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Rational Design of Phosphoinositide 3-Kinase α Inhibitors That Exhibit Selectivity over the Phosphoinositide 3-Kinase β Isoform†

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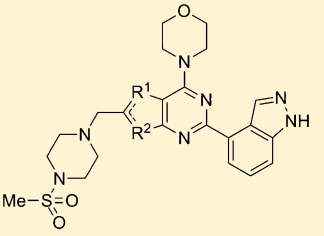
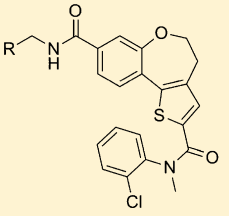
Supporting Information

ABSTRACT: Of the four class I phosphoinositide 3-kinase (PI3K) isoforms, PI3Kα has justly received the most attention for its potential in cancer therapy. Herein we report our successful approaches to achieve PI3Kα vs PI3Kβ selectivity for two chemical series. In the thienopyrimidine series of inhibitors, we propose that select ligands achieve selectivity derived from a hydrogen bonding interaction with Arg770 of PI3Kα that is not attained with the corresponding Lys777 of PI3Kβ. In the benzoxepin series of inhibitors, the selectivity observed can be rationalized by the difference in electrostatic potential between the two isoforms in a given region rather than any specific interaction.



R^1 = S, R^2 = CH_2 PI3Kβ/PI3Kα = 11

R^1 = CH_2, R^2 = S PI3Kβ/PI3Kα = **111**



R = CH_2NH_2 PI3Kβ/PI3Kα = 8

R = H PI3Kβ/PI3Kα = **87**

INTRODUCTION

The phosphoinositide 3-kinases (PI3Ks) are attractive targets for the design of small molecule inhibitors because of the frequent occurrence of aberrant signaling of this pathway in several different disease states. Within the PI3 kinase family, there are four class I PI3 kinase isoforms (α, β, δ, and γ).[1] PI3Kβ has been targeted for thrombosis prevention or treatment, and small molecules that display selectivity for this isoform have been reported.[1−3] PI3Kδ and PI3Kγ have been identified as targets for inflammatory, autoimmune, and respiratory indications.[4] Accordingly, compounds that display modest to high levels of isoform selectivity have been reported for the inhibition of PI3Kδ, PI3Kγ, or both.[1,5] For its promise in the treatment of cancer, inhibition of PI3Kα has received considerable attention.[6] However, despite the significant effort to identify inhibitors of PI3Kα, there are only few reports of PI3Kα inhibitors that either specifically inhibit this isoform or achieve selectivity relative to any of the other isoforms.[1,7]

We previously reported our efforts to identify PI3Kα inhibitors including clinical candidate **1** (GDC-0941).[8] Each of our previous disclosures culminated with molecules that are highly selective relative to other kinases but inhibit each of the four class I PI3K isoforms with minimal selectivity (Table 1).

As a continuation of this work, we became interested in studying the biological effects of inhibitors of PI3Kα that had differential selectivity profiles relative to one or more of the other isoforms. Among the selectivity profiles we were interested in evaluating was inhibition of PI3Kα with selectivity over PI3Kβ. This particular selectivity profile was of interest because of the potential role of PI3Kβ in insulin signaling.[9] Because of this potential critical role, it is reasonable to speculate whether or not the tolerability of PI3Kα inhibitors for the treatment of cancer might be improved if they have selectivity over PI3Kβ. However, at the onset of our studies it was unclear whether reduced PI3Kβ inhibition would compromise efficacy. Taken together, compounds with high PI3Kβ/PI3Kα selectivity were of interest to us as tools for studying the implication on efficacy and safety. At the onset of this effort, designing PI3K inhibitors that displayed selectivity over PI3Kβ presented a challenge because no crystal structure of PI3Kβ had been reported.[10] On the other hand, cocrystal structures containing PI3K inhibitors have been available for PI3Kγ for several years.[11] More recently, crystal structures of PI3Kδ[12] (cocrystallized with inhibitors) and PI3Kα[13] have been reported.[14]

To guide our attempts at achieving PI3Kα vs PI3Kβ selectivity, we utilized a public crystal structure of PI3Kα[15] along with a homology model of PI3Kβ developed from a PI3Kδ crystal structure.[16] While each of the class I PI3Ks exhibits a high degree of homology within the active site of the enzyme, there are differences in primary sequence among residues that are predicted to reside on the periphery of the active site in a solvent exposed region (Figure 1). These

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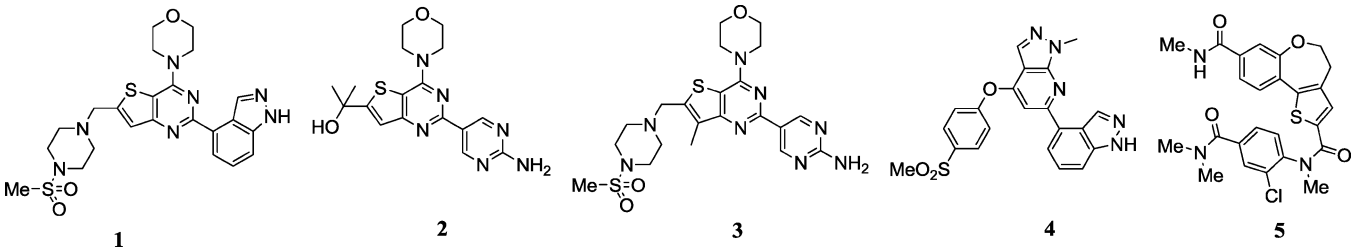
Table 1. Class I PI3K IC_{50}s of Key Compounds



1 2 3 4 5

	IC_{50} (nM)			
compd	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ
1	3	33	3	66
2	3	12	16	16
3	4	86	5	15
4	7	31	11	8
5	5	46	2	5

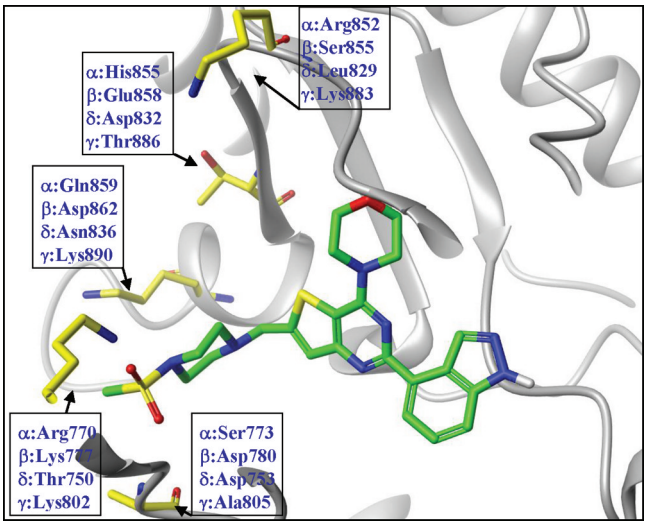


Figure 1. Cocrystal structure of **1** in PI3Kγ (PDB code 3DBS). Residues nearest the active site that are different between PI3Kα and at least one other isoform are highlighted.

differences presented an opportunity using our thienopyrimidine scaffold to achieve the desired selectivity. In addition, there is the potential for disparate conformational dynamics within the P-loop (Met804-Pro810, PI3Kγ numbering).

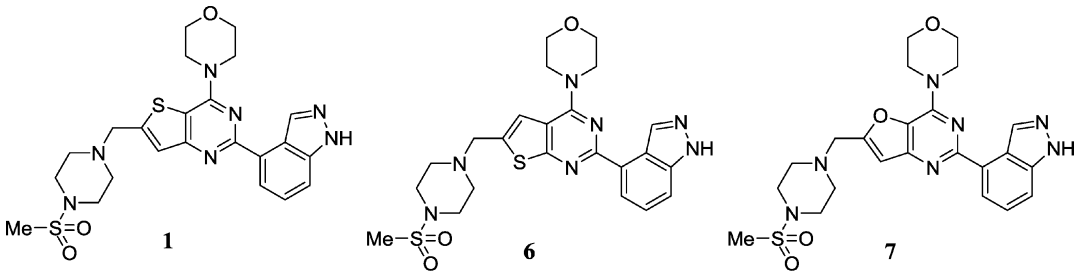
We discuss below our results in gaining selectivity for PI3Kα relative to PI3Kβ on two distinct scaffolds. With each of the two scaffolds studied, the selectivity observed can be explained using our homology model of PI3Kβ.[17] These studies lend support to the use of our homology model of PI3Kβ for compound design as well as provide opportunity to evaluate the desirability of this selectivity profile.

RESULTS AND DISCUSSION

We first prepared compounds that achieve PI3Kβ/PI3Kα selectivity fortuitously when evaluating analogues of **1**. **1** is just modestly selective for PI3Kα relative to PI3Kβ (Table 2). However, modification of the central core of the thienopyrimidine to the isomeric thiophene (**6**, Table 2) resulted in significantly improved PI3Kβ/PI3Kα selectivity as a result of notable reduction in PI3Kβ inhibition.

A cocrystal structure of **1** in PI3Kγ shows that a sulfonamide oxygen achieves a hydrogen bond with the backbone NH of Ala805 (PI3Kγ).[8a] Our models suggest that this interaction is likely maintained in the other PI3K isoforms with **1** hydrogen bonding with Ser773 backbone NH in PI3Kα (Figure 2a) and Asp780 backbone NH in PI3Kβ (Figure 2b). In addition, our model of **1** in PI3Kα suggests the other sulfonamide oxygen is capable of hydrogen bonding with Arg770 (Figure 2a). However, according to our model, this is unlikely in PI3Kβ in which Arg770 is now Lys777 (Figure 2b). This suggested

Table 2. Comparison of PI3Kα and PI3Kβ Potency for 1 and Related Analogues



1 6 7

	IC_{50} (nM)		
compd	PI3Kα	PI3Kβ	IC_{50}(PI3Kβ)/IC_{50}(PI3Kα)
1	3	33	11
6	3	332	111
7	3	194	65

dx.doi.org/10.1021/jm2007084 | J. Med. Chem. 2011, 54, 7815–7833

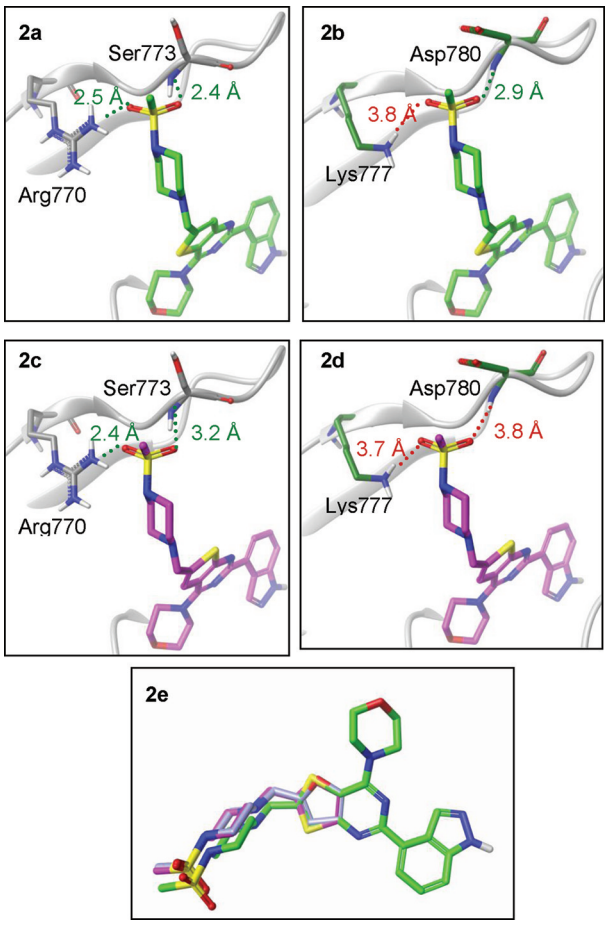


Figure 2. (a) Model of **1** in PI3Kα. Hydrogen bonds with Ser773 backbone NH and Arg770 are illustrated. (b) Model of **1** in PI3Kβ, illustrating hydrogen bond with Asp780 backbone NH but suboptimal distance to Lys777. (c) Model of **6** in PI3Kα. Hydrogen bonds with Ser773 backbone NH and Arg770 are illustrated. (d) Model of **6** in PI3Kβ, illustrating suboptimal hydrogen bonding distances to Asp780 backbone NH and Lys777. (e) Overlay of **1** (green), **6** (magenta), and **7** (lavender), with morpholine and indazole rigidly superimposed.

loss of a hydrogen bond is a possible explanation for the 10-fold reduced potency against that isoform. Upon modification of the central core to the isomeric thiophene **6**, the sulfonamide oxygens are positioned further away from the key backbone NH (Figure 2c,d). Still, our model suggests that **6** is able to achieve the two hydrogen bonds in PI3Kα (Figure 2c), while in PI3Kβ **6** is no longer able to achieve either of these hydrogen bonds. It is possible that this explanation accounts for why **6** is 100-fold less potent toward PI3Kβ relative to PI3Kα (Figure 2d). Additionally, compound **7**, in which the thiophene has been replaced by a furan, should display the piperazine sulfonylamide with a vector much closer to compound **6** than to **1** (Figure 2e). In the end, furanopyrimidine **7** achieves potency and selectivity similar to those of compound **6**.

Encouraged by the selectivity achieved with compounds **6** and **7**, we extended our studies to further evaluate contributions to isoform selectivity using the isomeric thiophene core of **6**. Table 3 highlights the SAR describing PI3Kβ/PI3Kα selectivity. A comparison of compounds **6** and **8** demonstrates that the indazole moiety contributes minimally to PI3Kβ selectivity and that the aminopyrimidine group improves potency against both PI3Kα and PI3Kβ isoforms. Entries **9** and **10** illustrate that the portion of the molecule that is directed toward the residue differences (R^1) is essential to the selectivity observed, as compounds without substitution of the thiophene have minimal selectivity. Having identified that the indazole does not contribute to PI3Kβ selectivity, we limited additional studies to the aminopyrimidine motif (R^2) that had previously been identified to have superior potency and pharmacokinetic properties.[18] That the sulfonamide oxygens are essential to achieving high PI3Kβ/PI3Kα selectivity is demonstrated with piperazine **11** and piperidine **12**. A comparison of **11** and **12** illustrates that a more basic center at the distal end of the ring erodes selectivity. Piperidinesulfonylamide **13** has potency and selectivity comparable to those of **8**, indicating that the remaining basic center does not impact either. The sulfone analogue **14** exhibits reduced selectivity when compared to compound **8** because of a modest drop in PI3Kβ potency. The position of the sulfonamide oxygens is critical, as demonstrated with compound **15** which had the lowest selectivity of any sulfone or sulfonamide containing analogue. Nevertheless, the 20-fold selectivity of compound **15** is still significant relative to the unsubstituted entry **10**. Entry **16** illustrates that a carbonyl functionality can also achieve good levels of selectivity. Finally, an aromatic ring could replace the heterocyclic ring present in the other examples. Arylsulfone **17** proved to be potent and had reasonable selectivity; however, it had poor solubility that prevented it from advancing further, as even at the higher concentrations required in cellular assays the compound precipitated over time. In general, the selectivity achieved is unique to the PI3Kβ isoform, as consistently low levels of selectivity (<10-fold) for PI3Kα were observed relative to PI3Kδ and PI3Kγ.

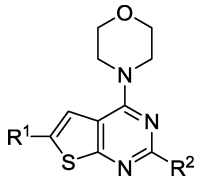
Having identified an approach to selectivity for PI3Kα over PI3Kβ, we were interested in whether we could apply the hypothesis to achieve the same type of selectivity on a distinct scaffold. Recently we disclosed initial efforts on a class of benzoxepins that are potent PI3Kα inhibitors.[8e] A cocrystal structure of a representative benzoxepin, **21**, with PI3Kγ is shown in Figure 3a. For the sake of comparison, Figure 3b shows an overlay of benzoxepin **21** and thienopyrimidine **1**. From this overlay it is apparent that substitution of the benzene ring of the benzoxepin offers a different vector compared with substitution of the thienopyrimidine class of compounds.

