81}Br)]$^+$.

*6-Bromo-1,2-dihydrospiro[indole-3,3′-thietane], **30***. To a solution of 6-bromospiro[indoline-3,3′-thietan]-2-one, **29** (0.260 g, 0.962 mmol), in toluene (39 mL) was added Red-Al (60% in toluene, 1.47 mL, 4.81 mmol) dropwise under an atmosphere of argon gas. The solution was stirred at 80 °C for 40 min, cooled in an ice bath, quenched with aqueous 2 N NaOH and treated with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give 6-bromo-1,2-dihydrospiro[indole-3,3′-thietane], **30**, as a tan solid. Product used without further purification in the next step. Mass spectrum (ESI): m/e = 256.0 [(M + H) (^{79}Br)]$^+$ and 258.0 [(M + H) (^{81}Br)]$^+$.

*1-Acetyl-6-bromo-1,2-dihydrospiro[indole-3,3′-thietane], **31***. To an ice cooled solution of 6-bromo-1,2-dihydrospiro[indole-3,3′-thietane], **30** (0.25 g, 0.96 mmol), 4-dimethylaminopyridine (5.89 mg, 0.048 mmol), and triethylamine (0.269 mL, 1.928 mmol) in CH_2Cl_2 (9.64 mL) was added acetyl chloride (0.137 mL, 1.928 mmol). The solution was stirred for 5 min at this temperature, the ice bath was removed and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into 2 N HCl aqueous solution and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 1-acetyl-6-bromo-1,2-dihydrospiro-[indole-3,3′-thietane], **31**, as a yellow solid. The product was used without further purification in the next step. Mass spectrum (ESI): m/e = 297.9 [(M + H) (^{79}Br)]$^+$ and 300.0 [(M + H) (^{81}Br)]$^+$.

*1-Acetyl-6-bromo-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-Dioxide, **32***. To a stirred ice-cooled solution of 1-acetyl-6-bromo-1,2-dihydrospiro[indole-3,3′-thietane], **31** (0.288 g, 0.97 mmol), in a mixture of water (2.4 mL), methanol (18.9 mL), and acetone (4.7 mL) was added a solution of Oxone (1.19 g, 1.93 mmol) in water (1.8 mL). The ice bath was removed, and the solution was stirred at room temperature for 4 h. The mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give 1-acetyl-6-bromo-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **32** (0.077 g, 24% from **30**) as a tan solid. Mass spectrum (ESI): m/e = 330.0 [(M + H) (^{79}Br)]$^+$ and 332.0 [(M + H) (^{81}Br)]$^+$.

*1-Acetyl-6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-Dioxide, **33***. To a microwave vessel were added sodium *tert*-butoxide (0.045 g, 0.466 mmol), morpholine, (0.030 mL, 0.350 mmol), XPhos (0.022 g, 0.047 mmol), $Pd_2(dba)_3$ (0.021 g, 0.023 mmol), and 1-acetyl-6-bromo-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **32** (0.077 g, 0.233 mmol), in 1,4-dioxane (2.3 mL). The suspension was deoxygenated with argon for 5 min and stirred at 110 °C for 90 min under microwave irradiation. The crude mixture was loaded directly onto a silica gel column (eluting with a gradient of 0−10% methanol in CH_2Cl_2) to give 1-acetyl-6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **33** (0.046 g, 59%), as a tan oil. Mass spectrum (ESI): m/e = 337.1 [M + H]$^+$.

*6-(4-Morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-Dioxide, **34***. To a solution of 1-acetyl-6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **33** (0.046 g, 0.137 mmol), in methanol (1.4 mL) was added 5.0 N HCl solution (0.27 mL, 1.37 mmol). The solution was stirred at 60 °C for 3 h, and then it was cooled to room temperature, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated in vacuo to give 6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **34** (0.026 g, 65%), as a brown solid. Mass spectrum (ESI): m/e = 295.1 [M + H]$^+$.

*tert-Butyl 6′-Bromo-2,2-dimethyl-2′-oxospiro[[1,3]dioxane-5,3′-indoline]-1′-carboxylate, **35***. To a solution of *tert*-butyl 6-bromo-3,3-bis(hydroxymethyl)-2-oxoindoline-1-carboxylate, **27** (1.00 g, 2.69 mmol), and 4-methylbenzenesulfonic acid hydrate (0.026 g, 0.134 mmol) in dimethylformamide (27 mL) was added 2,2-dimethoxypropane (0.49 mL, 4.03 mmol). The solution was stirred at room temperature overnight followed by the addition of additional 2,2-dimethoxypropane (0.49 mL, 4.03 mmol) and 4-methylbenzenesulfonic acid hydrate (0.026 g, 0.134 mmol). After stirring at 60 °C for 5 h, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were purified by column chromatography (eluting with a gradient of 0−30% ethyl acetate in hexane) to give *tert*-butyl 6′-bromo-2,2-dimethyl-2′-oxospiro[[1,3]dioxane-5,3′-indoline]-1′-carboxylate, **35** (0.520 g, 47%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 7.99 (1 H, d, J = 1.7 Hz), 7.68 (1 H, d, J = 8.0 Hz), 7.45 (1 H, dd, J = 8.12, 1.9 Hz), 4.18 (2 H, d, J = 11.5 Hz), 3.79 (2 H, d, J = 11.7 Hz), 1.43−1.64 (15 H, m). Mass spectrum (ESI): m/e = 434.0 [(M + Na) (^{79}Br)]$^+$ and 436.0 [(M + Na) (^{81}Br)]$^+$.

*2,2-Dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indolin]-2′-one, **36***. To a microwave vessel were added sodium *tert*-butoxide (0.19 g, 1.99 mmol), morpholine (0.13 mL, 1.49 mmol), XPhos (0.095 g, 0.20 mmol), $Pd_2(dba)_3$ (0.091 g, 0.099 mmol), and *tert*-butyl 6′-bromo-2,2-dimethyl-2′-oxospiro[[1,3]dioxane-5,3′-indoline]-1′-carboxylate, **35** (0.41 g, 0.99 mmol), in 1,4-dioxane (9.9 mL). The mixture was deoxygenated with argon for 5 min and stirred at 110 °C for 90 min under microwave irradiation. The resulting mixture was purified by column chromatography (eluting with a gradient of 10−70% ethyl acetate in hexane) to give 2,2-dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indolin]-2′-one, **36** (0.111 g, 35%), as a white solid. Mass spectrum (ESI): m/e = 319.2 [M + H]$^+$.

