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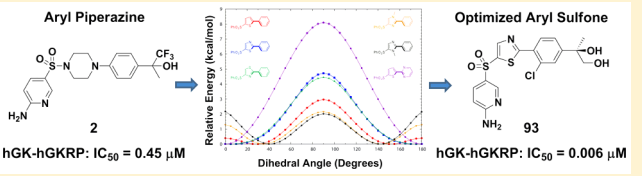
Small Molecule Disruptors of the Glucokinase−Glucokinase Regulatory Protein Interaction: 5. A Novel Aryl Sulfone Series, Optimization Through Conformational Analysis

Nuria A. Tamayo,*[,†] Mark H. Norman,[†] Michael D. Bartberger,*[,‡] Fang-Tsao Hong,[†] Yunxin Bo,[†] Longbin Liu,[†] Nobuko Nishimura,[†] Kevin C. Yang,[†] Seifu Tadesse,[†] Christopher Fotsch,[†] Jie Chen,[∥] Samer Chmait,[‡] Rod Cupples,[§] Clarence Hale,[§] Steven R. Jordan,[‡] David J. Lloyd,[§] Glenn Sivits,[§] Gwyneth Van,[⊥] and David J. St. Jean, Jr.[†]

[†]Department of Therapeutic Discovery—Medicinal Chemistry, [‡]Department of Therapeutic Discovery—Molecular Structure and Characterization, [§]Department of Metabolic Disorders, [∥]Department of Pharmacokinetics and Drug Metabolism, and [⊥]Department of Pathology, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320, United States

Supporting Information

ABSTRACT: The glucokinase−glucokinase regulatory protein (GK-GKRP) complex plays an important role in controlling glucose homeostasis in the liver. We have recently disclosed a series of arylpiperazines as in vitro and in vivo disruptors of the GK-GKRP complex with efficacy in rodent models of type 2 diabetes mellitus (T2DM). Herein, we describe a new class of aryl sulfones as disruptors of the GK-GKRP complex, where the central piperazine scaffold has been replaced by an aromatic group. Conformational analysis and exploration of the structure−activity relationships of this new class of compounds led to the identification of potent GK-GKRP disruptors. Further optimization of this novel series delivered thiazole sulfone **93**, which was able to disrupt the GK-GKRP interaction in vitro and in vivo and, by doing so, increases cytoplasmic levels of unbound GK.



INTRODUCTION

Glucokinase (GK) plays a central role in glucose homeostasis and is the major glucose phosphorylating enzyme expressed in hepatocytes and pancreatic β-cells.[1] It acts as a glucose sensor and regulates hepatic glucose metabolism in addition to glucose-dependent insulin secretion.[2] Glucokinase activators (GKAs) have been reported as a novel class of potential antidiabetic agents.[3] They are associated with a dual mechanism for lowering blood glucose by enhancing insulin secretion from pancreatic β-cells and increasing glucose uptake in the liver, and several have entered clinical development for the treatment of type 2 diabetes.[4,5] Although dual-acting (liver and pancreas) GKAs are efficacious, many have been associated with a significant risk for hypoglycemia, attributed in part to increasing insulin secretion at low glucose levels.[6] As an alternative, we have recently disclosed the discovery and optimization of small molecule GK-GKRP disruptors with excellent in vivo activity,[7−11] as exemplified by the aryl piperazines **1** and **2** (Figure 1).

We have also disclosed the cocrystal structure of *N*-aryl piperazine **1** bound to hGKRP,[9] in which it was established that the piperazine ring acts as a spacer, positioning the A- and C-rings in optimal orientations to allow hydrogen-bonding interactions between the small molecule and the protein. It was observed that the amino group on the pyridyl A-ring forms hydrogen bonding interactions with Gly181 and Met213, and the tertiary alcohol substituent on the C-ring forms an additional bifurcated hydrogen bonding interaction with Arg525 (Figure 2a).

To identify an alternative series in this program, we postulated that it would be possible to substitute the relatively flat central *N*-piperazine ring with other planar moieties such as aryl and heteroaryl groups that did not disrupt the key hydrogen bonding interactions between hGKRP and the substituents on the A- and C-rings (general structure **3**). To test this hypothesis, aryl sulfone **4** was prepared and tested for its ability to disrupt the hGK-hGKRP complex in an AlphaScreen biochemical assay[13] (**4**, IC_{50} = 1.01 μM vs **2**, IC_{50} = 0.454 μM). Although a 3-fold loss of potency was observed, this result was encouraging because it represented a novel series of GK-GKRP disruptors lacking a piperazine central ring. We obtained an X-ray cocrystal structure of aryl sulfone **4** bound to hGKRP (Figure 2b) in which the same key interactions between compound **4** and the protein were maintained as described for arylpiperazine **1**. Analysis of this cocrystal structure showed that the dihedral angle between the central B-ring and the Arg525-engaging C-ring was compressed to a value of approximately −15°, which is smaller than that typically observed for a biphenyl moiety in the free state (~40°).[14] This nonoptimal dihedral angle is a result of the steric constraints imposed by the floor residues Val28, Pro29, and the overhead residue Ala521.

We postulated that we should be able to improve the binding affinity of this new series by optimizing the dihedral angle

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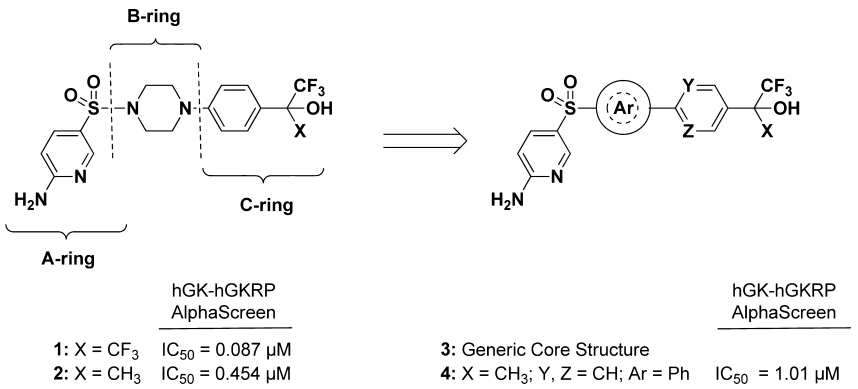

Figure 1. Aryl piperazine GK-GKRP disruptors (**1** and **2**), generic core structure used for SAR investigations (**3**), and aryl sulfone **4**.