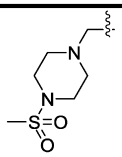
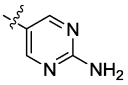
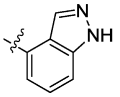
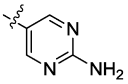
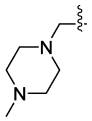
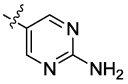
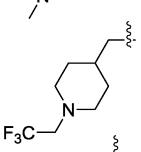
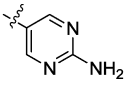
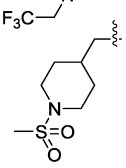
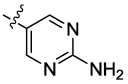
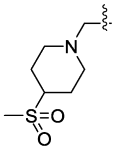
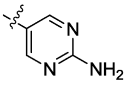
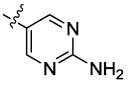
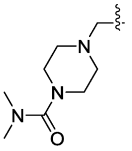
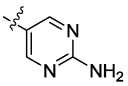
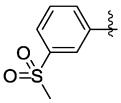
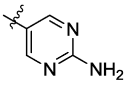
An initial SAR scan compared R^1 and R^2 substitution of thienobenzoxepins. An analysis of the specific substitution revealed that R^1 functionality generally led to increased likelihood of PI3Kβ/PI3Kα selectivity when compared to R^2 substitution (Figure 4). This result was unanticipated because it seemed that R^2 substitution would be able to grant access to Arg770 and Ser773 that we exploited for selectivity in the thienopyrimidine series (Figure 2). The apparent predisposal for the desired selectivity led us to prioritize our efforts to R^1 substitution to improve selectivity over PI3Kβ.

Revisiting the PI3Kα and PI3Kβ homology models we employed earlier, we recognized that in the vicinity of the R^1 position of the benzoxepin core there were a number of residues that differed between PI3Kα and PI3Kβ (see Figure 1). Importantly, there are several acidic residues in the area of PI3Kβ where R^1 substitution is positioned. This is in contrast to the same region of PI3Kα, in which there are no acidic residues. Anticipating that many of the solvent exposed residues would likely be flexible, making specific hydrogen bonding interactions difficult to achieve, we viewed the relevant region of the enzyme as an electrostatic potential map.[19] This model

dx.doi.org/10.1021/jm2007084 | J. Med. Chem. 2011, 54, 7815–7833

Table 3. Class I PI3K Isoform Selectivity for Isomeric Thienopyrimidines



Compound	R^1	R^2	PI3Kα Ki_{app}	PI3Kβ Ki_{app}	PI3Kβ Ki_{app}/ PI3Kα Ki_{app}
8			1 nM	69 nM	69
9	H		47 nM	1167 nM	4
10	H		9 nM	41 nM	5
11			5 nM	7 nM	1
12			2 nM	18 nM	9
13			0.4 nM	25 nM	63
14			1 nM	42 nM	42
15			2 nM	39 nM	20
16			2 nM	108 nM	54
17			1 nM	43 nM	43

suggested that simply incorporating highly electron rich or even lipophilic functionality should result in improved selectivity for PI3K*α* relative to PI3K*β*. On the other hand, incorporation of a positively charged functionality should lead to reduced selectivity. Figure 5a depicts a model of benzoxepin **21** bound to PI3K*α*, highlighting the electrostatic potential in the region accessible through substitution of the core at R^1. Figure 5b depicts the electrostatic potential map of PI3K*β* in the same area with the same compound included for reference.

Table 4 highlights that the electrostatic potential maps of PI3K*α* and PI3K*β* derived from a PI3K*α* crystal structure and our PI3K*β* homology model are indeed predictive of selectivity. Entry **18** established that the benzoxepin core without substitution of the benzene ring has good PI3K*α* potency and <20-fold selectivity relative to PI3K*β*. Compound **19** shows the impact of an uncharged R^1 substituent on PI3K*β*/PI3K*α* selectivity. In this case, the level of selectivity is increased to 82-fold. We found that many uncharged groups at R^1 resulted in

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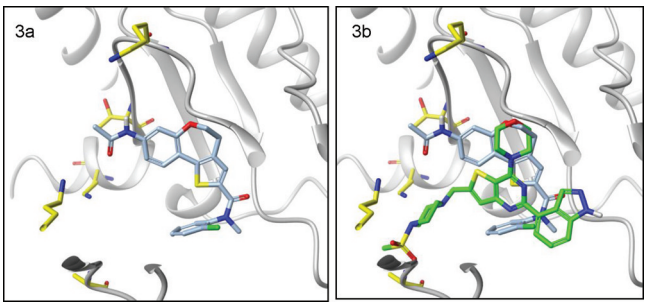

Figure 3. (a) Cocrystal structure of benzoxepin **21** in PI3Kγ (PDB code 3R7R). (b) Overlay of **1** in the cocrystal structure of **21** in PI3Kγ.

similarly enhanced PI3Kβ/PI3Kα selectivity. As further examples, nitrile **20**, acetamide **21**, and amides **22** and **23** all achieve greater than 50-fold selectivity for PI3Kα relative to PI3Kβ. However, incorporating a basic center diminishes selectivity as a result of increased affinity for PI3Kβ (**24**). Moreover, as the electrostatic potential map predicts, exact positioning of a positive charge is not essential to diminish PI3Kβ/PI3Kα selectivity as examples **24** and **25** demonstrate. When a negatively charged functionality was incorporated (**26**), the selectivity increased to nearly 100-fold. However, because the negative charge in **26** prevented the molecule from effectively permeating a cell membrane, this compound was not studied further. In contrast to the carboxylic acid in **26**, the related analogue **27** incorporated a basic amine that essentially negated the impact of R^1 substitution, as the potency and selectivity are comparable to those of the unsubstituted **18**. Substitution of R^2 also resulted in improvement in PI3Kβ/PI3Kα selectivity (compounds **28**–**30**), similar to how the same functionality improved selectivity at R^1 (compare compounds **20** and **30** and compare **23** and **29**).

It was interesting to note that substitution of R^3 with an amide resulted in diminished PI3Kβ/PI3Kα selectivity. For example, compound **31** has just 10-fold selectivity whereas the analogue without the amide at R^3 (compound **22**) has 87-fold selectivity. Moving the position of the *N*,*N*-dimethylamide from R^3 to R^4 resulted in a notable gain in selectivity (**32**). A similar trend was observed with *N*-methylpiperazineamides **33** and **34**. In this case, moving the amide to R^4 restores the selectivity found in the simpler analogue **22**. A cocrystal structure of compound **33** with PI3Kγ (Figure 6) shows that the piperazineamide carbonyl achieves a hydrogen bond with Ser806. A potential explanation for this reduction in selectivity is that, despite being conserved among the four isoforms, the conformation of Ser806 as part of the flexible G-loop is such that a hydrogen bond to it is more beneficial for PI3Kβ potency than for PI3Kα and so results in reduced selectivity. Similar to

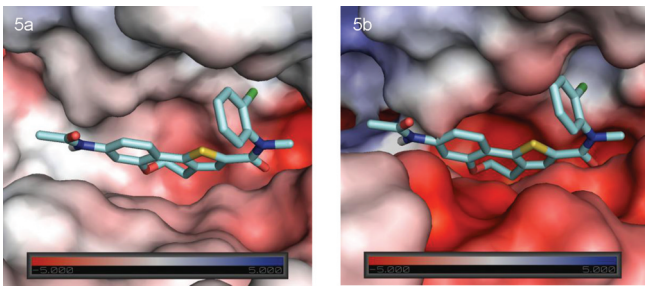

Figure 5. Poisson–Boltzmann electrostatic potentials plotted on the solvent accessible surfaces of PI3Kα crystal structure (PDB code 3HIZ) (a) and PI3Kβ homology model (b). Compound **21** is depicted for reference.

the thienopyrimidine series, benzoxepins **18**–**34** also generally display low levels of selectivity for PI3Kα relative to PI3Kδ and PI3Kγ.

A study including **6** was consistent with the apparent importance of PI3Kβ inhibition to inhibit proliferation of a cancer cell that has lost phosphatase and tensin homologue (PTEN) function.[20] Evaluation of compounds with enhanced PI3Kα to PI3Kβ enzyme selectivity in cell proliferation assays showed a qualitative trend for a lesser effect on decreasing proliferation in the PC3 cell line (PTEN-null) relative to decreasing proliferation in the MCF7.1 cell line (PI3Kα mutant) (Table 5). Specifically, in the thienopyrimidine series of molecules, the weakly selective **1** had close to equipotent activity in both cell lines, a trend that was also observed with the weakly selective benzoxepin **31**. Conversely, thienopyrimidines **6** and **13**, which displayed high levels of PI3Kβ/PI3Kα selectivity, were more potent in the MCF7.1 than the PC3 proliferation assay, with the same behavior observed with the structurally distinct benzoxepin **32**.

In addition to having high levels of PI3Kβ/PI3Kα selectivity, both series of molecules generally exhibit a very high level of selectivity over other kinases as well. In a panel of 101 kinases at Upstate, only one was inhibited by >80% by **6** when tested at 1 μM (CAMK2D). To represent the benzoxepin series of compounds, **21**, **22**, and **33** were each evaluated in a panel of 51 kinases provided by Invitrogen's SelectScreen service. In each case no kinases were inhibited by >50% at 1 μM test compound.

Of the compounds that displayed significant PI3Kβ/PI3Kα selectivity, **6**, **7**, and **32** were evaluated in rodent pharmacokinetics studies. Compounds **7** and **32** each had a clearance rate greater than liver blood flow in rats (data not shown). On the other hand, compound **6** had attractive pharmacokinetic properties in rats as well as mice and so was selected for further study in in vivo efficacy models.[20]

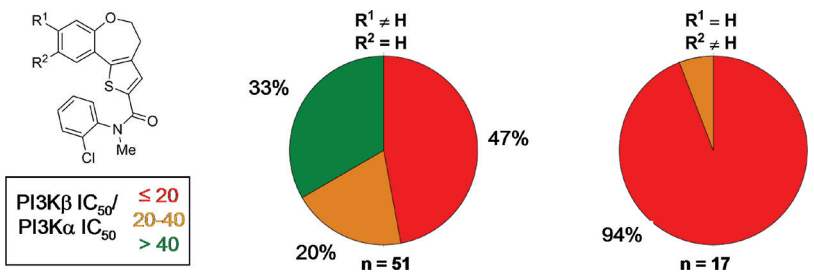

Figure 4. Correlation of the position of substitution on the benzoxepin core and level of PI3Kβ/PI3Kα selectivity.

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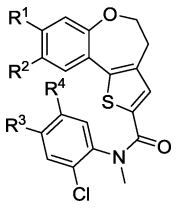
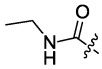
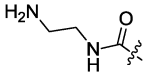
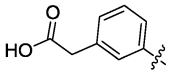
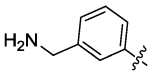
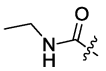
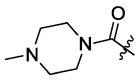
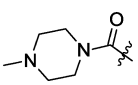
Table 4



Compound	R^1	R^2	R^3	R^4	PI3Kα Ki_{app}	PI3Kβ Ki_{app}	PI3Kβ Ki_{app}/ PI3Kα K_{iapp}
18	H	H	H	H	16 nM	272 nM	17
19		H	H	H	3 nM	247 nM	82
20		H	H	H	11 nM	582 nM	53
21		H	H	H	1 nM	114 nM	114
22		H	H	H	1 nM	87 nM	87
23		H	H	H	4 nM	55 nM	55
24		H	H	H	4 nM	33 nM	8
25		H	H	H	4 nM	31 nM	8
26		H	H	H	30 nM	2900 nM	97
27		H	H	H	23 nM	643 nM	28
28	H		H	H	1 nM	30 nM	30
29	H		H	H	1 nM	55 nM	55
30	H		H	H	3 nM	144 nM	48
31		H		H	2 nM	19 nM	10
32		H	H		3 nM	204 nM	68
33		H		H	5 nM	199 nM	40
34		H	H		48 nM	3870 nM	81

CHEMISTRY

The synthesis of the furan analogue **7** (Scheme 1) commenced with furan-3-carboxylic acid which was converted to the requisite amino group by Curtius rearrangement to give the Boc-protected amine **36**. A methyl ester was introduced at the 2-position of the furan by lithiation followed by quenching of the reaction with dimethyl carbonate. After deprotection of the amino group, chlorosulfonyl isocyanate was used to convert the amine (**37**) to a urea which then underwent cyclization in basic methanolic medium. The resulting pyrimidinedione was converted to **38** by the action of $POCl_3$ followed by incorporation of morpholine. Formylation of **38** led to a mixture of the aldehyde **39** and hemiacetal **40**. This mixture

dx.doi.org/10.1021/jm2007084 | J. Med. Chem. 2011, 54, 7815–7833

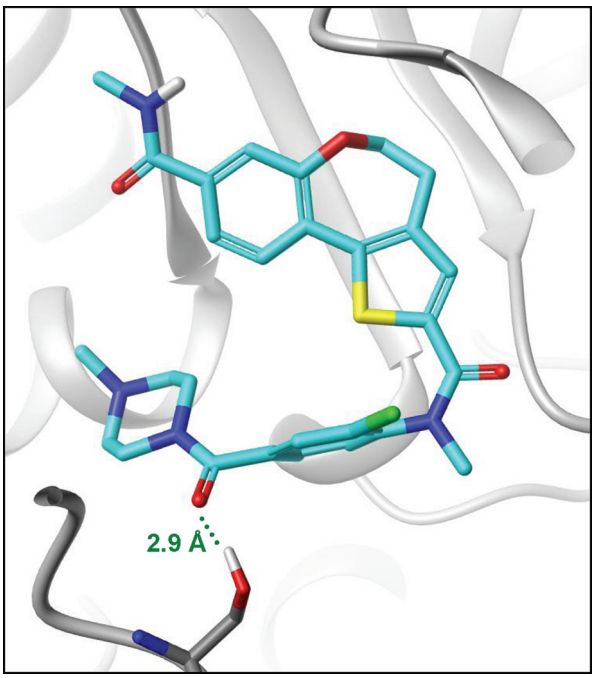


Figure 6. A cocrystal structure of PI3Kγ and **33** (PDB code 3T8M) shows a hydrogen bond between the piperazineamide carbonyl and Ser806.

smoothly underwent reductive amination to give **41** as a single product. Finally, Suzuki coupling yielded furanopyrimidine **7**.[21]

A general synthetic approach to thienopyrimidine analogues (Scheme 2) followed the course of the synthesis of **1** reported earlier.[8a] The commercially available amino ester **42** was cyclized to the pyrimidinedione in molten urea. This dione was subsequently converted to the dichloropyrimidine, and then morpholine was incorporated to yield **43**. At this stage, the intermediate could be converted to the benzylic alcohol and subsequently to the chloride. This chloride enabled smooth conversion to interemediate amines and led to desired products after Suzuki coupling. Alternatively, iodine could be introduced on the thiophene intermediate **43** and sequential Suzuki coupling yielded **17**.[22]

A representative synthesis of benzoxepins began with alkylation of 3-bromophenol with ethyl 4-bromobutanoate (Scheme 3). The ester of the resulting ether was saponified and subjected to acidic conditions to facilitate acylation. Ketone **45** was then homologated to the β-chlorovinylaldehyde using the Vilsmeier reagent and subsequently cyclized to the thiophene. Saponification of the resulting ester afforded acid **46**. Amide coupling provided the versatile intermediate **47**. This intermediate was utilized in the synthesis of numerous final compounds.[23]

CONCLUSION

Herein we have described two distinct approaches to achieving selectivity for PI3Kβ relative to PI3Kα. We suggest that the PI3Kβ/PI3Kα selectivity achieved in the thienopyrimidine series of inhibitors results from hydrogen bonding interactions between the ligand and Arg770 of PI3Kα that is not attained with the corresponding Lys777 of PI3Kβ. In the benzoxepin series of inhibitors, we postulate that the selectivity attained is a result of the difference in electrostatic potential between the two isoforms in a given region rather than any specific interaction or even the difference between one specific residue between the two enzyme isoforms. The approach to selectivity utilized in the benzoxepin series has the potential to be general and applicable to additional scaffolds as long as they contain the potential to occupy the critical space depicted in Figure 5. Each of the two approaches described lends credibility to the use of our PI3Kβ homology model. The approaches to gaining selectivity presented here should aid in the design of additional compounds that achieve selectivity either for or against PI3Kβ. Our studies of the impact of the selectivity over PI3Kβ in comparison to the pan-inhibitors previously reported are ongoing.