*2,2-Dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indoline], **37***. To a solution of 2,2-dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indolin]-2′-one, **36** (0.11 g, 0.35 mmol), in toluene (14 mL) was added Red-Al (60% in toluene, 0.53 mL, 1.74 mmol). After stirring at 80 °C for 40 min, the solution was poured into a mixture of ice and 2 N NaOH. The product was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography (eluting with a gradient of 5−60% ethyl acetate in hexane) gave 2,2-dimethyl-6′-morpholinospiro-[[1,3]dioxane-5,3′-indoline], **37** (0.056 g, 53%), as a white solid. Mass spectrum (ESI): m/e = 305.2 [M + H]$^+$.

*1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-Dioxide, **38***. To a microwave vial were added sodium *tert*-butoxide (0.017 g, 0.177 mmol), Ruphos (4.12 mg, 8.83 μmol), 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (0.025 g, 0.093 mmol), 6-(4-morpholinyl)-1,2-dihydrospiro[indole-3,3′-thietane] 1′,1′-dioxide, **34** (0.026 g, 0.088 mmol), and XPhos precatalyst (6.5 mg, 8.8 μmol) in toluene (0.6 mL). The suspension was deoxygenated with argon for 5 min and then stirred at 100 °C for 1 h under microwave irradiation. Purification by column chromatography (eluting with a gradient of 0−10% methanol in CH_2Cl_2) gave a yellow solid, which was repurified by reverse phase HPLC (10−60% acetonitrile in water) to give 1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-1,2-dihydrospiro-[indole-3,3′-thietane] 1′,1′-dioxide, **38** (0.012 g, 26%), as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.71 (1 H, d, J = 4.9 Hz), 7.99−8.05 (1 H, m), 7.83−7.94 (3 H, m), 7.50−7.56 (2 H, m), 7.49 (1 H, d, J = 8.3 Hz), 6.40 (1 H, dd, J = 8.4, 2.1 Hz), 5.58 (1 H, d, J = 2.0 Hz), 4.72 (1 H, dd, J = 13.6, 2.3 Hz), 4.55−4.63 (3 H, m), 4.35 (1 H, d, J = 10.0 Hz), 4.25 (1 H, d, J = 10.0 Hz), 3.58 (4 H, t, J = 4.9 Hz), 2.82−2.93 (4 H, m), 2.24 (3 H, s). HRMS (ESI): m/z 531.1868 [M + H]$^+$ ($C_{29}H_{27}FN_4O_3S$ requires 531.1867).

*1′-(7-Fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-2,2-dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indoline], **39***. To a microwave vial were added sodium *tert*-butoxide (0.035 g, 0.37 mmol), Ruphos (8.6 mg, 0.018 mmol), 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)-quinoline, **23d** (0.053 g, 0.19 mmol), 2,2-dimethyl-6′-morpholinospiro-[[1,3]dioxane-5,3′-indoline], **37** (0.056 g, 0.18 mmol), and XPhos precatalyst (0.014 g, 0.018 mmol) in toluene (1.2 mL). The suspension was deoxygenated with argon for 5 min and stirred at 100 °C for 90 min under microwave irradiation. Purification by column chromatography (eluting with a gradient of 10−60% ethyl acetate in hexane) gave 1′-(7-fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-2,2-dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indoline], **39** (0.057 g, 57%), as a yellow solid. Mass spectrum (ESI): m/e = 541.3 [M + H]$^+$.

*(1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-2,3-dihydro-1H-indole-3,3-diyl)dimethanol, **40***. To a solution of 1′-(7-fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-2,2-dimethyl-6′-morpholinospiro[[1,3]dioxane-5,3′-indoline], **39** (0.057 g, 0.105 mmol), in THF (1 mL) was added 1.0 N HCl (1.05 mL, 1.05 mmol).

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After stirring at room temperature for 1 h, the solution was purified by column chromatography (eluting with a gradient of 0−10% methanol in CH_2Cl_2) to give (1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6-(4-morpholinyl)-2,3-dihydro-1*H*-indole-3,3-diyl)dimethanol, **40** (0.027 g, 0.054 mmol, 51%), as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.72 (1 H, d, J = 4.9 Hz), 8.03 (1 H, td, J = 7.7, 1.7 Hz), 7.97 (1 H, dd, J = 9.3, 6.1 Hz) 7.92 (1 H, d, J = 7.8 Hz), 7.84 (1 H, dd, J = 10.1, 2.6 Hz), 7.47−7.57 (2 H, m), 7.06 (1 H, d, J = 8.1 Hz), 6.21 (1 H, dd, J = 8.2, 2.1 Hz), 5.45 (1 H, d, J = 2.0 Hz), 4.91 (1 H, t, J = 5.3 Hz), 4.84 (1 H, t, J = 5.3 Hz), 3.79−3.91 (2 H, m), 3.72 (2 H, d, J = 5.4 Hz), 3.65 (2 H, dd, J = 5.4, 1.2 Hz), 3.58 (4 H, t, J = 4.9 Hz), 2.76−2.89 (4 H, m), 2.29 (s, 3 H). HRMS (ESI): m/z 501.2294 $[M + H]^+$ ($C_{29}H_{29}FN_4O_3$ requires 501.2303).

*3,3-Dimethyl-6-(pyridin-4-yl)indoline, **41**.* A solution of 6-iodo-3,3-dimethylindoline, **6** (100 mg, 0.36 mmol), 4-pyridinylboronic acid (54 mg, 0.44 mmol), Na_2CO_3 (78 mg, 0.73 mmol) and $Pd(PPh_3)_4$ (42 mg, 0.037 mmol) in acetonitrile (2 mL) and water (1 mL) was heated in a microwave reactor for 2 h at 110 °C. After this time the reaction mixture was partitioned between ethyl acetate and water. The separated organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography (SiO_2, hexane:ethyl acetate, 1:0 to 1:1) gave 3,3-dimethyl-6-(pyridin-4-yl)indoline, **41** (26 mg, 32% yield). Mass spectrum (ESI): m/e = 225.2 $[M + H]^+$.