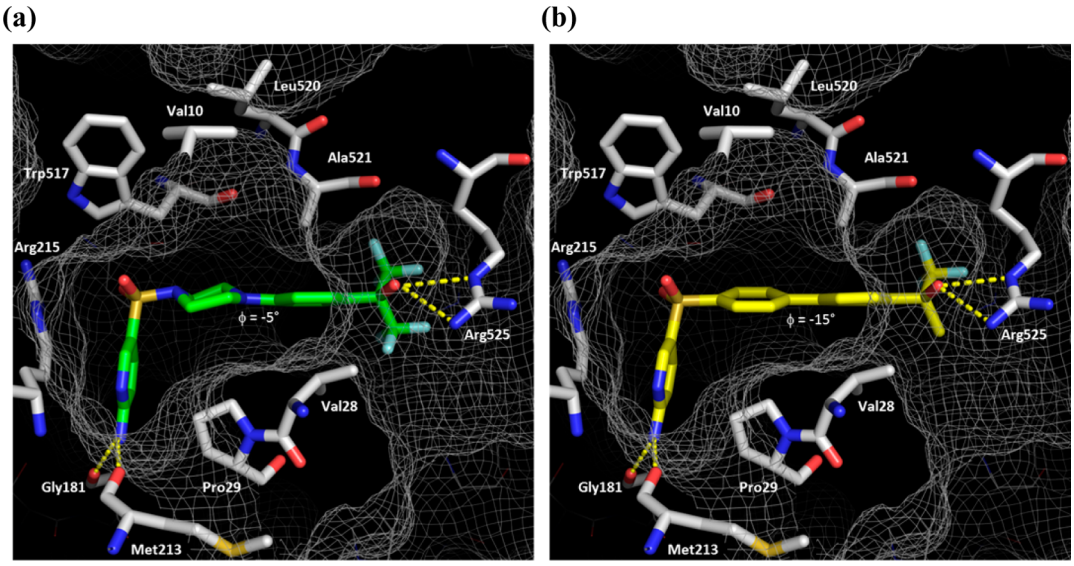

Figure 2. (a) X-ray cocrystal structure of *N*-aryl piperazine **1** bound to hGKRP. (b) X-ray cocrystal structure of aryl sulfone **4** bound to hGKRP. Hydrogen bonds are shown by dashed yellow lines. The dihedral angles (ϕ) between the B- and C-rings are also shown.[12]

between the B- and C-rings, while maintaining the key hydrogen bonding interactions elsewhere in the binding site. Toward this goal, a novel series of biaryl sulfones (**3**) with different 5- and 6-membered aryl and heteroaryl groups were designed based on their capacity to adopt a minimum-energy conformation with a dihedral angle between the two rings (B−C) that is closer to −15°. The new analogues were tested for their ability to disrupt the hGK-hGKRP complex and were also evaluated in vitro for their metabolic stability in rat liver microsomal (RLM) preparations. This investigation provided an understanding of the optimal biaryl (B−C) ring system and resulted in the discovery of a novel series of hGK-hGKRP disruptors, exemplified by thiazole **93**. This compound potently disrupted the GK-GKRP complex in vitro in rat hepatocytes and also showed a dose-dependent effect on nuclear rat GK translocation in vivo.

CHEMISTRY

The preparation of the unsubstituted biaryl sulfones **4**, **12**, **13**, and **17** is outlined in Scheme 1. Copper catalyzed coupling of 2-chloro-5-iodopyridine (**5**) and 4-bromothiophenol (**6**) led to the formation of the corresponding biaryl thioether under relatively mild conditions.[15] Oxidation of the thiol group to the sulfone using 3-chloro peroxybenzoic acid (mCPBA), followed by displacement of the chloride with ammonia provided **7**. Bromide **7** was coupled with boronic ester **8**[16] to give biaryl sulfone **4** in excellent yield. Alternatively, **7** could be converted into boronic ester **9** and then coupled to heterocyclic chlorides **10**[10] and **11**[10] yielding sulfones **12** and **13**, respectively. The synthesis of the bipyridyl analogue, **17**, required the use of organostannane **16**[16] as the coupling partner in the palladium-catalyzed reaction. The requisite biaryl thioether **15** was prepared by a copper-catalyzed reaction between iodopyridine **5** and 6-aminopyridine-3-thiol (**14**). Stille coupling of aryl sulfide **15** and organostannane **16** followed by oxidation of the resulting thioether with oxone provided bipyridyl sulfone **17** in moderate yield.

The syntheses of C-ring substituted pyridylsulfones are outlined in Scheme 2. Suzuki-Miyaura coupling reaction of boronic ester **9** with chloropyridines **18**[11] and **19**[11] gave pyridine sulfones **20** and **21**, respectively. Chloropyridine **20** was converted to cyanopyridine **22** by microwave assisted palladium-catalyzed cyanation using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) as the ligand. Alternatively, copper-free Sonagashira coupling of **20** with a variety of terminal alkynes in the presence of Cs_2CO_3 or K_2CO_3 afforded derivatives **23**-**27** in good yields.