EXPERIMENTAL SECTION

Chemistry. All solvents and reagents were used as obtained. ^{1}H NMR spectra were recorded with a Bruker Avance DPX400 spectrometer or a Varian Inova 400 NMR spectrometer and referenced to tetramethylsilane. Chemical shifts are expressed as δ units using tetramethylsilane as the external standard (in NMR description, s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak). All final compounds were purified to >95% chemical purity, as assayed by HPLC (Waters Acquity UPLC column, 21 mm × 50 mm, 1.7 μm) with a gradient of 0–90% acetonitrile (containing 0.038% TFA) in 0.1% aqueous TFA, with UV detection at 254 and 210 nm and with CAD detection with an ESA Corona detector.

Compounds **1**–**4** have been described previously.[8]

***tert*-Butyl Furan-3-ylcarbamate (36).** 3-Furoic acid (5.60 g, 1.0 equiv) was dissolved in *tert*-butanol (200 mL) and treated with triethylamine (10 mL, 1.4 equiv) and diphenylphosphorylazide (12 mL, 1.1 equiv). The mixture was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, then concentrated to 50 mL and poured into saturated aqueous $NaHCO_3$. The mixture was stirred at 0 °C for 2 h. Solid was collected by filtration and dried under high vacuum. The crude reaction mixture was purified by flash chromatography to yield **36** (6.95 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (br s, 1H), 7.27 (m, 1H), 6.27 (br s, 1H), 6.20 (br s, 1H), 1.50 (s, 9H). MS (ESI): m/z $(M + H)^+$ 184.1.

Methyl 3-Aminofuran-2-carboxylate (37). To a solution of *tert*-butyl furan-3-ylcarbamate (1.7 g, 1.0 equiv) in THF (50 mL) at −30 °C was added TMEDA (1.75 mL, 1.3 equiv) followed by 1.6 M solution of *n*-butyllithium (8.4 mL, 2.25 equiv, 1.6 M in hexanes). The reaction mixture was allowed to warm to 0 °C and stirred for 1 h before being cooled back to −30 °C. Dimethyl carbonate (2.4 mL, 3.0 equiv) was quickly added before the reaction mixture was allowed to

Table 5

	IC_{50} (nM)		EC_{50} (μM)			
compd	PI3Kα	PI3Kβ	MCF7.1	PC3	IC_{50}(PI3Kβ)/IC_{50}(PI3Kα)	EC_{50}(PC3)/ EC_{50}(MCF7.1)
1	3	33	0.39	0.34	11	0.9
6	3	332	0.39	0.97	111	2.5
13	1	75	0.11	0.41	75	3.7
31	2	22	0.4	0.5	10	1.3
32	3	204	0.11	0.72	69	6.4

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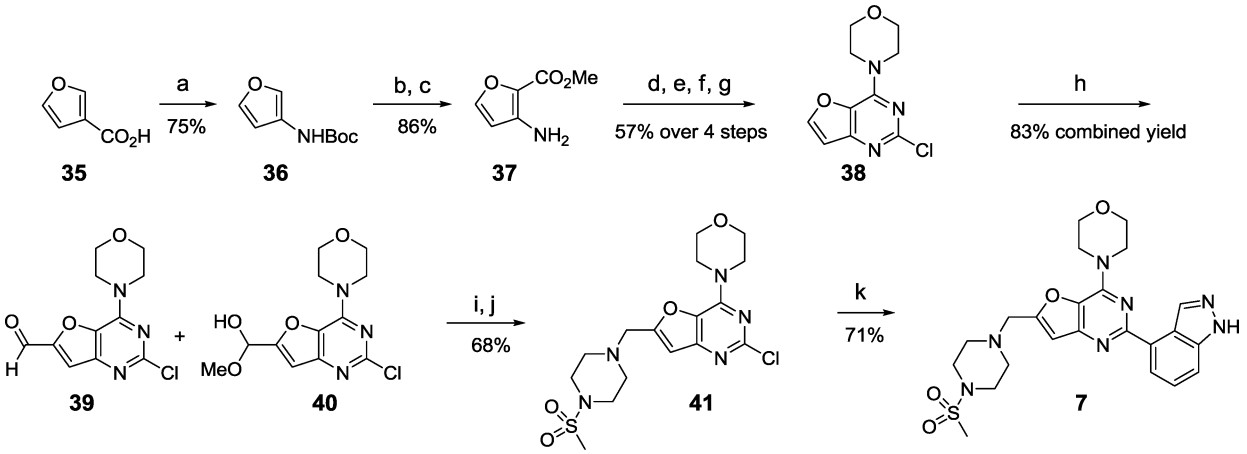
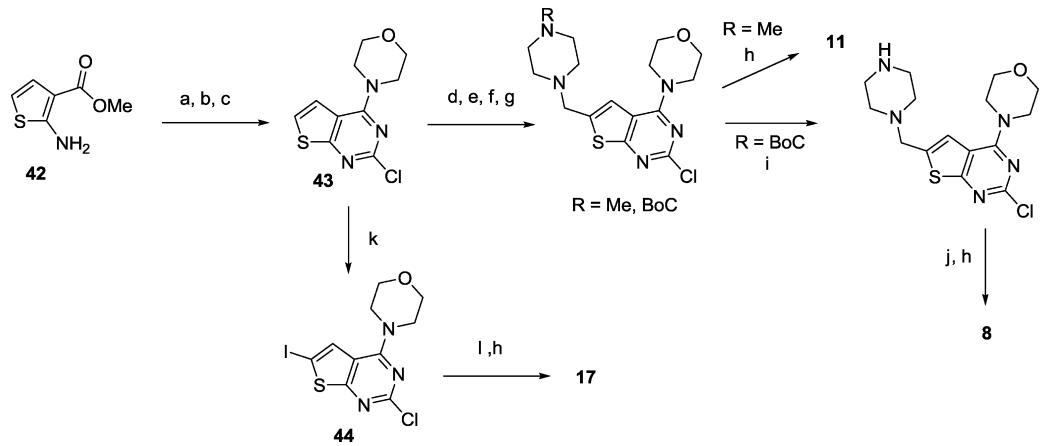
Scheme 1[a]



[a]Reagents and conditions: (a) DPPA, Et_3N, *t*-BuOH; (b) *n*-BuLi, TMEDA, $CO(OMe)_2$; (c) TFA, CH_2Cl_2; (d) ClO_2SNCO, CH_2Cl_2; (e) 1.5 M NaOH in MeOH; (f) $POCl_3$, *i*-Pr_2NEtN; (g) morpholine, MeOH; (h) *n*-BuLi, THF, −78 °C, DMF; (i) piperazinemethanesulfonamide HCl, $CH(OMe)_3$, DCE; (j) $NaBH(OAc)_3$; (k) indazole-4-boronic acid pinacol ester, $PdCl_2(PPh_3)_2$, Na_2CO_3, toluene/EtOH/water (4:2:1).

Scheme 2[a]



[a]Reagents and conditions: (a) $ClSO_2NC$, CH_2Cl_2, aq NaOH, aq HCl; (b) $POCl_3$, CH_3CN, reflux, 24 h; (c) morpholine, MeOH, 1 h; (d) *n*-BuLi, THF, −78 °C, DMF; (e) $NaBH_4$, MeOH; (f) $SOCl_2$, CH_2Cl_2; (g) HNRR′, *i*-Pr_2NEt, THF; (h) 2-aminopyrimidine-5-boronic acid pinacol ester, $PdCl_2(PPh_3)_2$, 1 M aq KOAc, CH_3CN, microwave, 150 °C, 15 min; (i) HCl, MeOH; (j) $MeSO_2Cl$, Et_3N, THF; (k) *n*-BuLi, THF, −78 °C, I_2; (l) 3-SO_2Me phenylboronic acid, $PdCl_2(PPh_3)_2$, 1 M aq Na_2CO_3, CH_3CN, microwave, 100 °C, 10 min.

warm to room temperature for 1 h. The reaction mixture was quenched with 2 M HCl, followed by addition of saturated aqueous NaCl. The mixture was extracted with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and concentrated. The crude reaction mixture was purified by flash chromatography to yield methyl 3-(*tert*-butoxycarbonylamino)furan-2-carboxylate (1.14 g, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.25 (br s, 1H), 3.92 (s, 3H), 1.52 (s, 9H). MS (ESI): m/z $(M + H)^+$ 242.1. This intermediate (1.14 g, 1.0 equiv) was dissolved in dichloromethane (8 mL) and treated with trifluoroacetic acid (5 mL). The reaction mixture was stirred at room temperature for 3 h and was then concentrated. Residue was dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. The mixture was extracted with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and concentrated. The crude reaction mixture was purified by flash chromatography to yield **37** (574 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 6.13 (d, J = 2.0 Hz, 1H), 4.57 (br s, 2H), 3.89 (s, 3H). MS (ESI): m/z $(M + H)^+$ 142.0.

2-Chloro-4-morpholinofuro[3,2-*d*]pyrimidine (38). To a solution of **37** (100 mg, 1.0 equiv) in dichloromethane (3 mL) at −78 °C was added chlorosulfonyl isocyanate (0.09 mL, 1.4 equiv) dropwise. The mixture was slowly warmed to room temperature and stirred for 40 min. The reaction was concentrated. To the residue was added 6 N HCl (3.5 mL), and the mixture was heated to 100 °C for 20 min. The reaction mixture was allowed to cool to room temperature and was neutralized with saturated aqueous $NaHCO_3$. Solid was collected by filtration to yield methyl 3-ureidofuran-2-carboxylate as a beige solid which was used in the next reaction without further purification (MS (ESI): m/z $(M + H)^+$ 185.1). The crude intermediate was suspended in methanol (6 mL) and treated with 1.5 M NaOH (1.5 mL). The reaction mixture was heated to reflux for 90 min. The reaction mixture was allowed to cool to room temperature and was acidified with 6 N HCl to pH 3. The mixture was concentrated. Methanol was added to the residue and the solid was filtered and dried at 95 °C under high vacuum for 24 h to yield furo[3,2-*d*]pyrimidine-2,4-diol (90 mg, 84% yield over two steps). ^1H NMR (300 MHz, DMSO) δ 11.22 (br s, 1H), 11.05 (br s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H). MS (ESI): m/z $(M + H)^+$ 153.0. This intermediate (39 mg, 1.0 equiv) was dissolved in $POCl_3$ (1.8 mL). The mixture was cooled to −40 °C, and *N*,*N*-diisopropylethylamine (0.45 mL) was slowly added. The reaction mixture was then heated to reflux for 48 h, then cooled to room temperature. The reaction mixture was poured into ice−water. The mixture was extracted with ethyl acetate. The combined organic

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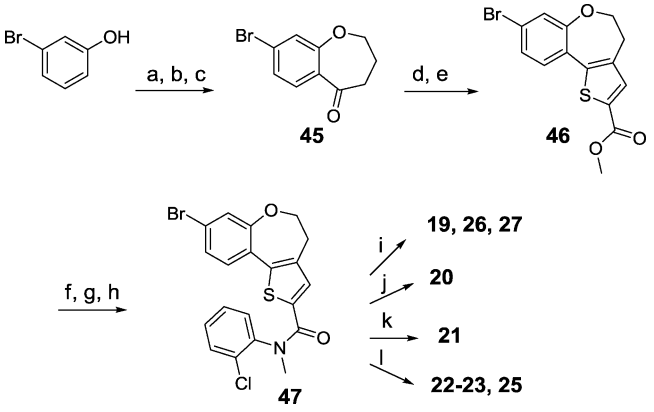
Scheme 3[a]



[a]Reagents and conditions: (a) ethyl 4-bromobutanoate, K_2CO_3, cat. NaI, acetone; (b) LiOH, H_2O, THF; (c) PPA, toluene; (d) $POCl_3$, DMF; (e) K_2CO_3, methyl thioglycolate, DMF; (f) LiOH, H_2O, THF; (g) $SOCl_2$; (h) *N*-methyl-2-chloroaniline, NEt_3, DMAP, CH_2Cl_2; (i) aryl boronate, $Pd(PPh_3)_4$, 1 M aq Na_2CO_3, DMF; (j) CuCN, DMF; (k) NH_2COCH_3, Cs_2CO_3, Xantphos, $Pd_2(dba)_3$, dioxane; (l) $Mo(CO)_6$, MeOH, THF, amine, Herrmann's catalyst, DBU.

layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to yield 2,4-dichlorofuro[3,2-*d*]pyrimidine (23 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.08 (m, 1H), 7.04−7.02 (m, 1H). MS (ESI): m/z $(M + H)^+$ 153.0. This intermediate (23 mg, 1.0 equiv) was suspended in methanol (1.7 mL) and treated with morpholine (0.09 mL, 4.0 equiv). The reaction mixture was stirred at room temperature for 2 h before being quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated to yield **38** (14 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 2.2 Hz, 1H), 6.79 (d, J = 2.2 Hz, 1H), 4.10−3.96 (m, 4H), 3.83 (dd, J = 6.2, 3.6 Hz, 4H). MS (ESI): m/z $(M + H)^+$ 240.0.

2-Chloro-4-morpholinofuro[3,2-*d*]pyrimidine-6-carbaldehyde (39). To a solution of **38** (40 mg, 1.0 equiv) in THF (1.7 mL) at −78 °C was added 1.6 M solution of *n*-butyllithium (0.14 mL, 1.3 equiv, 1.6 M in hexanes). The reaction mixture was stirred at −78 °C for 30 min. DMF (0.05 mL, 4.0 equiv) was added, and reaction mixture was allowed to slowly warm to room temperature and stirred for 90 min. The reaction was quenched with water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude reaction mixture was purified by flash chromatography to yield **39** (22 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.48 (s, 1H), 4.19−4.00 (m, 4H), 3.92−3.81 (m, 4H). MS (ESI): m/z $(M + H)^+$ 268.0.

2-Chloro-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)-4-morpholinofuro[3,2-*d*]pyrimidine (41). **39** (65 mg) was dissolved in 1,2-dichloroethane (9.7 mL) and treated with the hydrochloride salt of 1-methanesulfonylpiperazine (69 mg), sodium acetate (28 mg), and trimethyl orthoformate (0.27 mL). The reaction mixture was stirred at room temperature for 12 h. Sodium triacetoxyborohydride (62 mg) was added, and reaction mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude reaction mixture was purified by flash chromatography to yield **41** (70 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.04−3.97 (m, 4H), 3.87−3.80 (m, 4H), 3.73 (s, 2H), 3.32−3.25 (m, 4H), 2.80 (s, 3H), 2.70−2.63 (m, 4H). MS (ESI): m/z $(M + H)^+$ 416.1.

2-(1*H*-Indazol-4-yl)-6-((4-(methylsulfonyl)piperazin-1-yl)-methyl)-4-morpholinofuro[3,2-*d*]pyrimidine (7). **41** (40 mg, 1.0 equiv) was dissolved in toluene/ethanol/water (4:2:1, 1.6 mL) and treated with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (59 mg, 2.5 equiv), $PdCl_2(PPh_3)_2$ (6.8 mg, 0.10 equiv), and sodium carbonate (36 mg, 3.5 equiv). The vial was sealed and heated with stirring in the microwave to 150 °C for 15 min. The crude reaction mixture was concentrated and purified by reverse phase HPLC to afford **7** (42 mg, 88% yield). MS (ESI): m/z $(M + H)^+$ 498.2.