*4-(3,3-dimethyl-6-(pyridin-4-yl)indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **44a**.* **44a** was prepared according to general procedure B using 3,3-dimethyl-6-(pyridin-4-yl)indoline, **41** (0.026 g, 0.116 mmol), 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (0.032 g, 0.116 mmol), cesium carbonate (0.076 g, 0.232 mmol), $Pd_2(dba)_3$ (0.011 g, 0.012 mmol) and (±) BINAP (0.011 g, 0.017 mmol) in toluene (3 mL). After purification by HPLC, 4-(3,3-dimethyl-6-(pyridin-4-yl)indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)-quinoline, **44a** (4.4 mg, 8% yield), was obtained. ^{1}H NMR (400 MHz, MeOD): δ ppm 8.75 (1 H, d, J = 4.7 Hz), 8.68 (2 H, m), 8.12−8.23 (3 H, m), 8.07 (1 H, dd, J = 9.4, 5.9 Hz), 7.96 (1 H, d, J = 7.8 Hz), 7.83 (1 H, dd, J = 9.8, 2.7 Hz), 7.65 (1 H, dd, J = 7.6, 4.9 Hz), 7.50 (2 H, m), 7.42 (1 H, m), 6.62 (1 H, s), 4.05 (1 H, d, J = 9.0 Hz), 3.90 (1 H, d, J = 9.4 Hz), 2.28 (3 H, s), 1.65 (3 H, s), 1.57 (3 H, s). HRMS (ESI): m/z 461.2156 $[M + H]^+$ ($C_{30}H_{25}FN_4$ requires 461.2143).

General Procedure D. A glass microwave reaction vessel was charged with the indoline (1 equiv) and chloroquinoline (1 equiv) fragments, followed by *N*-methyl-2-pyrrolidone and a 4.0 M solution of HCl in 1,4-dioxane (1 equiv). The resulting mixture was heated at 130 °C for 12 h. After this time the reaction mixture was partitioned between ethyl acetate and $NaHCO_3$ (saturated aqueous solution). The separated organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography on silica gave the desired coupling products.

*7-Fluoro-4-(6-iodo-3,3-dimethylindolin-1-yl)-3-methyl-2-(pyridin-2-yl)quinoline, **42**.* **42** was prepared according to general procedure D using 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (499 mg, 1.83 mmol), 6-iodo-3,3-dimethylindoline, **6** (500 mg, 1.831 mmol), and 4 M HCl in 1,4-dioxane (0.458 mL, 1.83 mmol) in *N*-methyl-2-pyrrolidinone (3 mL). After purification (40 g of SiO_2, eluting with a gradient of 0% to 30% ethyl acetate in hexane), 7-fluoro-4-(6-iodo-3,3-dimethylindolin-1-yl)-3-methyl-2-(pyridin-2-yl)quinoline, **42** (510 mg, 55% yield), was obtained as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.71−8.80 (1 H, m), 7.85−7.97 (3 H, m), 7.80 (1 H, dd, J = 9.2, 5.9 Hz), 7.42 (1 H, ddd, J = 7.0, 4.8, 1.7 Hz), 7.28−7.33 (1 H, m), 7.09 (1 H, dd, J = 7.7, 1.5 Hz), 6.91 (1 H, d, J = 7.6 Hz), 6.29 (1 H, d, J = 1.6 Hz), 3.70−3.84 (2 H, m), 2.37 (3 H, s), 1.53 (3 H, s), 1.47 (3 H, s). Mass spectrum (ESI): m/e = 510.0 $[M + H]^+$.

General Procedure E. A stirred solution of the haloquinoline (1 equiv) in 1,4-dioxane (0.1 M) was treated with $Pd(PCy_3)_2$ (0.1 equiv), bis(pinacolato)diboron (1.1 equiv), and KOAc (1.5 equiv). The mixture was heated at 100 °C for 2 h in a microwave reactor. After this time the reaction mixture was diluted with ethyl acetate and water. The separated organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo to give the boronic acids (or esters).

*4-(3,3-Dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **43**.* **43** was prepared according to procedure E using 7-fluoro-4-(6-iodo-3,3-dimethylindolin-1-yl)-3-methyl-2-(pyridin-2-yl)quinoline, **42** (180 mg, 0.353 mmol), $Pd(PCy_3)_2$ (11.8 mg, 0.018 mmol), bis(pinacolato)-diboron (99 mg, 0.389 mmol) and potassium acetate (52 mg, 0.530 mmol) in 1,4-dioxane (5.2 mL, 61.1 mmol). After purification (SiO_2, hexane:ethyl acetate, 1:0 to 1:1), 4-(3,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)-quinoline, **43** (75 mg, 42%), was obtained as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.75 (1 H, dt, J = 4.9, 1.4 Hz), 7.79−7.97 (4 H, m), 7.38−7.44 (1 H, m), 7.29−7.33 (1 H, m), 7.21−7.26 (2 H, m), 6.42 (1 H, s), 3.80 (1 H, d, J = 9.2 Hz), 3.72 (1 H, d, J = 9.0 Hz), 2.32−2.40 (3 H, m), 1.51−1.57 (3 H, m), 1.43−1.50 (3 H, m), 1.22−1.30 (12 H, m). Mass spectrum (ESI): m/e = 510 $[M + H]^+$.

General Procedure F. A stirred solution of the boronic acid (or ester) (1 equiv) in 1,4-dioxane (0.1M) was treated with $PdCl_2(PPh_3)_2$ (0.1 equiv), an aryl chloride (1 equiv) and sodium carbonate (2 equiv). The mixture was heated at 120 °C for 2 h in a microwave reactor. After this time the reaction mixture was diluted with ethyl acetate and water. The separated organic layer was washed with brine and then dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by reverse phase HPLC (10 to 60% acetonitrile in water) gave the substituted quinoline products.

*4-(1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-pyrimidinamine, **44b**.* **44b** was prepared according to procedure F using 4-(3,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)-quinoline, **43** (75 mg, 0.147 mmol), $PdCl_2(PPh_3)_2$ (10.3 mg, 0.015 mmol), 2-amine-4-chloropyrimidine (21.0 mg, 0.162 mmol) and sodium carbonate (26.5 mg, 0.442 mmol) in 1,4-dioxane (2.0 mL) and water (0.7 mL) and heating in a microwave reactor. After purification, 4-(1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1*H*-indol-6-yl)-2-pyrimidinamine, **44b** (18 mg, 26%), was obtained as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.66−8.83 (1 H, m), 8.17 (1 H, d, J = 5.5 Hz), 7.79−7.99 (4 H, m), 7.36−7.48 (2 H, m), 7.26−7.29 (2 H, m), 6.87 (1 H, d, J = 5.5 Hz), 6.62 (1 H, d, J = 1.6 Hz), 5.43 (2 H, br s), 3.82 (2 H, s), 2.29−2.44 (3 H, m), 1.58 (3 H, s), 1.52 (3 H, s). HRMS (ESI): m/z 477.2198 $[M + H]^+$ ($C_{29}H_{25}FN_6$ requires 477.2204).