The B-ring substituted bipyridines **34**−**40** and **45**−**48** were synthesized in five to six synthetic steps from (2,6-difluoropyridin-3-yl)boronic acid (**28**) (Scheme 3). Suzuki-Miyaura cross-

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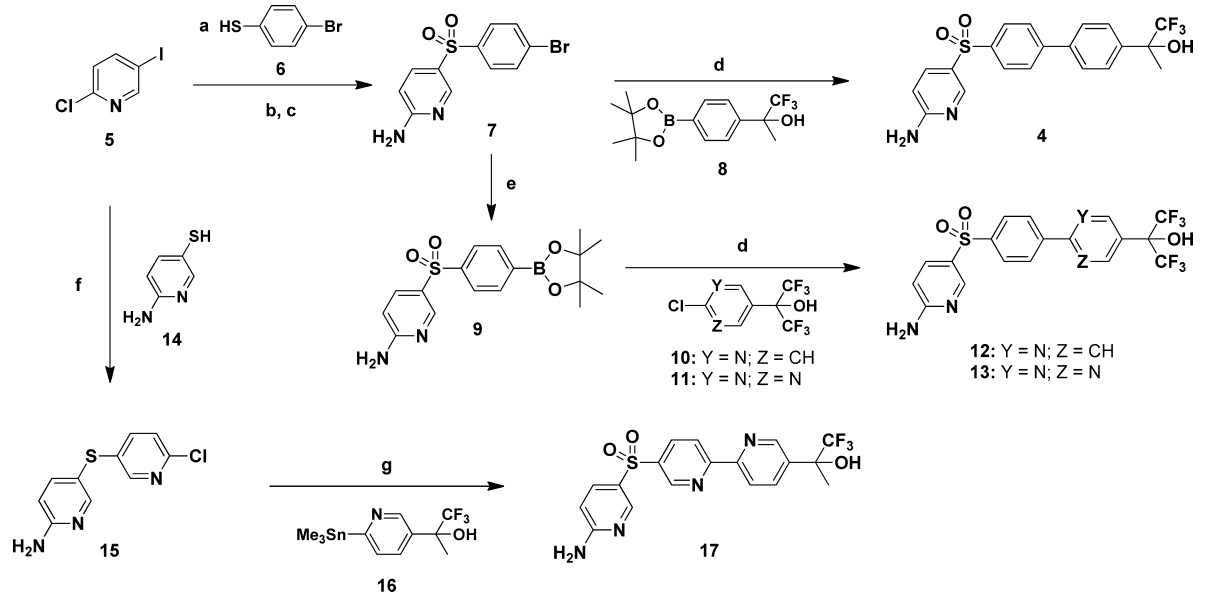
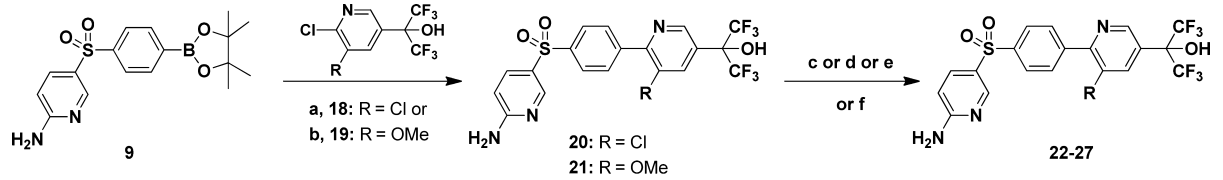
Scheme 1. Synthesis of Unsubstituted (6,6)-Biaryl Sulfones[a]



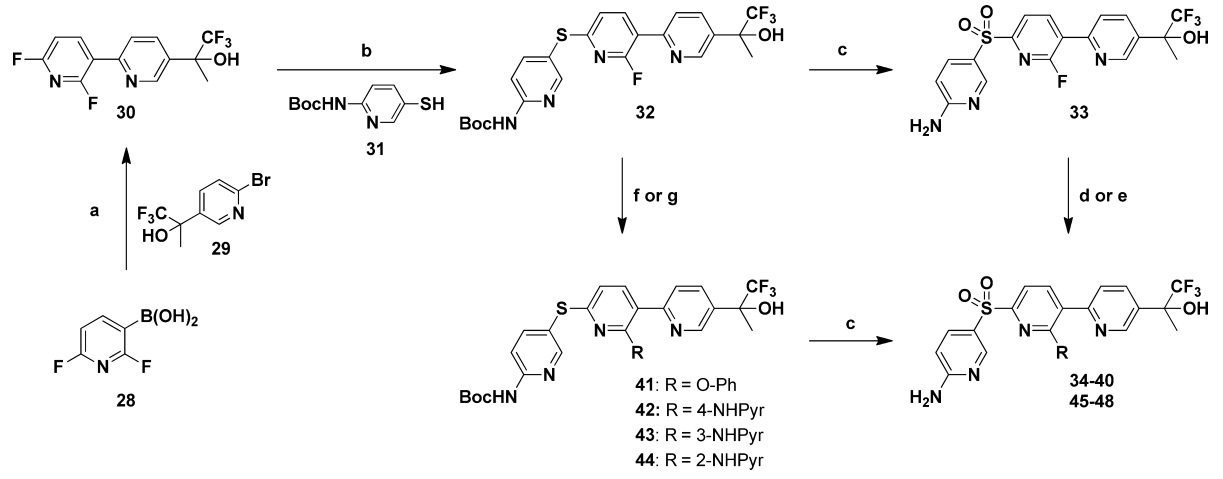
[a]Reagents and conditions: (a) CuI, K_2CO_3, ethylene glycol, IPA, 80 °C; (b) mCPBA, CH_2Cl_2, rt; (c) NH_4OH, EtOH, 120 °C; (d) $PdCl_2$(dppf), Cs_2CO_3, DME, water, 100 °C; (e) pinacol diborane, $PdCl_2$(dppf), KOAc, dioxane, 100 °C; (f) CuI, K_2CO_3, ethylene glycol, IPA, 90 °C; (g) $Pd(PPh_3)_4$, LiCl, dioxane, 90 °C; then, oxone, dioxane, water, rt.

Scheme 2. Synthesis of C-Ring Substituted Pyridyl Sulfones[a]



[a]Reagents and conditions: (a) $PdCl_2$(dppf), Cs_2CO_3, DME, water, 100 °C; (b) $PdCl_2$(AmPhos)$_2$, K_2CO_3, dioxane, water, 140 °C; (c) $Zn(CN)_2$, XPhos/$Pd_2(dba)_3$, DMF, 140 °C; (d) alkyne, XPhos precatalyst, Cs_2CO_3, MeCN, 80 to 140 °C; (e) alkyne, XPhos precatalyst, K_2CO_3, DMA, 110 °C; (f) alkyne, XPhos precatalyst, K_2CO_3, DMA, 110 °C; then TBAF, THF, rt.