4-(2-Chlorothieno[*2,3-d*]pyrimidin-4-yl)morpholine (43). A 5 L reaction vial equipped with a mechanical stirrer, internal temperature probe, and a nitrogen bubbler was charged with **42** (95 g) and CH_2Cl_2 (2.85 L), and the mixture was cooled to −60 °C. Chlorosulfonyl isocyanate was added at a rate such that the internal temperature remained at −60 to −55 °C. After completion of addition the mixture was allowed to warm to ambient temperature. The reaction was monitored for complete consumption of starting material by LC/MS. The reaction mixture was concentrated to dryness and the solid residue transferred back to the 5 L reaction vial by water (1.8 L). This mixture was heated at 75 °C for 1 h, then cooled to 30 °C. Next 10 M aqueous NaOH (200 mL) was added and this mixture was heated at 85 °C for 20 min before cooling to room temperature. The mixture was then acidified to pH 1 by the addition of concentrated HCl. The mixture was then stirred for 18 h at ambient temperature with a precipitate forming. This solid material was collected by vacuum filtration and the filter cake washed with water. The solid material was then dried in a vacuum oven at 55 °C for 24 h to afford thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione as an off white solid (80 g, 79%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.08 (d, J = 5.6 Hz, 1H), 7.12 (d, J = 5.6 Hz, 1H). ESI-MS: m/z = 169 $[M + H]^+$. This intermediate (16.8 g, 0.1 mol) was added to $POCl_3$ (100 mL), and the mixture was heated at reflux overnight. After $POCl_3$ was removed under reduce pressure an aqueous $NaHCO_3$ solution was added and extracted with EtOAc (300 mL × 2). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give 2,4-dichlorothieno[2,3-*d*]-pyrimidine (17.1 g, 84% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.07 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H). ESI-MS: m/z = 204 $[M + H]^+$. To a solution of the dichloropyrimidine intermediate (10.2 g, 50 mmol) in EtOH (100 mL), morpholine (6.1 g, 70 mmol) was added dropwise. The mixture was stirred at room temperature overnight. TLC showed that the reaction was completed. The reaction mixture was filtered and washed with a small amount of EtOH to give **43** (11.0 g, 85% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.78 (s,1H), 5.07 (s, 2H), 3.86 (t, J = 4.8 Hz, 4H), 3.72 (t, J = 4.8 Hz, 4H). ESI-MS: m/z = 255.8 $[M + H]^+$.

2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidine-6-carbaldehyde. To a solution of 4-(2-chlorothieno[2,3-*d*]pyrimidin-4-yl)-morpholine (25.5 g, 0.1 mol) in THF (200 mL) was added *n*-BuLi (64 mL, 0.16 mol) at −78 °C. The mixture was stirred for 2 h at −78 °C under N_2, and DMF (28 g, 0.4 mol) was added dropwsie. The reaction mixture was stirred for an additional hour at −78 °C, and the reaction was quenched by 0.5 M HCl. The mixture was extracted with CH_2Cl_2 (300 mL × 3), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc = 4:1) to give the desired product (21 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.01 (s, 1H), 4.08−4.03 (m, 4H), 3.91−3.86 (m, 4H). ESI-MS: m/z = 283.8 $[M + H]^+$.

(2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)-methanol. To a solution of 2-chloro-4-morpholinothieno[2,3-*d*]-pyrimidine-6-carbaldehyde (21 g, 0.07 mol) in MeOH (200 mL), $NaBH_4$ (4.1 g, 0.11 mol) was added at 0 °C. The mixture was stirred for 1 h. The mixture was quenched by 0.1 M HCl and extracted with CH_2Cl_2. It was dried and concentrated to give the crude product, which was used for the next step without further purification (18 g, 84%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.48 (s,1H), 5.74 (s, 1H), 4.68 (s, 1H), 3.83 (t, J = 4.8 Hz, 4H), 3.70 (t, J = 4.8 Hz, 4H). ESI-MS: m/z = 285.8 $[M + H]^+$.

4-(2-Chloro-6-(chloromethyl)thieno[2,3-*d*]pyrimidin-4-yl)-morpholine. To a solution of (2-chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methanol (18 g, 0.06 mol) in CH_2Cl_2 (400 mL), $SOCl_2$ (17 g, 0.15 mol) was added dropwise at 0 °C. The mixture was stirred for 30 min, concentrated, and dissolved in CH_2Cl_2 (200 mL). It was washed with aqueous $NaHCO_3$, concentrated, and purified by column chromatography (EtOAc/hexanes = 1:3) to give the desired

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product (16 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81(s, 1H), 5.09 (s, 2H), 3.87−3.85 (m, 4H), 3.74−3.73 (m, 4H). ESI-MS: m/z = 308.3 $[M + H]^+$.

***tert*-Butyl 4-((2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methyl)piperazine-1-carboxylate.** To a solution of 4-(2-chloro-6-(chloromethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (1.5 g, 5.0 mmol) in THF (50 mL) was added *tert*-butyl piperazine-1-carboxylate (1.86 g, 10 mmol) at room temperature. *i*-Pr_2NEt (1.3 g, 10 mmol) was added dropwise after 20 min, and the mixture was stirred at 70 °C overnight. The mixture was concentrated and purified by silica gel chromatography (CH_2Cl_2/MeOH = 40:1) to give the desired product (1.4 g, 65%). ESI-MS: m/z = 454.1 $[M + H]^+$.

4-(2-Chloro-6-(piperazin-1-ylmethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine. To a solution of *tert*-butyl 4-((2-chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methyl)piperazine-1-carboxylate (1.4 g, 3.2 mmol) in MeOH (20 mL) was added MeOH/HCl (4 M, 20 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. TLC showed the reaction was completed. The mixture was concentrated to afford the desired product as HCl salt, which was used for the next step without further purification (1.04 g, 87% yield). ESI-MS: m/z = 354.1 $[M + H]^+$.

4-(2-Chloro-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)-thieno[2,3-*d*]pyrimidin-4-yl)morpholine. To a solution of 4-(2-chloro-6-(piperazin-1-ylmethyl)thieno[2,3-*d*]pyrimidin-4-yl)-morpholine (1.4 g, 3.2 mmol) in THF (80 mL) was added Et_3N (1.29 g, 12.8 mmol) and $MeSO_2Cl$ (0.9 g, 8 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The mixture was quenched with ice−water and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product which was used for the next step without further purification (0.65 g, 42% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.77 (s, 1H), 4.49 (s, 2H), 3.97−3.67 (m, 6H), 3.56−3.40 (m, 6H), 3.07−2.99 (m, 4H), 2.35 (s, 3 H). ESI-MS: m/z = 432.0 $[M + H]^+$.

4-(2-(1*H*-Indazol-4-yl)-6-((4-(methylsulfonyl)piperazin-1-yl)-methyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (6). 4-(2-Chloro-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)thieno[2,3-*d*]-pyrimidin-4-yl)morpholine (412 mg) was combined with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (327 mg), $PdCl_2(PPh_3)_2$ (33 mg), 1 M aqueous sodium carbonate (3 mL), and acetonitrile (3 mL). The mixture was heated to 140 °C in a microwave reactor for 20 min. The contents were extracted with EtOAc, concentrated, then purified by reverse phase HPLC to yield **6** (193 mg, 39% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (m, 4H), 2.81 (s, 3H), 3.30 (m, 4H), 3.83 (s, 2H), 3.92−3.94 (m, 4H), 3.98−4.00 (m, 4H), 7.17 (s,1H), 7.50 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 8.31 (d, J = 7.0 Hz, 1H), 10.12 (br s,1H). ESI-MS: m/z = 514.10 $[M + H]^+$.

5-(6-((4-(Methylsulfonyl)piperazin-1-yl)methyl)-4-morpholinothieno[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (8). 4-(2-Chloro-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)thieno-[2,3-*d*]pyrimidin-4-yl)morpholine (150 mg, 0.35 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (144 mg, 0.7 mmol), Cs_2CO_3 (228 mg, 0.7 mmol), and dioxane/H_2O (3 mL/1 mL) were combined in a microwave tube. The mixture was purged with N_2 for 20 min. Then $Pd(dppf)Cl_2$ (51 mg, 0.07 mmol) was added. The reaction mixture was heated to 120 °C for 20 min under microwave irradiation. It was diluted with CH_2Cl_2 (50 mL), washed with water, and dried over Na_2SO_4. The solvent was removed by underduced pressure, and the residue was purified by HPLC to give the desired product (28 mg, 16%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (s, 2H), 7.77 (s, 1H), 7.31 (s, 2H), 4.49 (s, 2H), 3.97−3.77 (m, 8H), 3.37−3.35 (m, 8H), 2.99 (s, 3H). LCMS (ESI): m/z = 491.0 $[M + H]^+$.

4-(2-(1*H*-Indazol-4-yl)thieno[2,3-*d*]pyrimidin-4-yl)-morpholine (9). 4-(2-Chlorothieno[2,3-*d*]pyrimidin-4-yl)-morpholine (255 mg, 1 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (366 mg, 1.5 mmol), Cs_2CO_3 (652 mg, 2 mmol), and dioxane/H_2O (3 mL/1 mL) were combined in a microwave tube. It was bubbled with N_2 for 20 min. $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol) was added, and the mixture was heated under microwave irradiation to 120 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by HPLC to give the desired product (41 mg, 14% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98 (s, 1H), 8.28 (d, J = 0.8 Hz, 1H), 7.55−7.26 (m, 4H), 3.72 (t, J = 4.8 Hz, 4H), 3.72 (t, J = 4.8 Hz, 4H). ESI-MS: m/z = 337.8 $[M + H]^+$.

5-(4-Morpholinothieno[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (10). To a solution of **43** (0.256 g) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (263 mg) in acetonitrile (2.0 mL) was added 1 M aqueous sodium carbonate (1 mL). The reaction mixture was sealed with a rubber septum and degassed by purging nitrogen through the mixture via a syringe. Next bis-(triphenyphosphine)palladium dichloride (35 mg) was added under a nitrogen flush and the reaction vessel was sealed. The reaction mixture was heated on a Biotage Emrys Optimizer microwave at 160 °C for 10 min and then cooled to room temperature. The reaction mixture was diluted with EtOAc and neutralized by titration with concentrated HCl. A dark solid was removed from this reaction mixture by vacuum filtration through a small bed of Celite. The filtration pad was then flushed with EtOAc and water. The filtrate was transferred to a separatory funnel, and the organic layer was separated from the aqueous. The organic layer was dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was purified by RP-HPLC to give **10** (66 mg, 17% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (s, 2H), 7.34 (d, J = 6.1 Hz, 1H), 7.26 (d, J = 6.1 Hz, 1H), 4.01−3.96 (m, 4H), 3.90−3.86 (m, 4H). ESI-MS: MH + 1 = 315.1.

5-(6-((4-Methylpiperazin-1-yl)methyl)-4-morpholinothieno-[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (11). To a solution of 4-(2-chloro-6-(chloromethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (1.5 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added 1-methylpiperazine (0.5 g, 5.0 mmol) at room temperature. *i*-Pr_2NEt (0.78 g, 6.0 mmol) was added dropwise after 20 min, and the mixture was stirred at 40 °C for 3 h. LCMS showed that the reaction was completed. The mixture was concentrated and purified by silica gel (CH_2Cl_2/MeOH = 40:1) to give 4-(2-chloro-6-((4-methylpiperazin-1-yl)methyl)thieno[2,3-*d*]-pyrimidin-4-yl)morpholine (1 g, 83% yield). ESI-MS: m/z = 367.9 $[M + H]^+$. **11** was prepared as described for **10** from 4-(2-chloro-6-((4-methylpiperazin-1-yl)methyl)thieno[2,3-*d*]pyrimidin-4-yl)-morpholine (15% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.31 (s, 2H), 8.16 (s, 1H), 4.7 (s, 2H), 4.02−3.78 (m, 8H), 3.62−3.48 (m, 8H), 3.56 (t, J = 9.6 Hz, 4H), 3.33−3.11 (m, 8H), 2.81 (s, 3H). LCMS (ESI): m/z = 427.1 $[M + H]^+$.

Diethyl (2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methylphosphonate. A solution of 4-(2-chloro-6-(chloromethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (5.0 g, 16.5 mmol) in $P(OEt)_3$ (30 mL) was heated to 150 °C for 5 h. LCMS showed that the reaction was completed. The mixture was concentrated and purified by silica gel chromatography (CH_2Cl_2/EtOAc = 1:2) to give the desired product (6.0 g, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (s, 1H), 4.12 (q, J = 7.6 Hz, 4H), 3.93 (t, J = 4.4 Hz, 4H), 3.82 (t, J = 4.4 Hz, 4H), 3.34 (d, J = 22.0 Hz, 2H), 1.31 (t, J = 7.6 Hz, 6H).

***tert*-Butyl 4-((2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methylene)piperidine-1-carboxylate.** To a mixture of sodium hydride (746 mg, 31 mmol) in THF at 0 °C under N_2 was added diethyl (2-chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)-methylphosphonate (4.20 g, 10 mmol) in THF. The mixture was stirred for 30 min at 0 °C, and *tert*-butyl 4-oxopiperidine-1-carboxylate (2.0 g, 12 mmol) in THF was added. The mixture was stirred at room temperature for 3 h. TLC showed the reaction was completed. The mixture was filtered through Celite. The filtrate was concentrated and purified by chromatography to give the desired product (4.42 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (s, 1H), 6.40 (s, 1H), 3.94−3.92 (m, 4H), 3.84−3.82 (m, 4H), 3.53−3.48 (m, 4H), 2.65−2.60 (m, 2H), 2.40−2.35 (m, 2H), 1.49 (s, 9H). LCMS (ESI): m/z = 451.1 $[M + H]^+$.

4-(2-Chloro-6-(piperidin-4-ylidenemethyl)thieno[2,3-*d*]-pyrimidin-4-yl)morpholine. To a solution of *tert*-butyl 4-((2-chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methylene)-piperidine-1-carboxylate (4.42 g, 9.4 mmol) in methanol (10 mL) was

added HCl/MeOH, and the reaction mixture was stirred at room temperature for 4 h. LCMS showed the reaction was completed. Solvent was removed under reduced pressure to give the product without further purification (3.5 g, 96% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.18 (s, 2H), 7.58 (s, 1H), 6.51 (s, 1H), 3.67 (t, J = 4.4 Hz, 4H), 3.73 (t, J = 4.4 Hz, 4H), 3.15 (m, 4H), 2.81 (d, J = 6.4 Hz, 2H), 2.50 (d, J = 6.4 Hz, 2H).

4-(2-Chloro-6-(piperidin-4-ylmethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine. A mixture of 4-(2-chloro-6-(piperidin-4-ylidenemethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (3.4 g, 9.7 mmol) and Pd/C (170 mg) in methanol was stirred at room temperature under H_2 (1 atm) for 4 h. LCMS showed that the reaction was completed. Solvent was removed under reduced pressure to give the product without further purification (3.2 g, 90% yield). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31 (s, 1H), 3.95 (t, J = 4.4 Hz, 4H), 3.80 (t, J = 4.4 Hz, 4H), 3.40−3.20 (m, 2H), 3.01−2.90 (m, 4H), 1.97−1.93 (m, 3H), 1.53−1.43 (m, 2H). LCMS (ESI): m/z = 352.9 $[M + H]^+$.

4-(2-Chloro-6-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)-methyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine. To a solution of 4-(2-chloro-6-(piperidin-4-ylmethyl)thieno[2,3-*d*]pyrimidin-4-yl)-morpholine (0.6 g, 1.4 mmol) and *i*-Pr_2NEt (0.54 g, 4.2 mmol) in CH_2Cl_2 (20 mL) was added 2,2,2-trifluoroacetic anhydride (0.5 g, 2.8 mmol) at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was purified by column chromatography (petroleum ether/ethyl acetate, 5:1 to 2:1) to give crude 1-(4-((2-chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)-methyl)piperidin-1-yl)-2,2,2-trifluoroethanone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 4.57−4.54 (m, 1H), 3.92−3.89 (m, 4H), 3.82−3.85 (m, 4H), 3.14−3.07 (m, 1H), 2.82−2.74 (m, 3H), 1.95−1.83 (m, 3H), 1.38−1.21 (m, 3H). LCMS (ESI): M + H^+ = 449.1. To a solution of this intermediate intermediate (600 mg, 1.34 mmol) in THF was added BH_3/CH_3SCH_3 (10 M, 20 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 2 h. MeOH (75 mL) was added dropwise to the mixture at −15 °C. Solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexanes/EtOAc = 5:1 to 3:1) to afford 4-(2-chloro-6-((1- (2,2,2-trifluoroethyl)piperidin-4-yl)methyl)thieno[2,3-*d*]-pyrimidin-4-yl)morpholine (250 mg, 41% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 3.92−3.89 (m, 4H), 3.85−3.82 (m, 4H), 2.93−2.90 (m, 4H), 2.77−2.75 (d, 2H), 2.36−2.31 (m, 2H), 1.71−1.61 (m, 2H), 1.61−1.57 (m, 1H), 1.40−1.34 (m, 2H). LCMS (ESI): M + H^+ = 435.1.