*4-(1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-6-methyl-2-pyrimidinamine, **44c**.* **44c** was prepared according to procedure F using 4-(3,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **43** (70 mg, 0.14 mmol), 4-chloro-6-methylpyrimidin-2-amine (21.7 mg, 0.15 mmol), $Pd_2Cl_2(PPh_3)_2$ (9.6 mg, 0.014 mmol), and sodium carbonate (43.7 mg, 0.41 mmol) in 1,4-dioxane (3.1 mL) and water (0.79 mL), and heating in a microwave reactor. After purification, 4-(1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1*H*-indol-6-yl)-6-methyl-2-pyrimidinamine, **44c** (28 mg, 42%) was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.75 (1 H, d, J = 4.3 Hz), 7.76−7.96 (4 H, m), 7.34−7.46 (2 H, m), 7.28 (1 H, br s), 7.21−7.26 (1 H, m), 6.66−6.76 (1 H, m), 6.58 (1 H, d, J = 1.2 Hz), 5.19 (2 H, br s), 3.74−3.90 (2 H, m), 2.35−2.41 (3 H, m), 2.28−2.35 (3 H, m), 1.55−1.61 (3 H, m), 1.49−1.55 (3 H, m). HRMS (ESI): m/z 491.2353 $[M + H]^+$ ($C_{30}H_{27}FN_6$ requires 491.2361).

*Dimethyl 2-(5-bromo-3-nitropyridin-2-yl)malonate, **46**.* To a suspension of K_2CO_3 (44 g, 316 mmol) in dimethylformamide (105 mL, 105 mmol) at 0 °C was added dimethyl malonate (18 mL, 158 mmol) via syringe over 10 min. After this time 5-bromo-2-chloro-3-nitropyridine, **45** (25 g, 105 mmol), was added portionwise over 4 min. The reaction mixture was allowed to warm to room temperature overnight. After this time the reaction mixture was poured into 2.0 M HCl (300 mL) and diluted with ethyl acetate (500 mL). The separated organic layer was washed with LiCl (1.0 M aqueous solution, 100 mL) and brine (100 mL), and then it was dried over $MgSO_4$, filtered and evaporated in vacuo to give dimethyl 2-(5-bromo-3-nitropyridin-2-yl)malonate, **46** (34 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.88 (1 H, d, J = 2.2 Hz), 8.63 (1 H, d, J = 2.2 Hz), 5.50 (1 H, s), 3.83 (6 H, s). Mass spectrum (ESI): m/e = 333.0 $[(M + H)\ (^{79}Br)]^+$ and 335.0 $[(M + H)\ (^{81}Br)]^+$.

*Methyl 2-(5-Bromo-3-nitropyridin-2-yl)acetate, **47**.* A stirred solution of dimethyl 2-(5-bromo-3-nitropyridin-2-yl)malonate, **46** (34 g, 102 mmol), in DMSO (400 mL), LiCl (8.7 g, 204 mmol) and water

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(2.0 mL, 112 mmol) was heated at 150 °C for 12 h. After this time the reaction mixture was cooled to room temperature and diluted with ethyl acetate (700 mL) and 1.0 M aqueous HCl (200 mL). The separated organic layer was washed with LiCl (150 mL, 1.0 M aqueous solution), dried over $MgSO_4$, filtered and evaporated in vacuo until a volume of 100 mL. The mixture was left standing for 12 h, filtered and evaporated in vacuo to give methyl 2-(5-bromo-3-nitropyridin-2-yl)acetate, **47** (21 g, 75% yield), as a dark oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.86 (1 H, d, J = 2.0 Hz), 8.58 (1 H, d, J = 2.0 Hz), 4.30 (2 H, s), 3.74 (3 H, s). Mass spectrum (ESI): m/e = 275 [(M + H) (^{79}Br)]$^+$ and 277 [(M + H) (^{81}Br)]$^+$.

*Methyl 2-(5-Bromo-3-nitropyridin-2-yl)-2-methylpropanoate, **48**.* To a stirred solution of methyl 2-(5-bromo-3-nitropyridin-2-yl)acetate, **47** (10.7 g, 38.9 mmol), in dimethylformamide (120 mL) at 0 °C was added NaH (1.87 g, 46.7 mmol, 60% dispersion in oil) portionwise over 10 min. The reaction mixture was stirred under N_2 and allowed to warm to room temperature for 20 min. After this time the reaction mixture was cooled to 0 °C and iodomethane (2.92 mL, 46.7 mmol) was added via syringe over 10 min. The reaction mixture was allowed to warm to room temperature and stirred under N_2 for 18 h. After this time an additional portion of NaH (1.87 g, 46.7 mmol, 60% dispersion in oil) followed by iodomethane (2.92 mL, 46.7 mmol) was slowly added and the reaction mixture was stirred at room temperature for 4 h. After this time the reaction mixture was cooled to room temperature and diluted with ethyl acetate (300 mL). The organic layer was washed with $NaHCO_3$ (100 mL) and LiCl (2 × 60 mL), dried over $MgSO_4$ and concentrated in vacuo. The residual mineral oil from the NaH dispersion was removed by pipet and by a wash with hexane, affording methyl 2-(5-bromo-3-nitropyridin-2-yl)-2-methylpropanoate, **48** (10.35 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.84 (1 H, d, J = 2.2 Hz), 8.38 (1 H, d, J = 2.2 Hz), 3.66 (3 H, s), 1.68−1.75 (6 H, m). Mass spectrum (ESI): m/e = 303 [(M + H) (^{79}Br)]$^+$ and 305 [(M + H) (^{81}Br)]$^+$.