Scheme 3. Synthesis of B-Ring Substituted Bipyridyl Sulfones[a]



[a]Reagents and conditions: (a) $PdCl_2$(AmPhos)$_2$, KOAc, dioxane, water, 80 °C; (b) K_2CO_3, DMF, 80 °C; (c) conc. H_2SO_4, water, then sodium dichromate, 0 °C to rt; (d) amine, DMSO, 100 °C; (e) amine, KHMDS or LiHMDS, THF, −50−0 °C; (f) phenol, Cs_2CO_3, DMSO, 60 °C; (g) aminopyridine, LiHMDS, THF, 0 °C.

coupling of **28** with bromopyridine **29**[10] using AmPhos[17] gave bipyridyl intermediate **30**. The use of potassium acetate helped minimize the hydrolysis of the 2-fluoropyridine under the reaction conditions compared with stronger bases such as potassium or sodium carbonate. Base-mediated S_NAr reaction of fluoropyridine **30** with *tert*-butyl (5-mercaptopyridin-2-yl)-

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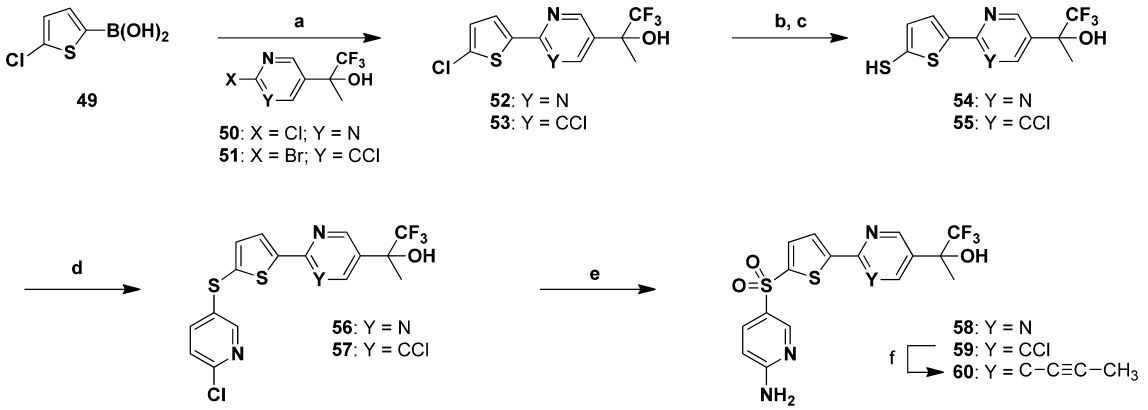
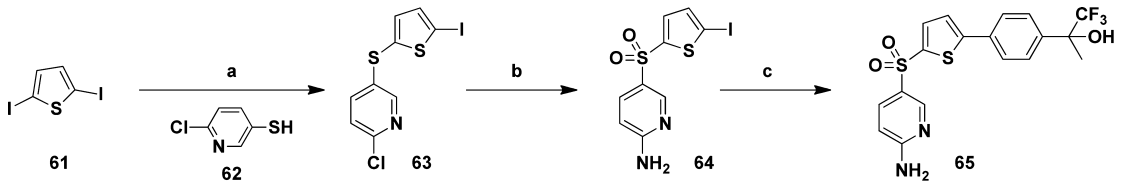
Scheme 4. Synthesis of Thiophene-Pyridine and Thiophene-Pyrimidine Analogues[a]



[a]Reagents and conditions: (a) $PdCl_2$(dppf), Cs_2CO_3, dioxane, 90 °C; (b) (4-methoxyphenyl)methanethiol, Josiphos/$Pd(OAc)_2$, NaO-*t*-Bu, DME, 90 °C; (c) TFA, 70 °C; (d) **5**, CuI, *N*,*N*-dimethyl-1,2-ethanediamine, K_2CO_3, DMSO, 90 °C; (e) mCPBA, CH_2Cl_2, 0 °C; then NH_4OH, dioxane, 120 °C; (f) propyne, XPhos precatalyst, Cs_2CO_3, MeCN, 80 °C.

Scheme 5. Synthesis of Thiophene-Phenyl Analogue (65)[a]



[a]Reagents and conditions: (a) CuI, *N*,*N*,-dimethylethane-1,2-diamine, K_2CO_3, DMSO, 80 °C; (b) mCPBA, CH_2Cl_2, rt; then NH_4OH, dioxane, 100 °C; (c) **8**, $PdCl_2$(dppf), Cs_2CO_3, dioxane, water, 100 °C.

carbamate (**31**) provided a 2:1 regioisomeric mixture of bipyridines from which the desired and major fluoropyridine **32** was isolated. Removal of the Boc group followed by oxidation using sodium dichromate afforded **33** in moderate yield. Reaction of fluoropyridine **33** with aliphatic amines, aniline, and benzylamine afforded pyridyl sulfones **34**-**40** in moderate to good yields. The lower yields obtained were due, in part, to the competing displacement of the sulfone when a strong base was used. The most successful strategy to overcome this issue, was to alter the order of the synthetic transformations. In the synthesis of analogues **45**-**48**, the substituent on the B-ring was introduced before the oxidation of the sulfide to the sulfone, thus avoiding the previously observed side reaction. Reaction of fluoropyridine **32** with phenol or aminopyridines led to sulfides **41**−**44** that were then oxidized to the target sulfones **45**−**48**, using sodium dichromate.