5-(4-Morpholino-6-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)-methyl)thieno[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (12). **12** was prepared as described for **10** from 4-(2-chloro-6-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methyl)thieno [2,3-*d*] pyrimidin-4-yl)-morpholine (14% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 2H), 6.94 (s, 1H), 5.30−5.29 (d, 2H), 3.94−3.91 (m, 4H), 3.91−3.86 (m, 4H), 2.99−2.92 (m, 4H), 2.81−2.79 (m, 2H), 2.36−2.30 (m, 2H), 1.74−1.70 (m, 2H), 1.42−1.39 (m, 2H), 1.42 (s, 1H). LCMS (ESI): m/z = 494.1 $[M + H]^+$.

5-(6-((1-(Methylsulfonyl)piperidin-4-yl)methyl)-4-morpholinothieno[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (13). 4-(2-Chloro-6-(piperidin-4-ylmethyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (100 mg) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Triethylamine (270 μL) and methanesulfonyl chloride (36 μL) were added, and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was utilized in a Suzuki coupling according to the procedure described for **10** to yield **13** (6 mg, 5% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 2H), 7.37 (s, 1H), 7.07 (s, 2H), 3.92−3.88 (m, 4H), 3.80−3.75 (m, 4H), 3.60−3.50 (m, 2H), 2.85 (app q, J = 12, 4 Hz), 2.83 (s, 3H), 2.69 (app t, J = 11.2 Hz), 1.75 (app t, J = 11.1 Hz, 3H), 1.33−1.20 (m, 2H). LCMS (ESI): m/z = 490.2 $[M + H]^+$.

5-(6-((4-(Methylsulfonyl)piperidin-1-yl)methyl)-4-morpholinothieno[2,3-*d*]pyrimidin-2-yl)pyrimidin-2-amine (14). A mixture of 4-methanesulfonyloxypiperidine-1-carboxylic acid *tert*-butyl ester (1.01 g) and sodium thiomethoxide (635 mg) was heated to 80 °C in DMF (10 mL). After 4 h, the reaction mixture was diluted with water, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give 4-methylsulfanylpiperidine-1-carboxylic acid *tert*-butyl ester (600 mg). This intermediate was dissolved in chloroform (15 mL), and m-CPBA (1.46 g) was added. After being stirred for 48 h, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford 4-methanesulfonylpiperidine-1-carboxylic acid *tert*-butyl ester (505 mg). Treatment of this intermediate with HCl in CH_2Cl_2 and MeOH yielded crude 4-methanesulfonylpiperidine as its HCl salt. This intermediate (252 mg) was added to 2-chloro-4-morpholinothieno[2,3-*d*]pyrimidine-6-carbaldehyde (250 mg) in 1,2-DCE (5 mL). Subsequently, triethyl orthoformate (330 μL) was added. After the mixture was stirred for 6 h, $Na(OAc)_3BH$ (530 mg) was added. The mixture was stirred overnight. The reaction was quenched by pouring onto water. The aqueous layer was extracted with dichloromethane, and the combined organics were dried over Na_2SO_4 and concentrated. This intermediate was reacted with 2-amino-5-boronic acid according to a similar Suzuki coupling procedure as described for compound **10** to afford **14** (12% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88−2.00 (m, 2H), 2.04−2.20 (m, 4H), 2.83−2.86 (m, 4H), 3.13−3.20 (m, 2H), 3.81 (s, 2H), 3.88−3.90 (m, 4H), 3.92−3.96 (m, 4H), 5.25 (br s, 2H), 7.18 (s, 1H), 9.37 (s, 1H). LCMS (ESI): m/z = 490.34 $[M + H]^+$.

***N*-((2-(2-Aminopyrimidin-5-yl)-4-morpholinothieno[2,3-*d*]-pyrimidin-6-yl)methyl)-*N*-methylmethanesulfonamide.** To a solution of 2-chloro-4-morpholinothieno[2,3-*d*]pyrimidine-6-carbaldehyde (100 mg., 0.350 mmol) in anhydrous THF (0.500 mL) was added methylamine as a 2.0 M solution in THF (0.700 mL, 2.0 equiv). This reaction mixture was stirred overnight at room temperature under nitrogen. The reaction mixture was concentrated in vacuo, and the resulting solid residue was taken into MeOH/THF, 1/1 (0.500 mL). Next, $NaBH_3$ was added as a solid in several aliquots. The resulting slurry was stirred at room temperature for 2 h. The reaction mixture was quenched with a minimum of dilute aqueous HCl. The reaction mixture was then diluted with excess EtOAc and washed with water (×1) and saline (×1). The organic was dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was carried forward with out purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 3.98 (s, 2H), 3.95−3.90 (m, 4H), 3.86−3.81 (m, 4H), 2.51 (s, 3H). LCMS (ESI): m/z = 299.0 $[M + H]^+$. The crude amine was dissolved in methylene chloride (5 mL), and the mixture was cooled to 0 °C under nitrogen. Methanesulfonyl chloride (130 μL) was added, and the mixture was stirred for 12 h at room temperature. The mixture was diluted with water and 1 M HCl, and the aqueous layer was extracted with CH_2Cl_2. The sample was dried over $MgSO_4$ and concentrated. Purification was by silica gel chromatography (0−5% MeOH in CH_2Cl_2) to give the title compound (108 mg, 84% yield). ^{1}H NMR (400 MHz, C_6D_6) δ 6.91 (s, 1H), 4.00 (s, 2H), 3.45−3.38 (m, 4H), 3.35−3.28 (m, 4H), 2.44 (s, 3H), 2.18 (s, 3H). LCMS (ESI): m/z = 377.0 $[M + H]^+$.

***N*-((2-(2-Aminopyrimidin-5-yl)-4-morpholinothieno[2,3-*d*]-pyrimidin-6-yl)methyl)-*N*-methylmethanesulfonamide (15).** **15** was prepared as described for **9** from *N*-((2-(2-aminopyrimidin-5-yl)-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)methyl)-*N*-methylmethanesulfonamide (9% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.10 (s, 2H), 7.61 (s, 1H), 4.51 (s, 2H), 3.97−3.87 (m, 4H), 3.82−3.68 (m, 4H), 3.00 (s, 3H), 2.88 (s, 3H). LCMS (ESI): m/z = 436.5 $[M + H]^+$.

4-((2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)-methyl)-*N*,*N*-dimethylpiperazine-1-carboxamide. To a solution of 2-chloro-4-morpholinothieno[2,3-*d*]pyrimidine-6-carbaldehyde (200 mg) in 1,2-dichlorethane (10 mL) was added piperazine-1-carboxylic acid dimethylamide hydrochloride (291 mg) and triethyl orthoformate (390 μL). The mixture was stirred for 2 h at room temperature. $Na(OAc)_3BH$ (674 mg) was added, and the resulting reaction mixture was stirred for 16 h at room temperature. The reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude compound was purified by silica

gel chromatography (4% MeOH in CH_2Cl_2) to yield the desired compound (0.12 g, 27% yield).

4-((2-(2-Aminopyrimidin-5-yl)-4-morpholinothieno[2,3-*d*]-pyrimidin-6-yl)methyl)-*N*,*N*-dimethylpiperazine-1-carboxamide (16). 4-((2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)-methyl)-*N*,*N*-dimethylpiperazine-1-carboxamide was reacted with 2-amino-5-boronic acid according to a similar Suzuki coupling procedure as described for compound **11** to afford **16** (47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (m, 4H), 2.84 (s, 6H), 3.32 (m, 4H), 3.79 (s, 2H), 3.89−3.91 (m, 4H), 3.95−3.97 (m, 4H), 5.24 (br s, 2H), 7.14 (s, 1H), 9.30 (s, 2H). MS (ESI+): $(M + H)^+$ 484.31.

4-(2-Chloro-5-iodothieno[2,3-*d*]pyrimidin-4-yl)morpholine. 4-(2-Chlorothieno[2,3-*d*]pyrimidin-4-yl)morpholine (500 mg) in THF (50 mL) was cooled to −78 °C. *n*-BuLi (2 mL, 2.5 M in hexane) was added, and the reaction mixture was warmed to −40 °C and stirred for 50 min. The mixture was then recooled to −78 °C, and a solution of I_2 (1000 mg) in THF (30 mL) was added. The reaction mixture was warmed to room temperature and after 30 min was quenched with water and diluted with CH_2Cl_2. The organic layer was separated, washed with saturated aqueous Na_2SO_3 and brine, then dried over Na_2SO_4, filtered, and concentrated to yield the desired compound (650 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 3.94−3.82 (m, 4H). MS (ESI+): $(M + H)^+$ 382.2.

5-(6-(3-(Methylsulfonyl)phenyl)-4-morpholinothieno[2,3-*d*]-pyrimidin-2-yl)pyrimidin-2-amine (17). 2-Chloro-6-iodo-4-morpholinothieno[2,3-*d*]pyrimidine (525 mg), 3-(methylsulfonyl)-phenylboronic acid (303 mg), and bis(triphenylphosphine)palladium-(II) dichloride (96 mg) in 1 M Na_2CO_3 aqueous solution (4.2 mL) and acetonitrile (9 mL) were heated to 100 °C in a sealed microwave reactor for 30 min. Upon completion, the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated. The crude mixture was purified by flash chromatography to yield 4-(2-chloro-6-(3-(methylsulfonyl)phenyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine which was used in the next step (MS (ESI+): $(M + H)^+$ 410.0). **17** was prepared as described for **10** from 4-(2-chloro-6-(3-(methylsulfonyl)-phenyl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (7% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 2H), 8.29−8.25 (m, 1H), 8.22−8.18 (m, 1H), 8.15 (s, 1H), 7.95−7.91 (m, 1H), 7.77 (t, J = 8 Hz, 1H), 7.24 (br s, 2H), 4.06−3.98 (m, 4H), 3.86−3.78 (m, 4H). MS (ESI+): $(M + H)^+$ 469.1.

4,5-Dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxylic Acid. $POCl_3$ (4.66 mL, 51.2 mmol) was added dropwise to 12 mL of DMF at 0 °C. After 30 min, 3,4-dihydrobenzo[*b*]oxepin-5(2*H*)-one (3.32 g, 20.5 mmol) was added as a solution in 15 mL of DMF. The solution was stirred, warming to room temperature over 2 h. The mixture was poured over ice−water, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over sodium sulfate, and concentrated. The residue was taken up in DMF (20 mL) and treated sequentially with potassium carbonate (5.66 g, 41 mmol) and then methyl thioglycolate (2.05 mL, 22.6 mmol). The mixture was heated at 50 °C overnight. Water was added and the mixture extracted with EtOAc. The combined organics were washed with brine, dried over sodium sulfate, and concentrated. Purification by flash column chromatography gave 4.22 g of the methyl ester as a light yellow solid. Then 3.0 g of the methyl ester (11.5 mmol) was taken up in 20 mL of THF and 10 mL of water and treated with LiOH (monohydrate, 970 mg, 2 equiv). The mixture was heated at 50 °C for 3 h. The solution was acidified with 2 N HCl and extracted with EtOAc and the combined organics were washed with brine, dried over sodium sulfate, and concentrated to give the acid as a colorless solid (2.64 g, 73% yield over two steps). ^{1}H NMR (500 MHz, DMSO) δ 13.11 (br s, 1H), 7.79−7.64 (m, 1H), 7.60 (s, 1H), 7.27 (ddd, J = 8.1, 7.3, 1.6 Hz, 1H), 7.11 (ddd, J = 7.9, 7.3, 1.3 Hz, 1H), 7.04 (dd, J = 8.1, 1.2 Hz, 1H), 4.31−4.26 (t, J = 5.2 Hz, 2H), 3.20 (t, J = 5.2 Hz, 2H).

***N*-(2-Chlorophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno-[2,3-*d*]oxepine-2-carboxamide (18).** A solution of the carboxylic acid (94 mg) was heated with 2 mL of $SOCl_2$ at 80 °C for 2 h. The mixture was concentrated by rotoevaporation, dissolved in 2 mL of CH_2Cl_2, and treated with a solution of 2-chloro-*N*-methylaniline (59 mg), Et_3N (0.11 mL), and a trace amount of DMAP. The mixture was allowed to warm to room temperature to stir overnight. The mixture was diluted with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were concentrated and the residue was purified by flash column chromatography (24 g SiO_2, 10−50% EtOAc in hexanes) to give **18** as a colorless solid (58 mg, 41% yield). ^{1}H NMR (500 MHz, DMSO) δ 7.69−7.60 (m, 2H), 7.57−7.48 (m, 2H), 7.41 (br d, J = 8.1 Hz, 1H), 7.23−7.18 (m, 1H), 7.06−7.01 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.61 (br s, 1H), 4.17 (t, J = 5.0 Hz, 2H), 3.27 s, 3H), 2.95 (br s, 2H). LCMS: $(M)^+$ 370.1.

8-Bromo-3,4-dihydrobenzo[*b*]oxepin-5(2*H*)-one (45). Solid 3-bromophenol (10.0 g, 58 mmol) was added portionwise to a stirred suspension of K_2CO_3 in acetone (100 mL) at room temperature. Sodium iodide (NaI, 1.0 g) was added, followed by ethyl 4-bromobutyrate (9.2 mL, 64 mmol). The reaction mixture was heated at 80 °C overnight, cooled to room temperature, diluted with water, and extracted with ethyl acetate to give crude ethyl 4-(3-bromophenoxy)butanoate that was used in the next saponification without purification. The above crude residue was taken up in 100 mL of THF and 50 mL of water and treated with lithium hydroxide LiOH (hydrate, 4.9 g). The whole was heated at 50 °C for 2 days. The mixture was cooled to room temperature and acidified to pH 1 with 2 N HCl. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine and dried over sodium sulfate to give crude 4-(3-bromophenoxy)butanoic acid as a sticky solid. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.24 (m, 1H), 7.13 (m, 1H), 7.11 (m, 1H), 6.95 (m, 1H), 3.99 (m, 2H), 2.37 (m, 2H), 1.94 (m, 2H). To a stirred suspension of polyphosphoric acid (PPA, ∼60 g) and Celite (∼40 g) in 100 mL of toluene were added crude 4-(3-bromophenoxy)butanoic acid (∼58 mmol) in one portion and 10 mL of toluene rinse. The resultant suspension was heated at 110 °C for 5 h. The toluene was decanted through a plug of Celite, and the remaining slurry was washed repeatedly with toluene and ethyl acetate. The eluent was concentrated and purified by flash column chromatography (4:1 hexane/EtOAc) to give **45** (7 g, ∼50% yield over two steps). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.55 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.35 (dd, J = 8.5, 1.5 Hz, 1H), 4.24 (t, J = 6.5 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H), 2.14 (m, 2H).

Methyl 8-Bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxylate (46). Phosphorus oxychloride (1.88 mL, 20.8 mmol) was added dropwise to DMF (5 mL) at 0 °C. After 30 min a solution of 8-bromo-3,4-dihydrobenzo[*b*]oxepin-5(2*H*)-one (2.0 g, 8. 3 mmol) in 8 mL of DMF was added dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 2 h, then poured slowly over rapidly stirred ice−water. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine, dried over sodium sulfate, and concentrated to give a crude residue which was used in the next step without purification. The residue was dissolved in 10 mL of DMF and treated sequentially with potassium carbonate (2.20 g, 16.6 mmol) and methyl thioglycolate (0.83 mL). The whole was heated at 50 °C overnight, cooled to room temperature, and diluted with water. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, and concentrated. The crude residue was purified by flash column chromatography (20−50% ethyl acetate in hexanes) to give **46** (2.20 g, 78% yield) as a colorless solid. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.70 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.31−7.28 (m, 2H), 4.32 (t, J = 5.0 Hz, 2H), 3.84 (s, 3H), 3.21 (t, J = 5.0 Hz, 2H).