*6-Bromo-3,3-dimethyl-1H-pyrrolo[3,2-b]pyridin-2(3H)-one, **49**.* To a stirred solution of methyl 2-(5-bromo-3-nitropyridin-2-yl)-2-methylpropanoate, **48** (2.94 g, 9.7 mmol), in acetic acid (55.4 mL) was added iron (powder, <10 μm, 2.71 g, 48.5 mmol). The gray reaction mixture was stirred at 100 °C for 45 min. After this time the reaction mixture was cooled to room temperature and filtered over Celite. The Celite was washed with acetic acid, and the filtrates were concentrated, affording a crude residue, which was purified by column chromatography on silica gel (80 g), eluting with a gradient of 0% to 50% ethyl acetate in hexane to provide 6-bromo-3,3-dimethyl-1*H*-pyrrolo[3,2-*b*]-pyridin-2(3*H*)-one, **49** (1.94 g, 83% yield), as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.42 (1 H, br s), 8.30 (1 H, d, J = 1.8 Hz), 7.37 (1 H, s), 1.46 (6 H, s). Mass spectrum (ESI): m/e = 241.0 [(M + H) (^{79}Br)]$^+$ and 243.0 [(M + H) (^{81}Br)]$^+$.

*6-Bromo-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine, **50**.* To a stirred suspension of 6-bromo-3,3-dimethyl-1*H*-pyrrolo[3,2-*b*]-pyridin-2(3*H*)-one, **49** (300 mg, 1.24 mmol), in toluene (3 mL) was added Red-Al (1.1 mL, 3.73 mmol, 65% in toluene) dropwise over 2 min. The reaction mixture was stirred at room temperature for 1 h and then cooled to 0 °C, diluted with ethyl acetate (80 mL) and treated with 1 N aqueous NaOH (30 mL) and water (20 mL). The separated organic layer was washed with 1 N NaOH (30 mL) and then dried over $MgSO_4$, filtered and evaporated in vacuo to give 6-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine, **50** (240 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.91 (1 H, d, J = 1.8 Hz), 6.92 (1 H, d, J = 1.8 Hz), 3.42 (2 H, s), 1.34 (6 H, s). Mass spectrum (ESI): m/e = 227.0 [(M + H) (^{79}Br)]$^+$ and 229.0 [(M + H) (^{81}Br)]$^+$.

*Diethyl 2-(5-Bromo-3-nitropyridin-2-yl)malonate, **51**.* To a suspension of K_2CO_3 (2223 g, 16.11 mol, 3 equiv) in dimethylformamide (5.4 L) was added diethyl malonate (1223 mL, 8.055 mol, 1.5 equiv) over a period of 15 min in an ice bath, followed by addition of 5-bromo-2-chloro-3-nitropyridine, **45** (1275 g, 5.37 mol), portionwise over a period of 15 min. The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The mixture was poured into 2 N aqueous HCl (15 L) and diluted with ethyl acetate (22 L). The organic layer was separated, washed with 1 M aqueous LiCl (2 × 5 L) and brine (5 L), dried over $MgSO_4$ and concentrated. Most of the residual dimethylformamide and diethyl malonate in the residue were removed by distillation under high vacuum to give 2022 g of crude diethyl 2-(5-bromo-3-nitropyridin-2-yl)malonate, **51**. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 8.88 (1 H, d, J = 2.2 Hz), 8.63 (1 H, d, J = 2.2 Hz), 5.45 (1 H, s), 4.30 (4H, m), 1.25 (6 H, m). Mass spectrum (ESI): m/e = 361.0 [(M + H) (^{79}Br)]$^+$ and 363.0 [(M + H) (^{81}Br)]$^+$.

*Ethyl 2-(5-Bromo-3-nitropyridin-2-yl)acetate, **52**.* To a stirred solution of diethyl 2-(5-bromo-3-nitropyridin-2-yl)malonate, **51** (2012 g, 5.57 mol), in DMSO (12 L) were added LiCl (1184 g, 27.86 mol) and water (120 mL, 6.684 mol), and the resulting mixture was heated at 150 °C overnight. After the reaction reached completion (monitored by LC−MS), the mixture was cooled to room temperature, poured into brine (10 L) and extracted with ethyl acetate (17 L). The suspension was filtered to remove insoluble material, and the phases were separated. The aqueous phase was further extracted with ethyl acetate (14 L), and the organic extracts were combined, washed with brine (3 × 5 L), dried over $MgSO_4$ and concentrated to give 1490 g of crude **52**. The crude was purified by column chromatography (eluting with hexane/ethyl acetate = 30:1 to 10:1) to afford ethyl 2-(5-bromo-3-nitropyridin-2-yl)acetate, **52** (1200 g, 76% yield from **51**). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.86 (1 H, d, J = 2.0 Hz), 8.58 (1 H, d, J = 2.0 Hz), 4.30 (2 H, s), 4.20 (2 H, m), 1.25 (3 H, m).

*Ethyl 2-(3-Amino-5-bromopyridin-2-yl)acetate, **53**.* To a solution of ethyl 2-(5-bromo-3-nitropyridin-2-yl)acetate, **52** (101 g, 0.349 mol), in degassed THF (400 mL) was added wet Raney-Ni (25 g), and the mixture was place under a H_2 atmosphere in a Parr shaker. When the hydrogen pressure was stable at 30 psi, the reaction mixture was checked by LC−MS, which showed that some hydroxylamine intermediate remained unreduced. An additional 11 g of wet Raney-Ni was added, and hydrogenation of the mixture was continued on a Parr shaker at 30 psi with monitoring of the reaction by LC−MS. On completion, the mixture was filtered through a pad of Celite, the pad was washed with methanol and the filtrate was concentrated to give ethyl 2-(3-amino-5-bromopyridin-2-yl)acetate, **53** (85 g, 96% yield), which was used for the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 7.76 (1 H, s, J = 2.4 Hz), 7.17 (1 H, s, J = 2.4 Hz), 5.05 (2 H, br s), 4.07 (2 H, m), 3.66 (2 H, s), 1.18 (3 H, m). Mass spectrum (ESI): m/e = 259.2 [(M + H) (^{79}Br)]$^+$ and 261.0 [(M + H) (^{81}Br)]$^+$.