The syntheses of analogues having a central thiophene group and a heterocyclic C-ring (**58**-**60**) began with a Suzuki-Miyaura palladium-catalyzed coupling reaction between commercially available 5-chloro-2-thienylboronic acid (**49**) and heterocyclic halides **50**[10] and **51**,[11] resulting in the formation of chlorothiophene analogues **52** and **53** (Scheme 4). It was important to control the temperature during these reactions because higher temperatures (>90 °C) led to the decomposition of the boronic acid and resulted in very low conversions. The 2-chlorothiophenes (**52** and **53**) were converted to 2-thiolthiophenes (**54** and **55**) by palladium-catalyzed reaction with (4-methoxyphenyl)methanethiol as a hydrogen sulfide surrogate. The reaction was optimized by the use of Josiphos[18] as the ligand. The high degree of steric hindrance and strong electron donating properties of this ligand, allowed for the preparation of the target intermediates in good yields. The sulfide intermediates were then deprotected in the presence of trifluoroacetic acid at 70 °C. The rest of the syntheses were completed in a similar way as previously described for the preparation of (6,6)-biaryls (Scheme 1) to provide the desired compounds **58** and **59**. Palladium-catalyzed coupling reaction of chloropyridine **59** with propyne gave the alkyne analogue **60**.

In the case of the aryl C-ring analogue **65** (Scheme 5), the order of the synthetic steps was modified. The synthesis started by a copper catalyzed *S*-arylation of diiodothiophene (**61**) with 6-chloropyridine-3-thiol (**62**). This reaction led to a mixture of mono- and dicoupled products, but **63**, the monocoupled product, could be isolated by silica gel column chromatography. Oxidation of sulfide **63** with mCPBA followed by displacement of the 2-chloro substituent with ammonia gave sulfone **64** that was then coupled with boronic ester **8** to form the target compound, **65**.

The thiazole analogues **86**−**94** needed for this investigation were prepared as outlined in Scheme 6. The syntheses started with palladium-catalyzed Stille cross-coupling reaction between 2-(tributylstannanyl)-1,3-thiazole (**66**) and aryl bromides **67**[8]-**69**, giving aryl thiazoles **70**, **71**, and **74**, respectively. Methylketone **71** was a versatile synthetic intermediate used for the preparation of other analogues. Thus, **71** was converted into the trifluoromethyl alcohol **72** by treatment with TMS trifluoromethane in the presence of TBAF at 0 °C. In an analogous way, **71** was also treated with methyl magnesium bromide to give the gem-dimethyl alcohol **73** in good yield. Finally, diol **75** was prepared by a two-step procedure involving a Corey-Chaykovsky epoxidation of **71** using trimethylsulfonium iodide[19] followed by hydrolysis of the epoxide intermediate to the diol in the presence of hydrochloric acid. Bromination of the thiazoles **70**, **72**−**75** with *N*-bromosuccinimide gave bromides

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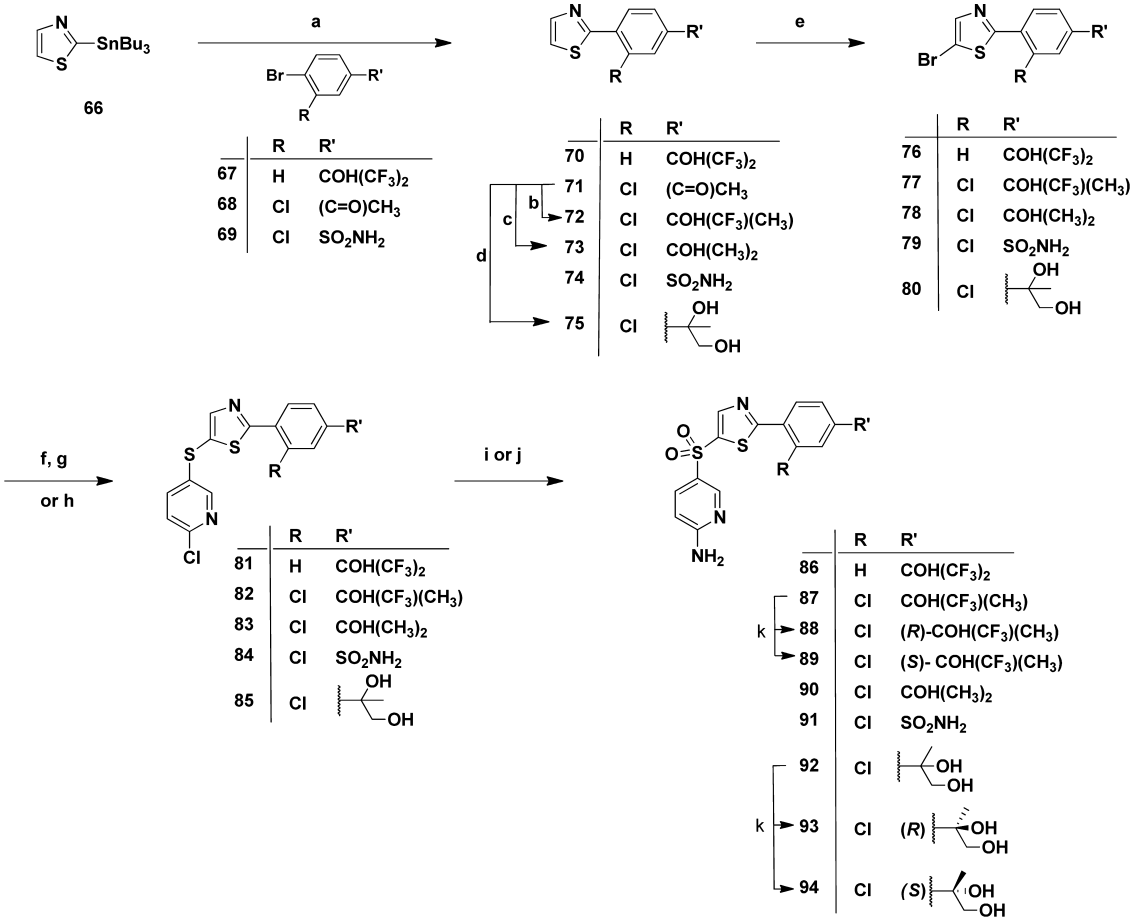
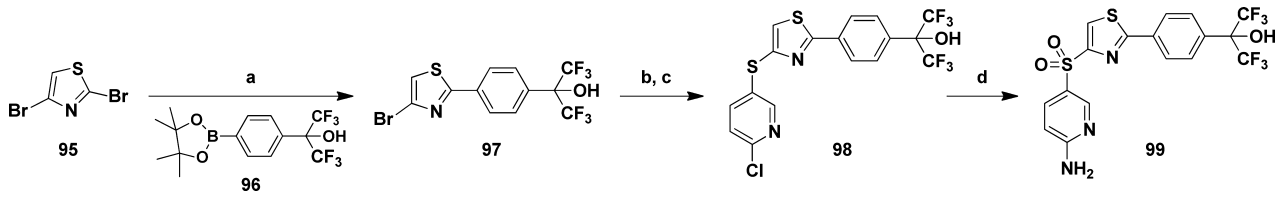
Scheme 6. Synthesis of Thiazole-Phenyl Analogues[a]