8-Bromo-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (47). A solution of **46** (2.0 g, 5.9 mmol) was suspended in 5 mL of THF and 5 mL of water. LiOH (monohydrate, 620 mg) was added in one portion. The mixture was heated at 50 °C for 3 h. The mixture was cooled to room temperature and acidified with 2 N HCl. The mixture was extracted with EtOAc and the combined organics were washed with brine and dried over sodium sulfate. The crude residue was dissolved in 7 mL of $SOCl_2$ and heated at 80 °C for 2 h. The mixture was cooled to room temperature and concentrated. The crude yellow residue was diluted

with CH_2Cl_2 (10 mL) and cooled to 0°C. A solution of 2-chloro-*N*-methyaniline (963 mg) and Et_3N (1.64 mL) in 5 mL of CH_2Cl_2 was added over a few minutes. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was diluted with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were concentrated and the residue was purified by flash column chromatography (80 g SiO_2, 10−50% EtOAc in hexanes) to give **47** as a colorless solid (2.10 g, 79% over three steps.). ^{1}H NMR (500 MHz, DMSO) δ 7.70−7.60 (m, 2H), 7.56−7.47 (m, 2H), 7.35 (br d, J = 8.2 Hz, 1H), 7.26−7.18 (overlapping m, 2H), 6.56 (br s, 1H), 4.19 (br t, J = 4.8 Hz, 2H), 3.31 (s, 3H), 2.94 (br s, 2H). MS (ESI+): $(M + H)^+$ 449.9.

***N*-(2-Chlorophenyl)-*N*-methyl-8-(1*H*-pyrazol-5-yl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (19).** A solution of **47** (200 mg, 0.47 mmol) in MeCN (1.5 mL) and water (1.5 mL) was treated with 3-pyrazoleboronic acid (65 mg) and potassium acetate (150 mg). The mixture was purged with nitrogen and then charged with $Pd(PPh_3)_4$ (41 mg). The mixture was heated by microwave irradiation at 140 °C for 20 min. The mixture was diluted with water and extracted with ethyl acetate. Purification by reverse phase HPLC gave **19** as a colorless solid (194 mg, 83% yield). ^{1}H NMR (400 MHz, DMSO) δ 13.30, 12.93 (br s, 0.2 + 0.8H, pyrazole tautomer NHs), 7.76−7.34 (overlapping m, 8H), 6.73 (s, 1H), 6.59 (br s, 1H), 4.20 (br s, 2H), 3.30 (s, 3H, obstructed by water), 2.97 (br s, 2H). LCMS: $(M)^+$ 436.1.

***N*-(2-Chlorophenyl)-8-cyano-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carboxamide (20).** A solution of **47** (50 mg, 0.11 mmol) in 1 mL of DMF was treated with CuCN (30 mg, 3 equiv). The mixture was heated by microwave irradiation at 250 °C for 20 min. Saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The combined extracts were filtered over Celite, concentrated and the residue was purified by reverse phase HPLC to give **20** (16 mg, 36% yield). ^{1}H NMR (500 MHz, DMSO) δ 7.66 (br s, 2H), 7.62−7.45 (overlapping m, 4H), 6.65 (br s, 1H), 4.23 (br s, 2H), 3.29 (br s, 3H), 3.01 (br s, 2H). LCMS: $(M)^+$ 395.1.

8-Acetamido-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (21). A solution of **47** (100 mg, 0.22 mmol), cesium carbonate (158 mg, 2.2 equiv), acetamide (20 mg, 1.5 equiv), and xantphos (13 mg, 0.10 equiv) in 2 mL of dioxane was sparged with nitrogen. Pd_2dba_3 (10 mg, 0.05 equiv) was added and the mixture heated at 100 °C in a sealed tube for 8 h. Water was added and the mixture extracted with EtOAc. Concentration and purification by reverse phase HPLC gave **21** (53 mg, 56% yield). ^{1}H NMR (500 MHz, DMSO) δ 10.03 (s, 1H), 7.65 (m, 2H), 7.52 (m, 2H), 7.36 (m, 2H), 7.18 (m, 1H), 6.50 (br s, 1H), 4.15 (br s, 2H), 3.27 (s, 3H), 2.91 (br s, 2H), 2.03 (s, 3H). LCMS: $(M)^+$ 427.1.

Methyl 2-((2-Chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate (22). Under ambient atmosphere, a solution of **47** (100 mg, 0.22 mmol) in 2 mL of THF was treated sequentially with molybdenum hexacarbonyl (58 mg, 0.22 mmol), methylamine (2.0 M in THF, 0.33 mL, 0.66 mmol), and Hermann's catalyst (31 mg, 15 mol %). DBU (0.02 mL, 0.11 mmol) was added and the vial quickly sealed. The mixture was heated by microwave irradiation at 150 °C for 20 min. The mixture was diluted with EtOAc and filtered over Celite. Concentration and purification by flash column chromatography and then reverse-phase HPLC gave **22** (25 mg, 26% yield). ^{1}H NMR (500 MHz, DMSO) δ 8.42 (br q, 1H), 7.70−7.60 (m, 2H), 7.57−7.50 (m, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 6.56 (br s, 1H), 4.20 (br s, 2H), 3.28 (s, 3H), 2.97 (br s, 2H), 2.75 (d, J = 4.5 Hz, 3H). LCMS: $(M)^+$ 427.1.

Methyl 2-((2-Chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate. A mixture of 8-bromo-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carboxamide (10 g, 0.022 mol), $Pd(OAc)_2$ (2.47 g, 0.011 mmol), dppf (10 g, 0.018 mol), and triethylamine (4.45 g, 0.044 mol) in DMF (50 mL) and MeOH (100 mL) was stirred under CO atmosphere (50 psi) at 70 °C for 2 days. After it was filtered and concentrated, the crude product was purified by column chromatography (hexanes/EtOAc = 5:1) to give the desired product (6.59 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 1.6, 7.2 Hz, 2H), 7.48−7.42 (m, 2H), 7.35−7.30 (m, 3H), 6.72 (s, 1H), 4.18 (t, J = 5.2 Hz, 2H), 3.83 (s, 3H), 3.33 (s, 3H), 2.99 (t, J = 5.2 Hz, 2H). MS (ESI+): $(M + H)^+$ 428.0.

2-[(2-Chlorophenyl)methylcarbamonyl]-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-8-carboxylic Acid. To a solution of methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]-thieno[2,3-*d*]oxepine-8-carboxylate (6.59 g, 15.4 mmol) in THF (25 mL) and water (25 mL) was added LiOH monohydrate (1.29 g). After the solution was heated at 50 °C for 2 h, it was cooled to room temperature and acidified with 2 N HCl. The precipitate was separated and dried to give the desired product (6.06 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.2, 8.0 Hz, 2H), 7.48−7.44 (m, 2H), 7.37−7.30 (m, 3H), 6.75 (s, 1H), 4.19 (t, J = 5.2 Hz, 2H), 3.33 (s, 3H), 3.00 (t, J = 5.2 Hz, 2H). MS (ESI+): $(M + H)^+$ 414.0.

2-((2-Chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-8-carbonyl Chloride. A solution of 2-[(2-chlorophenyl)methylcarbamonyl]-4,5-dihydro-6-oxa-1-thiabenzo-[*e*]azulene-8-carboxylic acid (200 mg, 0.24 mmol) in $SOCl_2$ (4 mL) was heated at 80 °C for 2 h. It was concentrated to give the crude acid chloride, which used in the next step without further purification.

***N*^{2}-(2-Chlorophenyl)-*N*^{8}-ethyl-*N*^{2}-methyl-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-2,8-dicarboxamide (23).** A solution of 2-[(2-chloro-phenyl)methylcarbamonyl]-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-8-carboxylic acid (200 mg, 0.24 mmol) in $SOCl_2$ (4 mL) was heated at 80 °C for 2 h. It was concentrated to give the crude acid chloride. The crude acid chloride was taken up in THF (20 mL) and added to a solution of $CH_3CH_2NH_2$ (42 mg, 0.92 mmol) and pyridine (0.2 mL) in THF (5 mL). After the mixture was stirred at room temperature overnight, it was concentrated, dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated to give the desired product (119 mg, 27% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53−7.47 (m, 2H), 7.42−7.33 (m, 2H), 6.73 (s, 1H), 6.03 (s, 1H), 4.23 (t, J = 4.8 Hz, 2H), 3.50−3.42 (m, 2H), 3.38 (s, 3H), 3.03 (t, J = 4.8 Hz, 2H), 1.27−1.21 (m, 3H). MS (ESI+): $(M + H)^+$ 441.0.

8-Bromomethyl-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azuene-2-carboxylic Acid (2-Chlorophenyl)methylamide. A mixture of 2-[(2-chlorophenyl)methylcarbamonyl]-4,5-dihydro-6-oxa-1-thiabenzo-[*e*]azulene-8-carboxylic acid methyl ester (1 g, 2.3 mmol) and lithium aluminum hydride in dry THF (30 mL) was stirred at 0 °C under nitrogen for 30 min and monitored by LCMS. The reaction mixture was quenched by the slow addition of water with stirring and warmed to room temperature. The aqueous layer was extracted with EtOAc, and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was recrystallized from MeOH to give crude 8-hydromethyl-4,5-dihydro-6-oxa-1-thiabenzo-[*e*]azuene-2-carboxylic acid (2-chlorophenyl)methylamide as a yellow solid (LCMS (ESI+): $(M + H)^+$ 399.9). To a solution of this intermediate (1.25 g, 3.13 mmol) in THF (20 mL) was added a solution of PBr_3 (0.88 mL) in CH_2Cl_2 (20 mL) dropwise. The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a yellow oil. The crude product was recrystallized from MeOH to give the titled product as a yellow solid (1.4 g, 48% yield over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, J = 7.6 Hz, 1H), 7.41−7.33 (m, 4H), 6.98 (dd, J = 2.4, 4.0 Hz, 2H), 6.73 (s, 1H), 4.38 (s, 2H), 4.21 (t, J = 5.2 Hz, 2H), 3.37 (s, 3H), 3.00 (t, J = 5.2 Hz, 2H). LCMS (ESI+): $(M + H)^+$ 461.8.

***N*-(2-Chlorophenyl)-*N*-methyl-8-((methylamino)methyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (24).** To a solution of CH_3NH_2 (0.25 mL) in EtOH was added Et_3N (0.5 mL) and 8-bromomethyl-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azuene-2-carboxylic acid (2-chlorophenyl)methylamide (250 mg, 0.55 mmol). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was added to water, and the aqueous layer was extracted with EtOAc (20 mL × 3). The sample was dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography (CH_2Cl_2/MeOH = 10:1) to give **24** as a light yellow solid (96 mg, 43%). ^{1}H NMR ($CDCl_3$, 400

MHz) δ 9.73 (br, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.37−7.29 (m, 4H), 7.15 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.82 (s, 1H), 4.12 (t, J = 4.8 Hz, 2H), 3.90 (s, 2H), 3.31 (s, 3H), 2.94 (t, J = 4.8 Hz, 2H), 2.45 (s, 3H). LCMS (ESI+): $(M + H)^+$ 412.9.

N^8-(2-Aminoethyl)-N^2-(2-chlorophenyl)-N^2-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2,8-dicarboxamide (25). **25** was prepared according to the procedure described for **23** from 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-8- carbonyl chloride (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.10 (m, 3H), 7.45−7.19 (m, 5H), 6.30 (s, 1H), 3.92 (s, 2H), 3.57−3.10 (m, 9H), 2.70−2.59 (m, 2H). MS (ESI +): $(M + H)^+$ 456.0.

(3-Bromophenyl)acetic Acid Methyl Ester. A solution of (3-bromophenyl)acetic acid (5 g, 23.3 mmol) and concentrated H_2SO_4 (2 mL) in CH_3OH (100 mL) was stirred at reflux for 3 h. The solution was cooled, concentrated, and diluted with water and EtOAc. The organic layer was washed with water and dried to give (3-bromophenyl)acetic acid methyl ester (5.1 g, 96%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.47 (s, 1H), 7.40 (m, 1H), 7.25 (m, 2H), 3.68 (s, 2H), 3.58 (s, 3H). ESI-MS, m/z $(M + H^+)$: 228.

[3-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]-acetic Acid Methyl Ester. A mixture of (3-bromophenyl)acetic acid methyl ester (2.0 g, 8.7 mmol), 4,4,5,5,4′,4′,5′,5′-octamethyl[2,2′]bi-[[1,3,2]dioxaborolanyl] (3.33 g, 13.1 mmol), KOAc (2.56 g, 26.1 mmol), and Pd(dppf)Cl_2 (400 mg) in DMSO (40 mL) was stirred at 80 °C for 4 h. The cooled solution was poured into water and extracted with EtOAc. The organic layer was washed with water, dried, concentrated, and purified by column to afford the crude product [3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]acetic acid methyl ester (1.6 g). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (s, 1H), 7.54 (d, J = 1.2 Hz, 1H), 7.3 (m, 2H), 3.7 (s, 2H), 3.6 (s, 3H), 1.28 (s, 12H).

Methyl 2-(3-(2-((2-Chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepin-8-yl)phenyl)acetate. A mixture of 8-bromo-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]voxepine-2-carboxamide (500 mg, 1.11 mmol), [3-(4,4,5,5-tetramethyl[1, 3, 2]dioxaborolan-2-yl)phenyl]acetic acid methyl ester (615 mg, 2.23 mmol), sodium carbonate (460 mg, 3.33 mmol), and Pd(dppf)Cl_2 (40 mg) in CH_3CN (4 mL) was heated under microwave irradiation at 100 °C for 50 min. The mixture was filtered through Celite, concentrated, and purified by preparative HPLC to afford the product methyl 2-(3-(2-((2-chlorophenyl)-(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepin-8-yl)-phenyl)acetate (200 mg, 35% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.65−7.63 (m, 2H), 7.62−7.48 (m, 5H), 7.47−7.32 (m, 2H), 7.24−7.22 (m, 2H), 6.57 (s, 1H), 4.19 (t, J = 4.8 Hz, 2H), 3.72 (s, 2H), 3.59 (s, 3H), 3.25 (s, 3H), 2.95(s, 2H). LCMS (ESI+): $(M + H)^+$ 518.2.

2-(3-(2-((2-Chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepin-8-yl)phenyl)acetic Acid (26). A mixture of methyl 2-(3-(2-((2-chlorophenyl)(methyl)-carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepin-8-yl)phenyl)-acetate (100 mg, 2.4 mmol) and LiOH (16.2 mg, 0.39 mmol) in THF/H_2O (10 mL/10 mL) was stirred at 50 °C for 2 h. After the solution was cooled, it was adjusted to pH 2 with HCl (aqueous, 6 N). The resulting solution was concentrated and extracted with EtOAc. The combined organic layer was washed with water and concentrated to afford the product (90 mg, 92% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.41 (m, 4H), 7.34−7.29 (m, 4H), 7.19 (s, 1H), 7.15−7.13 (m, 2H), 6.71 (s, 1H), 4.20 (t, J = 5.2 Hz, 2H), 3.64 (s, 2H), 3.33 (s, 3H), 2.98 (t, J = 5.2 Hz, 2H). LCMS (ESI+): $(M + H)^+$ 501.7.

***N*-(2-Chlorophenyl)-8-(3-cyanophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide.** A mixture of 8-bromo-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno [2,3-*d*]oxepine-2-carboxamide (500 mg, 1.11 mmol), 3-cyanophenylboronic acid (200 mg, 1.25 mmol), sodium carbonate (400 mg, 3 mmol), and Pd$(PPh_3)_2Cl_2$(100 mg) in CH_3CN (4 mL) was heated under microwave irradiation at 100 °C for 40 min. The mixture was filtered through Celite, concentrated, and purified by column to afford the product (400 mg, 69% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.70−7.59 (m, 3H), 7.58−7.42 (m, 4H), 7.40 (s, 1H), 6.65 (s, 1H), 4.28−4.19 (m, 2H), 3.25 (s, 3H), 2.98−2.90 (m, 2H). LCMS (ESI+): $(M + H)^+$ 471.1.