*6-Bromo-1H-pyrrolo[3,2-b]pyridin-2(3H)-one, **54**.* To a suspension of ethyl 2-(3-amino-5-bromopyridin-2-yl)acetate, **53** (925 g, 3.57 mol), in toluene (9.25 L) was added acetic acid (740 mL, 12.92 mol), and the resulting mixture was heated to reflux for 4 h. The mixture was cooled to room temperature, and the solvents were removed under reduced pressure. The resulting residue was suspended in toluene (2 L), filtered, washed with diethyl ether (×2) and dried to give 6-bromo-1*H*-pyrrolo-[3,2-*b*]pyridin-2(3*H*)-one, **54** (706 g, 93% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.70 (1 H, s), 8.17 (1 H, s), 7.31 (1 H, s), 3.57 (2 H, s). Mass spectrum (ESI): m/e = 213.0 [(M + H) (^{79}Br)]$^+$ and 215.1 [(M + H) (^{81}Br)]$^+$.

*6′-Bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-b]-pyridin]-2′(1′H)-one, **55**.* To an ice-cold suspension of NaH (351 g, 60% in mineral oil, 8.78 mol) in anhydrous THF (7 L) was added 6-bromo-1*H*-pyrrolo[3,2-*b*]pyridin-2(3*H*)-one, **54** (706 g, 3.31 mol), portionwise under nitrogen over a period of 30 min. The resulting mixture was stirred at room temperature for 30 min. Bis(2-chloroethyl) ether (582 mL, 4.965 mol) was added over a period of 15 min, followed by NaI (49.65 g, 0.331 mol). The resulting mixture was heated to 60 °C and stirred overnight. The mixture was cooled to 0 °C, and acetic acid (24 mL) was added. The mixture was then poured into ice−water (6 L) with vigorous stirring and extracted with CH_2Cl_2 (3 × 8 L), and the combined organic extracts were washed with brine (3 × 5 L), dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was triturated with CH_2Cl_2 (350 mL), filtered, washed with CH_2Cl_2 (2 × 150 mL) and dried to give 6′-bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridin]-2′(1′*H*)-one, **55** (136 g, 14% yield) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.83 (1 H, s), 8.25 (1 H, d, J = 2.4 Hz), 7.41 (1 H, J = 2.4 Hz), 3.94−4.07 (2 H, m), 3.87−3.92 (2 H, m), 1.76−1.85 (2 H, m), 1.63−1.69 (2 H, m). Mass spectrum (ESI): m/e = 282.9 [(M + H) (^{79}Br)]$^+$ and 285.0 [(M + H) (^{81}Br)]$^+$.

*6′-Bromo-1′,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-b]-pyridine], **56**.* To an ice-cold suspension of 6′-bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridin]-2′(1′*H*)-one, **55**

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(136 g, 0.48 mol), in anhydrous toluene (950 mL) was added Red-Al (440 mL, 1.44 mol, 65% in toluene) under nitrogen over a period of 25 min. The resulting mixture was stirred at room temperature, and the reaction was monitored by LC−MS. After 1.5 h, the mixture was cooled using an ice bath and 2 N aqueous NaOH (600 mL) was carefully and slowly added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 800 mL), and the combined organic extracts were washed with brine (2 × 500 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give 112 g of crude **56**, which was triturated with cold CH_2Cl_2 (100 mL). The solid was filtered, washed with cold CH_2Cl_2 (2 × 50 mL) and dried to give 78 g of compound **56** as an off-white solid. The mother liquor was concentrated and triturated with cold CH_2Cl_2 (30 mL) again, and the solid was filtered, washed with cold CH_2Cl_2 (2 × 20 mL) and dried to give an additional 7.8 g of compound **56**. The mother liquor was purified by column chromatography (eluting with CH_2Cl_2/methanol = 100:1) to afford another 5.6 g of compound **56**. All the fractions were combined to give 6′-bromo-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine], **56** (91.4 g, 71% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 7.70 (1 H, s), 6.89 (1 H, d, J = 2.4 Hz), 6.17 (1 H, J = 2.4 Hz), 3.84−3.91 (2 H, m), 3.42−3.50 (4 H, m), 1.79−1.88 (2 H, m), 1.48−1.52 (2 H, m). Mass spectrum (ESI): m/e = 269.1 [(M + H) (^{79}Br)]$^+$ and 271.2 [(M + H) (^{81}Br)]$^+$.

*4-(6-Bromo-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **57**.* **57** was prepared according to procedure D using 6-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine, **50** (108 mg, 0.48 mmol), 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (130 mg, 0.48 mmol), and 4.0 M solution of HCl in 1,4-dioxane (0.12 mL, 0.48 mmol) in *N*-methyl-2-pyrrolidone (0.5 mL) and heating at 150 °C for 3 h in the microwave. After purification (SiO_2, hexane:ethyl acetate, 1:0 to 1:3), 4-(6-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **57** (100 mg, 45% yield), was obtained as a yellow film. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.69−8.75 (1 H, m), 7.94 (1 H, d, J = 1.8 Hz), 7.87−7.92 (2 H, m), 7.81−7.86 (1 H, m), 7.75 (1 H, dd, J = 9.2, 5.9 Hz), 7.37−7.41 (1 H, m), 7.29−7.35 (1 H, m), 6.32 (1 H, d, J = 1.8 Hz), 3.76−3.90 (2 H, m), 2.37 (3 H, s), 1.58 (3 H, s), 1.52 (3 H, s). Mass spectrum (ESI): m/e = 463 [(M + H) (^{79}Br)]$^+$ and 465 [(M + H) (^{81}Br)]$^+$.

*4-(3,3-Dimethyl-6-(4-morpholinyl)-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-7-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **58**.* To a stirred solution of 4-(6-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo-[3,2-*b*]pyridin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **57** (75 mg, 0.162 mmol), in toluene (6 mL) were added Pd_2dba_3 (3.8 mg, 0.016 mmol), XPhos (15.4 mg, 0.032 mmol), sodium *tert*-butoxide (31.1 mg, 0.324 mmol) and morpholine (16.9 μL, 0.194 mmol). The reaction mixture was heated to 120 °C for 3 h. After this time the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in methanol (2.0 mL) and filtered using a 13 mm syringe filter. Purification by reverse phase HPLC (20 to 80% acetonitrile in water) gave 4-(3,3-dimethyl-6-(4-morpholinyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-7-fluoro-3-methyl-2-(2-pyridinyl)quinoline, **58** (35 mg, 46% yield), as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.70−8.77 (1 H, m), 7.75−7.96 (4 H, m), 7.60 (1 H, d, J = 2.7 Hz), 7.41 (1 H, ddd, J = 7.1, 5.0, 1.6 Hz), 7.30 (1 H, ddd, J = 9.1, 8.1, 2.7 Hz), 5.83 (1 H, d, J = 2.3 Hz), 3.82 (2 H, s), 3.69−3.77 (4 H, m), 2.91−3.06 (4 H, m), 2.38 (3 H, s), 1.57−1.64 (3 H, m), 1.50−1.56 (3 H, m). HRMS (ESI): m/z 470.2355 [M + H]$^+$ ($C_{28}H_{28}FN_5O$ requires 470.2357).