[a]Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, DMF, 90 °C; (b) CsF, $TMSCF_3$, DME, 0 °C; then TBAF, THF, 0 °C; (c) MeMgBr, THF, 0 °C; (d) $(CH_3)_3SOI$, KO-*t*-Bu, DMSO, rt; then HCl (1N), 0 °C; (e) NBS, DMF, 70 °C; (f) methyl 3-sulfanylpropanoate, Xantphos/$Pd_2(dba)_3$, DIPEA, dioxane, 120 °C; then KO-*t*-Bu, THF, −78 °C; (g) **5**, CuI, K_2CO_3, ethylene glycol, IPA, 80−90 °C; (h) **62**, Xantphos/$Pd_2(dba)_3$, dioxane, 120 °C; (i) mCPBA, CH_2Cl_2, 0 °C; then NH_4OH, dioxane, 120 °C; (j) Na_2WO_4, H_2O_2, AcOH, 0 °C; then NH_4OH, EtOH, 100 °C; (k) chiral separation by SFC (the absolute stereochemistries of compounds **88**, **89**, **93**, and **94** were arbitrarily assigned).

Scheme 7. Synthesis of Thiazole-Phenyl Analogue (99)[a]



[a]Reagents and conditions: (a) $PdCl_2(dppf)$, Cs_2CO_3, DME, water, 90 °C; (b) methyl 3-sulfanylpropanoate, Xantphos/$Pd_2(dba)_3$, DIPEA, dioxane, 120 °C; then KO-*t*-Bu, THF, −78 °C; (c) **5**, CuI, K_2CO_3, ethylene glycol, IPA, 80 °C; (d) mCPBA, CH_2Cl_2, rt; then NH_4OH, EtOH, 120 °C.

76−**80** that were then converted into biaryl thiols by palladium-catalyzed coupling reactions with methyl 3-sulfanylpropanoate, a thiol surrogate. Deprotection of the thiol with potassium *tert*-butoxide and copper-catalyzed cross-coupling between the thiols and 2-chloro-5-iodopyridine (**5**) led to the biaryl sulfides **81** and **82** in moderate yields. Alternatively, a one-step procedure was developed to streamline the synthesis. This involved the direct palladium-catalyzed cross-coupling reaction of 6-chloropyridine-3-thiol (**62**) with bromothiazoles **78**−**80** giving the target biaryl sulfides (**83**−**85**) in moderate yields. Oxidation of the thiols (**81**−**85**) to the sulfones was accomplished using mCPBA or sodium tungstate-hydrogen peroxide that in some cases, gave cleaner reactions. Treatment of the resulting chloropyridines with ammonia led to the 2-aminopyridine analogues **86**, **87**, and **90**−**92**. Chiral separation of the racemic sulfone **87** gave the two enantiomerically pure analogues **88** and **89**. Similarly, the racemic diol **92** was also subjected to chiral purification leading to diols **93** and **94**.

The synthesis of analogue **99** is described in Scheme 7, palladium-catalyzed cross-coupling of 2,4-dibromothiazole (**95**) with 1,1,1,3,3,3-hexafluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (**96**)[16] gave compound **97** in good yield. We were able to employ 2,4-dibromothiazole as the starting material due to the higher reactivity of the 2- vs the 4-

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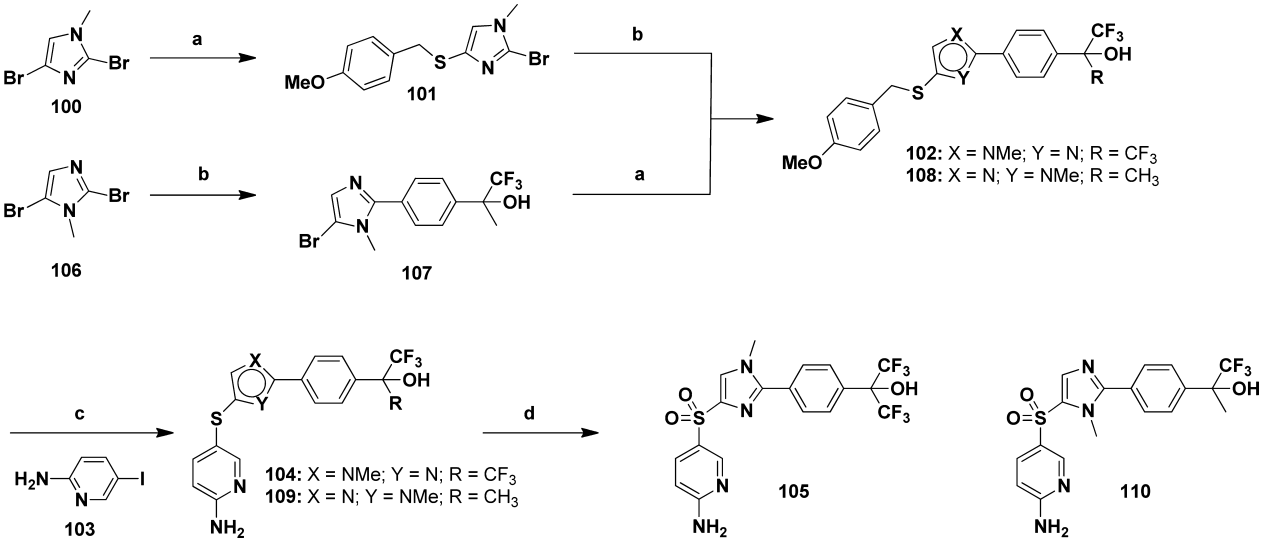
Scheme 8. Synthesis of Imidazole-Phenyl Analogues (105 and 110)[a]



[a]Reagents and conditions: (a) (4-methoxyphenyl)methanethiol, JosiPhos/Pd(OAc)$_2$, NaO-*t*-Bu, DME, 90 °C; (b) **96** or **8**, PdCl$_2$(dppf), Cs$_2$CO$_3$, dioxane, water, 100 °C; (c) TFA, 70 °C; then **103**, CuI, *N*,*N*-dimethylethane-1,2-diamine, K$_2$CO$_3$, DMSO, 90 °C; (d) mCPBA, CH$_2$Cl$_2$, 0 °C.