8-(3-(Aminomethyl)phenyl)-*N*-(2-chlorophenyl)-*N*-methyl-4,5-dihydrobenzo[b]thieno[2,3-*d*]oxepine-2-carboxamide (27). A solution of *N*-(2-chlorophenyl)-8-(3-cyanophenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (300 mg, 0.63 mmol), Raney Ni (1 g), and $NH_3{\cdot}H_2O$ (2.5 mL) in MeOH (50 mL) was stirred at 30 °C under hydrogen atmosphere (50 psi). The reaction mixture was filtered through Celite, concentrated, washed with water, and purified by preparative TLC to afford **27** (34 mg, 11% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.38 (s, 2H), 7.87 (s, 1H), 7.71−7.65 (m, 3H), 7.34−7.41 (m, 6H), 7.35 (s, 1H), 6.59 (s, 1H), 4.22 (s, 2H), 4.07 (s, 2H), 3.33 (s, 3H), 2.98 (s, 2H). LCMS (ESI+): $(M + H)^+$ 475.1.

N^2-(2-Chlorophenyl)-N^2-methyl-4,5-dihydrobenzo[*b*]thieno-[2,3-*d*]oxepine-2,9-dicarboxamide (28). To a mixture of **30** (120 mg) and K_2CO_3 (49 mg) in dry DMSO (2 mL) was added 33% H_2O_2 (40 μL). The reaction mixture stirred overnight at room temperature. Ice was added to the resulting solution, and the solid formed was collected, washed with water, and dried to afford **30** (119 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, J = 1.81 Hz, 1H), 7.60−7.55 (m, 2H), 7.45−7.39 (m, 3H), 7.03 (d, J = 8.44 Hz, 1H), 6.71 (s, 1H), 5.75 (br s, 2H-NH_2), 4.28 (t, J = 5.06 Hz, 2H), 3.42 (s, 3H), 3.04 (t, J = 5.02, 2H). LCMS (ESI+): $(M + H)^+$ 413.14.

N^2-(2-Chlorophenyl)-N^9-ethyl-N^2-methyl-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-2,9-dicarboxamide (29). A mixture of **28** (70 mg), TFA (37.5 μL), triethylsilane (80 μL), and acetaldehyde (28 μL) in acetonitrile was stirred at room temperature overnight and then was concentrated. Purification on silica yielded **29** (34 mg, 46% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (m, 1H), 7.47−7.44 (m, 2H), 7.36−7.29 (m, 3H), 6.91 (d, J = 8.41 Hz, 1H), 6.59 (s, 1H), 5.94 (m, 1H), 4.17 (t, J = 5.10 Hz, 2H), 3.43 (m, 2H), 3.32 (s, 3H), 2.93 (t, J = 5.07 Hz, 2H), 1.21 (t, J = 7.28, 3H). LCMS (ESI+): $(M + H)^+$ 482.15.

3-Bromo-4-(2-thiophen-3-ylethoxy)benzonitrile. To a solution of 3-bromo-4-hydroxybenzonitrile (8.50 g) in THF (200 mL) were added 2-(3-thienyl)ethanol (4.42 mL) and triphenylphosphine (11.80 g). The mixture was cooled to 0 °C, and diethylazodicarboxylate (7.09 mL) was added dropwise. The mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue redissolved in diethyl ether (100 mL). The mixture was stirred for 10 min at 0 °C and then filtered. The filtrate was washed with saturated aqueous sodium carbonate (80 mL), 1 M HCl (80 mL), and brine, dried over $MgSO_4$, concentrated, then purified on silica gel to afford the desired compound (11.7 g, 95% yield).

4,5-Dihydro-6-oxa-1-thiabenzo[*e*]azulene-9-carbonitrile. To a solution of 3-bromo-4-(2-thiophen-3-ylethoxy)benzonitrile (3.08 g) in DMF (20 mL) was added palladium acetate (224 mg), PPh_3 (525 mg), and K_2CO_3 (2.76 g), and the mixture was heated at 90 °C for 16 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (60 mL) and filtered. The filtrate was washed with brine, dried over $MgSO_4$, concentrated, and purified by silica gel chromatography to afford the title compound (1.75 g, 77% yield).

2-Bromo-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-9-carbonitrile. To a solution of 4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-9-carbonitrile (4.58 g) in CH_2Cl_2 (30 mL) and acetic acid (30 mL) was added *N*-bromosuccinimide (3.95 g), and the mixture was stirred for 16 h at room temperature. Water (100 mL) was added and the solid collected by filtration and air-dried to give the title compound (3.0 g, 49% yield).

9-Cyano-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-2-carboxylic Acid. To a solution of 2-bromo-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-9-carbonitrile (1.0 g) in THF (25 mL) at −78 °C was added *n*-BuLi (1.44 mL), and the mixture was allowed to warm to −10 °C over 1 h. The mixture was then recooled to −78 °C, and carbon dioxide was bubbled through the solution for 15 min. The mixture was then allowed to warm to room temperature over 4 h. The reaction was quenched with water (5 mL) and the product extracted into saturated aqueous Na_2CO_3 (30 mL). The aqueous layer was washed with ethyl acetate (30 mL) and then acidified to pH 2−3 with

2 M HCl. The product was then extracted into ethyl acetate and the organic layers were dried over $MgSO_4$ and concentrated to give the title compound (0.43 g, 48% yield).

***N*-(2-Chlorophenyl)-9-cyano-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carboxamide (30).** To a solution of 9-cyano-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-2-carboxylic acid (300 mg) in CH_2Cl_2 (10 mL) was added DMF (1 drop) and oxalyl chloride (0.165 mL), and the mixture was stirred for 30 min at room temperature. The mixture was concentrated, and the residue was dissolved in acetonitrile (10 mL). To this solution were added 2-chloro-*N*-methylaniline (0.165 mL) and K_2CO_3 (308 mg), and the mixture was stirred for 16 h at room temperature. The mixture was partitioned between water (40 mL) and ethyl acetate (30 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified on silica to afford **30** (149 mg, 34% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 1.65 Hz, 1H), 7.57 (m, 1H), 7.47−7.38 (m, 4 H), 7.03 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 4.29 (t, J = 5.02 Hz, 2 H), 3.41 (s, 3H), 3.08 (t, J = 5.00 Hz, 2H). LCMS (ESI+): $(M + H)^+$ 395.

4-Amino-3-chloro-*N*,*N*-dimethylbenzamide. *i*-Pr_2NEt (116 mL, 699.5 mmol) was added to a suspension of dimethylamine hydrochloride (28.51 g, 349.6 mmol) in THF (600 mL). The mixture was stirred at room temperature for 0.5 h. Then 4-amino-3-chlorobenzoic acid (30.00 g, 174.8 mmol) and HATU (86.41 g, 227.2 mmol) were added to the above suspension separately. The reaction mixture was stirred for an additional 1.5 h. It was concentrated, and the residue was partitioned between EtOAc (300 mL) and water (150 mL). The organic phase was washed with water, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel chromatography (hexanes/EtOAc = 1:1) to afford the pure product (34.72 g, 89% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 4.24 (br, 2H), 3.05 (s, 6H).

8-Bromo-*N*-(2-chloro-4-(dimethylcarbamoyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-*d*]oxepine-2-carboxamide. A solution of 8-bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxylic acid (25.00 g, 76.9 mmol) in $SOCl_2$ (200 mL) was heated at 90−100 °C for 3 h. It was concentrated to give the crude acid chloride. A suspension of the acid chloride in THF (600 mL) was treated with a solution of 4-amino-3-chloro-*N*,*N*-dimethylbenzamide (18.23 g, 92.3 mmol) and pyridine (14 mL) in THF (200 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. After it was concentrated, water (200 mL) was added to the mixture. The resulting precipitate was collected by filtration, washed with water, and dried to give the desired product (29.88 g, 77% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.14 (s, 1H), 7.86 (s, 1H), 7.67−7.57 (m, 3H), 7.40−7.25 (m, 3H), 4.32 (t, J = 5.2 Hz, 2H), 3.21 (t, J = 5.2 Hz, 2H), 2.95 (s, 3H), 2.92 (s, 3H).

8-Bromo-*N*-(2-chloro-4-(dimethylcarbamoyl)phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide. To solution of 8-bromo-*N*-(2-chloro-4-(dimethylcarbamoyl)-phenyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (29.0 g, 57.3 mmol) and Cs_2CO_3 (37.40 g, 114.7 mmol) in DMF (600 mL) was slowly added CH_3I (30 mL, 479.8 mmol). The reaction mixture was stirred at room temperature overnight. DMF (about 200 mL) was removed under reduced pressure, and water (100 mL) was added to the mixture.. The resulting precipitate was filtered, washed with water, and dried to give the desired product (29.50 g, 99% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.72−7.68 (m, 2H), 7.52−7.49 (m, 1H), 7.30−7.20 (m, 3H), 6.76 (s, 1H), 4.19 (s, 2H), 3.29 (s, 3H), 3.00 (s, 3H), 2.96 (s, 2H), 2.93 (s, 3H).

Methyl 2-((2-Chloro-4-(dimethylcarbamoyl)phenyl)(methyl)-carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate. A mixture of 8-bromo-*N*-(2-chloro-4-(dimethylcarbamoyl)phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno-[2,3-*d*]oxepine-2-carboxamide (27.0 g, 51.9 mmol), dppf (23.20 g, 41.9 mmol), $Pd(OAc)_2$ (5.8 g, 25.8 mmol), and Et_3N (27 mL) in DMF (270 mL) and MeOH (400 mL) was stirred under a CO atmosphere (50 psi) at 70 °C for 2 days. The reaction mixture was filtered, and the filtrate was concentrated. The crude product was purified by silica gel chromatography (hexanes/EtOAc = 1:1) to give the product (23.0 g, 89% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.74−7.69 (m, 2H), 7.58−7.47 (m, 4H), 6.79 (s, 1H), 4.23 (t, J = 4.8 Hz, 2H), 3.83 (s, 3H), 3.31 (s, 3H), 3.01 (br, 5H, CH_2), 2.94 (s, 3H).

2-((2-Chloro-4-(dimethylcarbamoyl)phenyl)(methyl)-carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylic Acid. Methyl 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)-(methyl)carbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate (25.0 g, 50.1 mmol) was dissolved in THF (50 mL) and water (50 mL). The solution was treated with LiOH·H_2O (5.26 g, 125.3 mmol). The reaction mixture was stirred at room temperature for 2 h. THF was removed under reduced pressure, and the mixture was acidified by HCl (2 N). The resulting precipitate was filtered, washed with water, and dried to give desired product (20.00 g, 82% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66−7.60 (m, 3H), 7.46−7.42 (m, 3H), 6.99 (s, 1H), 4.23 (t, J = 5.0 Hz, 2H), 3.39 (s, 3H), 3.14 (s, 3H), 3.07 (t, J = 5.0 Hz, 2H), 3.02 (s, 3H).

***N*^{2}-(2-Chloro-4-(dimethylcarbamoyl)phenyl)-*N*^{2},*N*^{8}-dimethyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2,8-dicarboxamide (31).** To a suspension of H_2NMe·HCl (5.02 g, 74.4 mmol) in THF (180 mL), *i*-Pr_2NEt (16.83 g, 130.2 mmol) was added. The mixture was stirred at room temperature for 0.5 h. Then 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-8-carboxylic acid (9.00 g, 18.6 mmol) and HATU (21.22 g, 55.8 mmol) were added to the above suspension separately. The reaction mixture was stirred at room temperature for 2 h. Solvent was removed, and the resulting mixture was dissolved in CH_2Cl_2 (200 mL), washed with HCl (2 N, 200 mL) and water (100 mL), and dried over Na_2SO_4. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH = 10:1) to give the product (3.70 g, 40% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (s, 1H), 7.42−7.29 (m, 4H), 6.92 (s, 1H,), 6.34 (d, J = 4.0 Hz, 1H), 4.20 (t, J = 5.0 Hz, 2H), 3.37 (s, 3H), 3.12 (s, 3H), 3.04−2.98 (m, 8H, CH_2). LCMS (ESI+): $(M + H)^+$ 498.2.

3-Amino-4-chloro-*N*,*N*-dimethylbenzamide. 3-Amino-4-chlorobenzoic acid (3.11 g), dimethylamine hydrochloride (2.96 g), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexofluorophosphate (8.09 g), and *N*,*N*-diisopropylethylamine (12.6 mL) were combined in 50 mL of anhydrous tetrahydrofuran, and the mixture was allowed to stir for 12 h. The reaction mixture was partitioned with saturated sodium bicarbonate and ethyl acetate. The organic layer was concentrated and then purified by silica gel chromatography on a Teledyne ISCO 140 g functionalized amine column to give the desired compound (3.5 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.21 (d, J = 8.1 Hz, 1H), 6.84−6.79 (d, J = 1.7 Hz, 1H), 6.72−6.66 (dd, J = 8.2, 1.7 Hz, 1H), 4.40−3.90 (s, 2H), 3.07 (s, 3H), 2.97 (s, 3H). LCMS (ESI+): $(M + H)^+$ = 199.0

8-Bromo-*N*-(2-chloro-5-(dimethylcarbamoyl)phenyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide. 8-Bromo-4,5-dihydrothieno[3,2-*d*][1]benzoxepine-2-carboxylic acid (816 mg) was suspended in thionyl chloride (10 mL) and heated at 85 °C with a Vigreux condensation column attached for 2 h. The mixture was cooled to room temperature and concentrated. Then 35 mL of anhydrous THF was added and the mixture was cooled to 0 °C. 3-Amino4-chloro-*N*,*N*-dimethylbenzamide (548.3 mg) in 5 mL of anhydrous THF and pyridine (0.609 mL) were added. The mixture was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was concentrated and purified by silica gel chromatography (0−100% ethyl acetate in heptanes) to give the desired product (1.09 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.49 (br s, 1H), 7.65−7.59 (d, J = 8.5 Hz, 1H), 7.51−7.6 (d, 1H), 7.49−7.46 (br s, 1H), 7.28−7.25 (m, 2H), 7.25−7.23 (d, J = 1.7 Hz, 1H), 7.23−7.21 (br s, 1H), 4.42−4.34 (t, J = 5.1 Hz, 2H), 3.33−3.23 (t, J = 5.1 Hz, 2H), 3.14−3.08 (br s, 6H). LCMS (ESI+): $(M + H)^+$ = 506.1.

8-Bromo-*N*-(2-chloro-5-(dimethylcarbamoyl)phenyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide. 8-Bromo-*N*- [2-chloro-5-(dimethylcarbamoyl)phenyl]-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide (1.09 g) was dissolved in DMF (50 mL), and cesium carbonate (843 mg) was added followed by methyl iodide (0.15 mL). The mixture was stirred

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at room temperature overnight. The mixture was diluted with water, and the aqueous layer was extracted with ethyl acetate. The sample was purified by silica gel chromatography (25−100% ethyl acetate in heptanes) and concentrated to give the desired compound (1.12 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.54 (d, J = 8.2 Hz, 1H), 7.49−7.43 (dd, J = 8.2, 1.9 Hz, 1H), 7.41−7.37 (d, J = 1.9 Hz, 1H), 7.25−7.22 (d, J = 3.6 Hz, 1H), 7.17−7.12 (d, J = 2.0 Hz, 1H), 7.10−7.02 (dd, J = 8.5, 2.0 Hz, 1H), 6.93−6.87 (s, 1H), 4.25−4.16 (t, J = 5.2 Hz, 2H), 3.44−3.34 (s, 3H), 3.09−3.05 (s, 3H), 3.03−2.99 (m, J = 2.9 Hz, 3H), 2.88−2.84 (br s, 3H). LCMS (ESI+): $(M + H)^+$ = 520.0.

Methyl 2-(2-Chloro-5-(dimethylcabamoyl)-phenylcarbamoyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate (32). **32** was prepared in analogy to **22** (33% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.56−8.37 (d, J = 4.6 Hz, 1H), 7.79−7.64 (m, 2H), 7.61−7.37 (m, J = 36.2, 11.3 Hz, 4H), 6.78−6.64 (s, 1H), 4.23−4.16 (t, J = 4.0 Hz, 2H), 3.31−3.27 (s, 3H), 3.03−2.98 (d, J = 5.9 Hz, 5H), 2.98−2.95 (s, 3H), 2.89−2.85 (s, 3H), 2.78−2.73 (d, J = 4.5 Hz, 3H). LCMS (ESI+): $(M + H)^+$ = 498.9

Methyl 4-Amino-3-chlorobenzoate. $SOCl_2$ (42.7 mL, 585 mmol) was slowly added into MeOH (300 mL) at 0 °C, and the solution was stirred for 1 h at 0 °C. Then 4-amino-3-chlorobenzoic acid (20.0 g, 117 mmol) was added into the above solution in one portion at 0 °C. After addition, it was allowed to reach room temperature and stirred for 2 days. The reaction mixture was concentrated to remove the solvent and the remaining $SOCl_2$. Water (200 mL) was added to the residue, and $NaHCO_3$ (11.80 g, 140 mmol) was added in one portion. The mixture was stirred at room temperature for half an hour, and it was extracted with EtOAc (150 mL × 2). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give the desired product (20.45 g, 94% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 1H), 7.76−7.73 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.48 (s, 2H), 3.84 (s, 3H). LCMS (ESI+): $(M + H)^+$ 185.8.