*4-(1-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-6-yl)-2-pyrimidinamine, **59**.* First step: Preparation was according to procedure E using 4-(6-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **57** (100 mg, 0.22 mmol), $Pd(PCy_3)_2$ (14.4 mg, 0.022 mmol), bis(pinacolato)diboron (60 mg, 0.24 mmol) and potassium acetate (35 mg, 0.32 mmol) in 1,4-dioxane (4.0 mL) and heating at 120 °C in the microwave for 1 h. After aqueous workup, 1-(7-fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-6-ylboronic acid (92 mg, 100% yield) was obtained as a colorless film. Mass spectrum (ESI): m/e = 429 [M + H]$^+$. Product used without further purification in the next step.

Second step: Preparation was according to procedure F using 1-(7-fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-6-ylboronic acid (92 mg, 0.215 mmol), $PdCl_2(PPh_3)_2$ (15.12 mg, 0.021 mmol), 2-amine-4-chloropyrimidine (30.6 mg, 0.236 mmol) and sodium carbonate (68.3 mg, 0.644 mmol) in 1,4-dioxane (2.5 mL) and water (0.5 mL) and heating in the microwave for 1 h at 120 °C. After purification, 4-(1-(7-fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)-2-pyrimidinamine, **59** (38 mg, 37% yield), was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.68−8.80 (1 H, m), 8.49 (1 H, d, J = 2.0 Hz), 8.26 (1 H, d, J = 5.5 Hz), 7.72−7.99 (4 H, m), 7.41 (1 H, ddd, J = 7.0, 5.1, 2.0 Hz), 7.29−7.34 (1 H, m), 6.93 (1 H, d, J = 5.1 Hz), 6.77−6.86 (1 H, m), 5.16 (2 H, br s), 3.77−3.95 (2 H, m), 2.27−2.44 (3 H, m), 1.61−1.68 (3 H, m), 1.51−1.60 (3 H, m). HRMS (ESI): m/z 478.2154 [M + H]$^+$ ($C_{28}H_{24}FN_7$ requires 478.2157).

*tert-Butyl 6′-Bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo-[3,2-b]pyridine]-1′(2′H)-carboxylate, **60**.* To a stirred solution of 6′-bromo-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine], **56** (10.0 g, 37.2 mmol), in THF (100 mL) were added Boc_2O (9.73 g, 44.6 mmol), triethylamine (7.77 mL, 55.7 mmol) and DMAP (0.908 g, 7.43 mmol), and the reaction mixture was stirred at room temperature for 24 h. After this time an additional portion of Boc_2O (2.0 g, 9.17 mmol) and DMAP (0.3 g, 2.46 mmol) was added and the reaction mixture was stirred at room temperature for an additional 24 h. After this time the reaction mixture was partitioned between ethyl acetate (300 mL) and saturated $NaHCO_3$ (50 mL). The separated organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. Column chromatography (hexane:ethyl acetate, 1:0 to 1:2) gave *tert*-butyl 6′-bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine]-1′(2′*H*)-carboxylate, **60** (12.12 g, 88% yield), as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.06−8.33 (2 H, m), 4.03−4.13 (2 H, m), 3.90 (2 H, br s), 3.58 (2 H, td, J = 11.7, 2.2 Hz), 2.11−2.23 (2 H, m), 1.60 (11 H, br s). Mass spectrum (ESI): m/e = 369.0 [(M + H) (^{79}Br)]$^+$ and 371.2 [(M + H) (^{81}Br)]$^+$.

*tert-Butyl 6′-morpholino-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-b]pyridine]-1′(2′H)-carboxylate, **61**.* To a stirred solution of *tert*-butyl 6′-bromo-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]-pyridine]-1′(2′*H*)-carboxylate, **60** (16.2 g, 43.9 mmol), in toluene (300 mL) were added morpholine (3.82 mL, 43.9 mmol), sodium *tert*-butoxide (8.43 g, 88 mmol), Pd_2dba_3 (2.0 g, 2.19 mmol) and 2-(dicyclohexylphosphino)-2′,4′,6′,-triisopropylbiphenyl (2.09 g, 4.39 mmol), and the reaction mixture was heated at reflux for 90 min. After this time the reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was partitioned between ethyl acetate (400 mL) and water (100 mL). The separated organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. Column chromatography (hexane:ethyl acetate, 1:0 to 1:1) gave *tert*-butyl 6′-morpholino-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine]-1′(2′*H*)-carboxylate, **61** (11.2 g, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.73−7.83 (2 H, m), 4.01−4.13 (2 H, m), 3.86 (6 H, br s), 3.58 (2 H, td, J = 11.6, 2.3 Hz), 3.18 (4 H, br s), 2.10−2.23 (2 H, m), 1.47−1.67 (11 H, m). Mass spectrum (ESI): m/e = 376.2 [M + H]$^+$.

*6′-Morpholino-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo-[3,2-b]pyridine], **62**.* To a stirred solution of *tert*-butyl 6′-morpholino-2,3,5,6-tetrahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine]-1′(2′*H*)-carboxylate, **61** (11 g, 29.3 mmol), in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (67.7 mL, 879 mmol). The reaction mixture was stirred at room temperature for 3 h. After this time the reaction mixture was evaporated in vacuo and partitioned between ethyl acetate (60 mL) and 1.0 M aqueous HCl (200 mL). The separated aqueous layer was washed with ethyl acetate (50 mL). The separated aqueous layer was then basified to pH 14 with aqueous NaOH and extracted with ethyl acetate (2 × 200 mL) and CH_2Cl_2 (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo to give 6′-morpholino-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]-pyridine], **62** (6.8 g, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.60−7.62 (1 H, m), 6.38−6.50 (1 H, m), 4.07 (2 H, dt, J = 11.8, 4.3 Hz), 3.82−3.87 (4 H, m), 3.53−3.61 (4 H, m), 3.09−3.14 (4 H, m), 2.09−2.18 (2 H, m), 1.60−1.64 (2 H, m). Mass spectrum (ESI): m/e = 276.2 [M + H]$^+$.