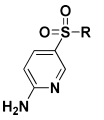
bromo substituent in a palladium-catalyzed coupling reaction. Palladium-catalyzed coupling with methyl 3-sulfanylpropanoate, followed by deprotection of the thiol with potassium *tert*-butoxide, and copper-catalyzed cross-coupling with 2-chloro-5-iodopyridine (**5**) led to the biaryl sulfide **98**. This compound was then oxidized to the sulfone with mCPBA and treated with ammonia to give the thiazole analogue **99**.

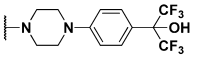
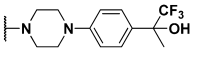
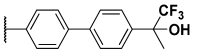
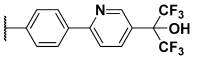
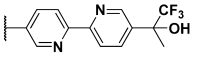
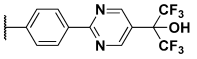
The last two analogues needed in this investigation, *N*-methyl imidazoles **105** and **110**, were prepared according to the routes detailed in Scheme 8. First, 2,4-dibromo-1-methyl-1*H*-imidazole (**100**) underwent palladium-catalyzed cross-coupling with (4-methoxyphenyl)methanethiol, to give thiol **101**. The aryl C-ring was introduced by a Suzuki-Miyaura coupling leading to the biaryl sulfide **102**. Deprotection of the sulfide with trifluoroacetic acid, followed by a copper catalyzed arylation with 2-amino-iodopyridine (**103**) gave compound **104**. Oxidation of **104** with mCPBA provided the target *N*-methylimidazole **105**. For the preparation of the regiosiomeric *N*-methylimidazole **110**, the order of the synthetic steps was altered. First, 2,5-dibromo-1-methyl-1*H*-imidazole (**106**) was coupled with boronic ester **8** to give biaryl **107** that was subsequently coupled with (4-methoxyphenyl)methanethiol. The rest of the sequence to prepare **110** was similar to that previously described for **105**.

RESULTS AND DISCUSSION

The compounds described herein were tested for their ability to disrupt the hGK-hGKRP interaction in a biochemical AlphaScreen assay[13] and the data is reported as IC$_{50}$ values in Tables 1−5. The in vitro rat microsomal stabilities of these analogues are also shown in the same tables. In our previous work on GK-GKRP disruptors, we disclosed a series of piperazine analogues with potent in vitro and in vivo activities, exemplified by aryl piperazine **1**. X-ray crystallographic studies revealed that the piperazine ring acts as a spacer properly positioning the A- and C-rings in the binding cavity. The sulfonamide functionality provided the required length and "L-shaped" trajectory for the amino group in the pyridine ring to form key hydrogen-bond interactions with Gly181 and Met213 on the protein (Figure 2a). The aryl C-ring attached to the piperazine core navigated a

Table 1. SAR of Unsubstituted 6,6-Biaryl Analogues



Cmpd No.	R	hGK-hGKRP AlphaScreen IC$_{50}$ (μM)[a]	RLM CL$_{int}$ (μL/min/mg)[b]
1		0.087 ± 0.009	<14
2[c]		0.454 ± 0.108	<14
4[c]		1.176 ± 0.173	<14
12		0.358 ± 0.094	<14
17[c]		0.434 ± 0.172	<14
13		0.104 ± 0.037	<14

[a]Data reported as the mean and SD where $n \geq 3$. [b]In vitro rat microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM. [c]Racemic mixture.

hydrophobic channel delineated by Ala521(above), and Val28 and Glu32 (below), serving to present the terminal carbinol functionality in a hydrogen bonding interaction with both terminal and internal nitrogen atoms of the Arg525 side chain.

Based on our hypothesis that the *N*-aryl piperazine in **1** could be replaced with an aromatic ring, biaryl sulfone **4** was prepared and tested. While a 3-fold loss in potency was observed (**4** vs **2**, Table 1), the cocrystal structure of sulfone **4** bound to hGKRP

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revealed that the ligand was able to achieve the same hydrogen-bonding interactions with the protein as the parent piperazine **1** (Figure 2b). However, as previously discussed, the dihedral angle between the B- and C-rings was found to be higher in energy than the global minimum.

To investigate the conformations of this type of B−C-ring system, a quantum mechanical conformational analysis was performed[20] on four model 6,6-biaryl sulfones (structures I to IV), where the B-ring was phenyl or pyridine and the C-ring was phenyl, pyridine, or pyrimidine (Figure 3). Substitution of one or

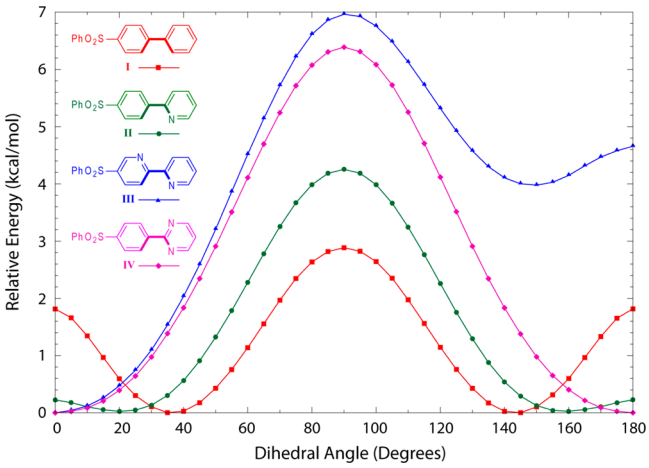

Figure 3. SCRF-B3LYP/6-31G* dihedral profile of (6,6)-biarylsulfone structures (I−IV). The scanned dihedral angle is depicted in bold.