Methyl 4-(8-Bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-3-chlorobenzoate. 8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-*d*]oxepine-2-carboxylic acid (25.0 g, 77 mmol) was dissolved in $SOCl_2$ (300 mL). After the reaction mixture was heated at reflux for 4 h it was concentrated to remove the remaining $SOCl_2$ to give the crude 8-bromo-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carbonyl chloride. NaH (6.15 g, 154 mmol, 60% in mineral oil) was slowly added to the solution of methyl 4-amino-3-chlorobenzoate (25.55 g, 154 mmol) in THF (200 mL). The suspension of the above acid chloride (25.42 g, 77 mmol) in THF (300 mL) was added into the above solution at 0 °C. After addition, the reaction mixture was stirred at room temperature overnight. Solvent was removed and the residue was washed with water and dried to give the desired product (15.5 g, 49% yield). LCMS (ESI+): $(M + H)^+$ 506.0.

Methyl 4-(8-Bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno-[2,3-*d*]oxepine-2-carboxamido)-3-chlorobenzoate. To a solution of methyl 4-(8-bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-3-chlorobenzoate (18.16 g, 37 mmol) and Cs_2CO_3 (24.01 g, 74 mmol) in DMF (500 mL) was added CH_3I (23 mL, 368 mmol). The reaction mixture was stirred at room temperature overnight. DMF was removed under reduced pressure, and water (200 mL) was added to the mixture. The resulting precipitate was filtered, washed with water, and dried to give the desired product (15.0 g, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 1.6 Hz, 1H), 7.99 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.43−7.08 (m, 4H), 6.73 (s, 1H), 4.21 (t, J = 5.2 Hz, 2H), 3.96 (s, 3H), 3.39 (s, 3H), 2.99 (t, J = 5.2 Hz, 2H). LCMS (ESI+): $(M + H)^+$ 506.0.

4-(8-Bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-3-chlorobenzoic Acid. To the suspension of methyl 4-(8-bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno [2,3-*d*]oxepine-2-carboxamido)-3-chlorobenzoate (1.0 g, 1.97 mmol) in THF (8 mL) and H_2O (8 mL) was added LiOH·H_2O (166 mg, 3.96 mmol). The reaction mixture was stirred at room temperature overnight. It was acidified with HCl (2 N) to pH 2−3 and concentrated to remove most of the solvent. The resulting precipitate was washed with water and dried to give the desired product (0.58 g, 57% yield). LCMS (ESI+): $(M + H)^+$ 491.8.

8-Bromo-*N*-(2-chloro-4-(4-methylpiperazine-1-carbonyl)-phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide. To a mixture of 1-methylpiperazine (0.32 g, 3.2 mmol), *i*-Pr_2NEt (1.2 mL, 6.9 mmol), and HATU (0.79 g, 2.08 mmol) in THF (20 mL) was added 4-(8-bromo-*N*-methyl-4,5-dihydrobenzo-[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)-3-chlorobenzoic acid (0.79 g, 1.6 mmol) under nitrogen at room temperature. The reaction mixture was stirred overnight, diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel flash column chromatography (hexanes/EtOAc = 2:1) to give the titled product (0.82 g, 89% yield). LCMS (ESI+): $(M + H)^+$ 573.9.

N^2-(2-Chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N^2,N^8-dimethyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2,8-dicarboxamide (33). A suspension of 8-bromo-*N*-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carboxamide (450 mg, 0.78 mmol), $Pd(OAc)_2$ (9 mg, 0.039 mmol), Xantphos (45 mg, 0.078 mmol), $MeNH_2$·HCl (79 mg, 1.15 mmol), and Na_2CO_3 (240 mg, 2.3 mmol) in toluene (10 mL) was heated at 80 °C under an atmosphere of CO (balloon) overnight. Then it was filtered, concentrated, and purified by silica gel flash column chromatography (hexanes/EtOAc = 1:3) to give the titled product (162 mg, 38% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1H), 7.43−7.31 (m, 5H), 6.97 (s, 1H), 6.35 (q, J = 4.8 Hz, 1H), 4.24 (t, J = 5.2 Hz, 2H), 3.80 (s, 2H), 3.45 (s, 2H), 3.39 (s, 3H), 3.07 (t, J = 5.2 Hz, 2H), 2.99 (d, J = 4.8 Hz, 3H), 2.52 (s, 2H), 2.32 (s, 5H). LCMS (ESI+): $(M + H)^+$ 553.0.

Methyl 3-Amino-4-chlorobenzoate. $SOCl_2$ (107 mL, 1.47 mol) was slowly added to MeOH (800 mL) at 0 °C, and the solution was stirred for 1 h at 0 °C. Then 3-amino-4-chlorobenzoic acid (50.0 g, 0.29 mmol) was added to the above solution in one portion at 0 °C. It was allowed to reach room temperature and stirred for 2 days. The reaction mixture was concentrated to remove the solvent and remaining $SOCl_2$. Water (200 mL) was added to the residue and basified with saturated $NaHCO_3$ solution to pH > 7, and the resulting precipitate was filtered and dried to give the desired product (49 g, 91% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.26 (m, 3H), 4.18 (br, 2H), 3.88 (s, 3H).

Methyl 3-(8-Bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-4-chlorobenzoate. A solution of 8-bromo-4,5-dihydro-6-oxa-1-thiabenzo[*e*]azulene-2-carboxylic acid (25 g) in $SOCl_2$ (200 mL) was heated at 80°C for 3 h. It was concentrated to give the crude acid chloride. A suspension of the crude acid chloride (~0.077 mol) from the above in THF (1000 mL) at 0 °C was treated with a solution of 3-amino-4-chlorobenzoic acid methyl ester (15.7 g, 1.1 equiv) and pyridine (30 mL) in THF (100 mL). The mixture was allowed to reach room temperature overnight. The volume of reaction mixture was reduced by 50% under reduced pressure, and it was diluted with water. The resulting precipitate was filtered and washed with water and Et_2O. The filter cake was dried to a constant weight under vacuum to give the desired product (32.9 g, 87% yield). LCMS: (ESI, m/z) = 494 $[M + H]^+$.

Methyl 3-(8-Bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno-[2,3-*d*]oxepine-2-carboxamido)-4-chlorobenzoate. To a solution of methyl 3-(8-bromo-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-4-chlorobenzoate (32 g, 65 mmol) and Cs_2CO_3 (42.4 g, 130 mmol) in DMF (500 mL) was added CH_3I (12 mL, 195 mmol). The reaction mixture was stirred at room temperature overnight. DMF was removed under reduced pressure, and water was added to the mixture. The resulting precipitate was filtered, washed with water, and dried to give the desired product (31 g, 94% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07−7.08 (m, 6H), 6.81 (s, 1H), 4.22 (t, J = 5.2 Hz, 2H), 3.94 (s, 3H), 3.40 (s, 3H), 3.01 (t, J = 5.2 Hz, 2H).

3-(8-Bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]-oxepine-2-carboxamido)-4-chlorobenzoic Acid. To a suspension of methyl 3-(8-bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)-4-chlorobenzoate (31 g, 61 mmol) in THF (200 mL) and H_2O (100 mL) was added LiOH·H_2O (6.42 g, 153

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mmol). The reaction mixture was stirred at room temperature overnight. Then it was acidified with HCl (2 N) to pH 2−3 and concentrated. The resulting precipitate was washed with water and dried to give the desired product (27.3 g, 91% yield). LC-MS: (ESI, m/z) = 494 $[M + H]^+$.

8-Bromo-*N*-(2-chloro-5-(4-methylpiperazine-1-carbonyl)-phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide. To a mixture of 1-methylpiperazine (1.22 g, 12.18 mmol), *i*-Pr_2NEt (3 mL), and HATU (2.78 g, 7.31 mmol) in THF (60 mL) was added 3-(8-bromo-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)-4-chlorobenzoic acid (3.0 g, 6.09 mmol) under nitrogen at room temperature. The reaction mixture was stirred overnight, diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the titled product (3.3 g, 94% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.74−7.21 (m, 6H), 6.67 (s, 1H), 4.18 (t, J = 4.4 Hz, 2H), 3.31−2.12 (m, 16H). LCMS: (ESI, m/z) = 574.0 $[M + H]^+$.

***N*^{2}-(2-Chloro-5-(4-methylpiperazine-1-carbonyl)phenyl)-*N*^{2},*N*^{8}-dimethyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2,8-dicarboxamide (34).** A suspension of 8-bromo-*N*-(2-chloro-5-(4-methylpiperazine-1-carbonyl)phenyl)-*N*-methyl-4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine-2-carboxamide (500 mg, 0.87 mmol), $Pd(OAc)_2$ (10 mg, 0.0435 mmol), Xantphos (50 mg, 0.087 mmol), $MeNH_2$·HCl (88 mg, 1.30 mmol), and Na_2CO_3 (277 mg, 2.61 mmol) in toluene (10 mL) was heated at 80 °C under CO (1 atm) overnight. It was filtered and concentrated, and the crude product was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 40:1 to 20: 1) to give **33** (149 mg, 31%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−6.94 (m, 7H), 6.23 (s, 1H), 4.23 (t, J = 4.8 Hz, 2H), 3.79−2.09 (m, 19H). LCMS: (ESI, m/z) = 553 $[M + H]^+$.

Characterization of Biochemical and Cellular Activity in Vitro. Enzymatic activity of the class I PI3K isoforms was measured using a fluorescence polarization assay that monitors formation of the product 3,4,5-inositol triphosphate molecule (PIP3), as it competes with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidylinositide 3-phosphate product results in a decrease in fluorescence polarization signal as the labeled fluorophore is displaced from the GRP-1 protein binding site. Class I PI3K isoforms were purchased from Perkin-Elmer or were expressed and purified as heterodimeric recombinant proteins. Tetramethylrhodamine-labeled PIP3 (TAMRA-PIP3), di-C8-PIP2, and PIP3 detection reagents were purchased from Echelon Biosciences. PI3K isoforms were assayed under initial rate conditions in the presence of 10 mM Tris (pH 7.5), 25 μM ATP, 9.75 μM PIP2, 5% glycerol, 4 mM $MgCl_2$, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, 2% (v/v) DMSO at the following concentrations for each isoform: PI3Kα,β at 60 ng/mL; PI3Kγ at 8 ng/mL; PI3Kδ at 45 ng/mL. After assay for 30 min at 25 °C, reactions were terminated with a final concentration of 9 mM EDTA, 4.5 nM TAMRA-PIP3, and 4.2 μg/mL GRP-1 detector protein before reading fluorescence polarization on an Envision plate reader. IC_{50} values were calculated from the fit of the dose−response curves to a four-parameter equation. Apparent K_i values were determined at a fixed concentration of ATP near the measured K_m for ATP for each isoenzyme and were calculated by fitting of the dose−response curves to an equation for tight-binding competitive inhibition. All IC_{50} and apparent K_i values represent geometric mean values of a minimum of three determinations. These assays generally produced results within 2-fold of the reported mean.

Antiproliferative cellular assays were conducted using PC3 and MCF7.1 human tumor cell lines provided by the ATCC or Genentech Research Laboratories, respectively. MCF7.1 is an in vivo selected line developed at Genentech and originally derived from the parental human MCF7 breast cancer cell line (ATCC, Manassas, VA). Cell lines were cultured in RPMI supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 μg/mL streptomycin, 10 mM HEPES, and 2 mM glutamine at 37 °C under 5% CO_2. MCF7.1 cells or PC3 cells were seeded in 384-well plates in medium at 1000 or 3000 cells/well, respectively, and incubated overnight prior to the addition of compounds to a final DMSO concentration of 0.5% v/v. MCF7.1 cells and PC3 cells were incubated for 3 and 4 days, respectively, prior to the addition of CellTiter-Glo reagent (Promega) and reading of luminescence using an Analyst plate reader. For antiproliferative assays, a cytostatic agent such as aphidicolin and a cytotoxic agent such as staurosporine were included as controls. Dose−response curves were fit to a four-parameter equation, and relative EC_{50} values were calculated using the Assay Explorer software. All cellular EC_{50} values represent geometric mean values of a minimum of two determinations, and these assays generally produced results within 3-fold of the reported mean.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

A homology model of human PI3Kβ in PDB format and the sequence alignment of human PI3Kβ and mouse PI3Kδ that was used for model building. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

†The coordinates of **33** in PI3Kγ have been deposited with PDB code 3T8M.

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■ ABBREVIATIONS USED

PI3K, phosphoinositide 3-kinase; PDB, Protein Data Bank; PTEN, phosphatase and tensin homologue; SAR, structure−activity relationship; CAMK2D, calcium/calmodulin-dependent protein kinase type II δ; Boc, *tert*-butyl carbamate; DPPA, diphenylphosphorylazide; TMEDA, tetramethylethylenediamine; TFA, trifluoroacetic acid; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DCE, 1,2-dichloroethane; THF, tetrahydrofuran; PPA, polyphosphoric acid; DMAP, 4-dimethylaminopyridine; DBU, diazobicyloundecane; m-CPBA, 3-chloroperoxybenzoic acid; HATU, *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotiazol-1-yl)uronium hexafluorophosphate; PIP3, 3,4,5-inositol triphosphate

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(16) The sequences of the kinase domains of the four PI3K isoforms from multiple species were aligned using PSI-BLAST (NCBI). A mouse PI3Kδ structure (PDB code 2WXP) was chosen as the template because among all available structures, it shares with human PI3Kβ the highest level of sequence homology both overall and around the active site. In addition, residues 1−114 at the amino terminus, which is expected to be far removed from the active site according to the known structures, were omitted in modeling. Finally, sequence alignment was manually refined (sequence identity of 52%; see Supporting Information) before a model of human PI3Kβ in complex with GDC-941 (from the template) was built using PRIME (Schrödinger, LLC) with standard parameters.

(17) A comparison of our homology model of PI3Kβ with the recently reported 3.3 Å cocrystal structure of PI3Kβ and **1** (ref 10) shows that the homology model correctly predicted the confirmation of the P-loop (Lys771-Ser775, numbering from PDB code 2Y3A), validating the choice of PI3Kδ as the homology template for the binding pocket.

(18) The aminopyrimidine group also adds mTOR inhibition and in many cases improved in vivo Cl. For details see refs 8b and 8c.

(19) Electrostatic potential maps were computed using a Poisson−Boltzmann (PB) equation solver APBS Tools2 plugin for PyMOL (14a-c). Calculation was performed in nonlinear PB mode with these standard parameters: protein dielectric set as 2 and solvent dielectric as 78; atomic charges and radii assigned according to the AMBER force field; 0.150 M concentration for the +1 and −1 ion species; solvent radius of 1.4 Å; system temperature of 310 K. The molecule surface was computed using the option "similar to cubic spline, but with 7th order polynomial", colored by the "potential on solvent accessible surface", and visualized in PyMOL, version 1.2r3pre (Schrödinger, LLC). (a) Baker, N. A.; Sept, D; Joseph, S; Holst, M. J.; McCammon, J. A. Electrostatics of Nanosystems: Application to Microtubules and the Ribosome. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10037−10041. (b) Dolinsky, T. J.; Nielsen, J. E.; McCammon, J. A.; Baker, N. A. PDB2PQR: An automated Pipeline for the Setup, Execution,and Analysis of Poisson−Boltzmann Electrostatics Calculations. *Nucleic Acids Res.* **2004**, *32*, W665−W667. (c) Lerner, M. G.; Carlson, H. A. *APBS Plugin for PyMOL*; University of Michigan: Ann Arbor, MI, 2006.

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