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1′-(7-Fluoro-3-methyl-2-(2-pyridinyl)-4-quinolinyl)-6′-(4-morpholinyl)-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-b]pyridine], ***63***. To a stirred solution of 6′-morpholino-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine], **62** (5.55 g, 20.17 mmol), and 4-chloro-7-fluoro-3-methyl-2-(pyridin-2-yl)quinoline, **23d** (5.5 g, 20.17 mmol), in toluene (400 mL) were added Xphos-precatalyst (1.49 g, 2.02 mmol) and sodium *tert*-butoxide (3.88 g, 40.3 mmol), and the reaction mixture was heated at 90 °C for 3 h. After this time the reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was dissolved in ethyl acetate (700 mL) and washed with citric acid (2 × 100 mL) and 1 M NaOH (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography (330 g of SiO_2, gradient: (CH_2Cl_2 and CH_2Cl_2:methanol:NH_4OH (9:1:0.4) from 1:0 to 8:2). The fractions containing pure product were combined and evaporated in vacuo. The resulting yellow solid was taken up in ethanol (60 mL) and evaporated in vacuo. The product was then dried under vacuum (150 mmHg) while heating at 130 °C for 72 h to give 1′-(7-fluoro-3-methyl-2-(pyridin-2-yl)quinolin-4-yl)-6′-morpholino-1′,2,2′,3,5,6-hexahydrospiro[pyran-4,3′-pyrrolo[3,2-*b*]pyridine], **63** (4.2 g, 41% yield), as a yellow powder. Purity by HPLC (λ = 230 nm): 99.6%. Residual solvent by GC/MS: 0.3% ethanol. Water by KF: 1.2% w/w. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.75 (1 H, dd, J = 3.3, 1.0 Hz), 7.83−7.97 (3 H, m), 7.75 (1 H, dd, J = 9.2, 6.1 Hz), 7.62 (1 H, d, J = 2.3 Hz), 7.41 (1 H, ddd, J = 7.0, 5.1, 2.0 Hz), 7.28−7.34 (1 H, m), 5.83 (1 H, d, J = 2.3 Hz), 4.09−4.23 (2 H, m), 3.95−4.04 (2 H, m), 3.71−3.80 (4 H, m), 3.52−3.62 (2 H, m), 3.01 (4 H, q, J = 4.4 Hz), 2.32−2.46 (5 H, m), 1.74−1.91 (2 H, m). HRMS (ESI): m/z 512.2461 $[M + H]^+$ ($C_{30}H_{30}FN_5O_2$ requires 512.2463).

■ ASSOCIATED CONTENT

Supporting Information

(i) In vitro biological assays, (ii) in vivo study protocols, (iii) determination of cocrystal structures of **24f** and **63** with PI3Kγ; (iv) enzyme selectivity data for compound **63**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Boc, *tert*-butoxycarbonyl; CIA, collagen induced arthritis; Cl, clearance; CYP3A4, cytochrome P450 3A4; CYP2D6, cytochrome P450 2D6; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; HLM, human liver microsomes; hPXR, human pregnane x receptor; KLH, keyhole limpet hemocyanin; PBS, phosphate buffer solution; PI3K, phosphoinositide 3-kinases; PK, pharmacokinetic; PPA, polyphosphoric acid; Red-Al, sodium bis(2-methoxyethoxy)aluminumhydride; qd, once a day; RLM, rat liver microsomes; RuPhos, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; SEM, standard error of the mean; S_NAr, nucleophilic aromatic substitution; SAR, structure−activity relationship; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; XPhos precatalyst, chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)-phenyl)]Pd(II) methyl *tert*-butyl ether

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(17) This assay was used to quantify the on-target PI3Kδ cellular potency of our inhibitors. See Supporting Information for assay details.

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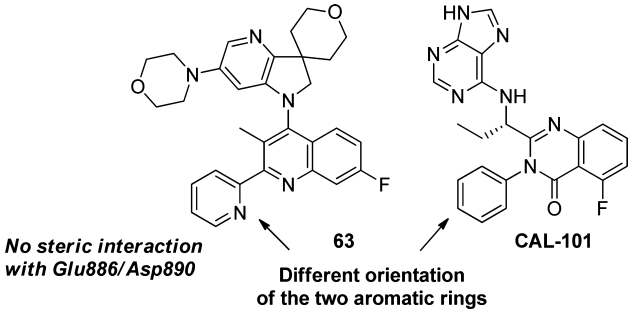
(24) Akt phosphorylation inhibition of the S473 residue in MDA-MB-468 cells was measured. See Supporting Information for assay details.

(25) PI3Kγ was used as a structural surrogate for PI3Kδ.

(26) To rationalize the superior PI3Kβ inhibitory activity of **63** relative to other propeller shape PI3K inhibitors (i.e., CAL-101), docking studies of these two compounds in a homology model of PI3Kβ were performed. These studies showed that, when inhibitor **63** and CAL-101 bind to PI3Kβ, the position occupied by the quinoline is different from the position occupied by the quinazolinone ring. Specifically, the quinoline in **63** is shifted further away from the loop at the bottom of the mouth region in the ribose pocket relative to the quinazolinone ring in CAL-101. This difference allows the 2-pyridyl ring in **63** to avoid the unfavorable steric interaction of this substituent with the amino acid residues in the bottom of the mouth region of PI3Kβ (Glu886 and Asp890), which would explain the improved PI3Kβ potency of **63** relative to CAL-101.



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(33) A second collagen injection was administered at day 6 in all the animals.

(34) Inhibitor **63** was dosed in 2% HPMC, 10% Captisol, 1% Pluronic F and 87% water.

(35) Measures of the tibiotarsal (ankle) joint were taken using calipers. See Supporting Information for a detailed description of this study.

(36) Methotrexate (MTX), 0.075 mg/kg, dosed as a 1% carboxymethyl cellulose aqueous solution, was used as a positive control.

(37) Analogue **63** had a free fraction of 6.8% in rat plasma.