more of the *ortho* C−H bonds of the B- and/or C-rings with nitrogen atoms was predicted to reduce the internal energy penalty for coplanarization by replacing the eclipsing C−H interactions with sterically less-demanding and electrostatically favorable CH···N contacts. For the biphenyl core (structure I) the binding conformation ($\Phi_{B-C} \approx 15°$) lies approximately 1 kcal/mol above the ~35° global minimum and does not represent a stationary point. In contrast, aza analogs (structures II−IV) were predicted to virtually eliminate the internal energy penalty required for binding (Figure 3, relative energy <0.2 kcal/mol at $\Phi_{B-C} \approx 15°$).

Therefore, we began modifying our lead sulfone **4** by replacing the B- and C-rings with the 6-membered heterocycles suggested by the conformational analysis.[21] Pyridine derivative **12** demonstrated a 4-fold improvement in activity, achieving potency similar to that of the starting piperazine analogue **2** (see Table 1). Introduction of an additional nitrogen in the B-ring, giving rise to bipyridyl analogue **17**, was well tolerated providing an analogue with approximately the same potency as pyridine **12**. Incorporation of a pyrimidine group as the C-ring (**13**) resulted in yet another 3-fold improvement in biochemical activity compared to **12** (**13**, IC_{50} = 104 nM). In addition, all of these analogues possessed excellent metabolic stability when incubated with rat liver microsomes (<14 μL/min/mg). Having improved the biochemical potency more than 10-fold (**13** vs **4**), sulfone **13** was tested in a cellular assay where nuclear to cytoplasmic GK translocation in rat primary hepatocytes was quantified. Unfortunately, pyrimidine **13** did not demonstrate measurable activity in this assay (EC_{50} > 12.5 μM). The large cell shift observed for sulfone **13** in this assay was difficult to rationalize. Rat primary hepatocytes are complex structures and many factors might influence the overall activity in this assay. Attempts to correlate potency with cell permeability and subsequently physicochemical properties (log *P*, PSA, pK_a) were unsuccessful.[22]

In spite of the lack of cellular potency, we were encouraged by the improved biochemical potency of **13**; therefore, we sought to further explore substitution at the C-ring, as a potential access point to a previously identified "shelf" region of the protein comprised of Ala27-Val28-Pro29. We hypothesized that improving the biochemical potency as well as the physicochemical properties would be required to obtain significant cellular potency in this series.

The shelf region sits just below the biaryl plane, next to Tyr24 and above the region delimited by Ala27-Pro29. We sought to introduce substituents that would allow additional interactions with the protein while maintaining the two key hydrogen bonding areas previously described that anchor the ligand to the protein. The results of a series of C-ring substituted pyridines are reported in Table 2. Small groups at the ortho position were detrimental for activity (compounds **20**−**22**). We speculated that this loss of potency could be due to the disfavorable torsional strain between the ortho substituent on the C-ring and the ortho hydrogen on the central phenyl ring. To access the shelf region and maintain the optimal torsional angle between the B- and C-rings, a sterically minimal alkynyl functionality, which would project further into the pocket, was employed. Consistent with our hypothesis, the alkyne analogue **23** was 4-fold more potent than the pyridine **12**, and also demonstrated cellular potency in the rat translocation assay (EC_{50} = 3.55 μM). Unfortunately, this substituent also conferred poor rat in vitro metabolic stability (CL_{int} = 177 μL/min/mg), making it a poor candidate for in vivo evaluation. Given the fact that the alkyne group was tolerated, additional analogues were prepared with polar substitutions at the alkyne terminus (compounds **24**-**27**). Introduction of primary or secondary alcohols gave analogues (**24** and **26**) that were equipotent to the methyl alkyne **23** in the biochemical assay, but were significantly more potent in the cellular assay as well as more stable in rat liver microsomes (EC_{50} = 0.6 and 0.83 μM, CL_{int} = 36 and 29 μL/min/mg, respectively). A 3-fold improvement in biochemical potency was obtained by methylation of the terminal alcohol (**25**); however, this substitution did not improve the cellular potency and was also detrimental for in vitro stability in rat liver microsomes. The tertiary alcohol **27** was also prepared and, although very stable in vitro (CL_{int} < 14 μL/min/mg), a 5-fold loss in binding potency was observed as compared with the secondary alcohol (**26** vs **27**, IC_{50} 42 vs 211 nM). Based on this SAR, we observed that the introduction of a polar group was beneficial to obtain submicromolar potencies in the rat functional hepatocyte assay, which led to a decrease in the large cell shift previously observed.

Given the planar nature of unsubstituted pyridine **12**, we hypothesized that we should also be able to reach the shelf region of the protein from the central B-ring, a novel approach since this could not be accomplished with our previous piperazine series. To maintain the optimal dihedral angle between the B- and C-rings, we postulated that we could lock the conformation of the ligand by the introduction of an intramolecular hydrogen bond between the substituent on the B-ring and the nitrogen of the C-ring pyridine. The effects on biochemical activity observed when substituents were appended to the B-ring through an amine or ether linkage are reported in Table 3. Aliphatic amines were well tolerated with potencies roughly decreasing as the size of the substituents increased [**34**, (R = NHMe) > **35**, (R = NHEt) > **36**,

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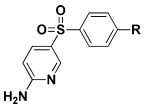
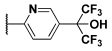
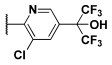
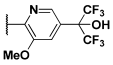
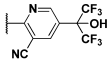
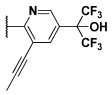
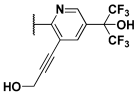
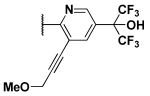
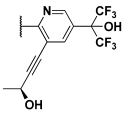
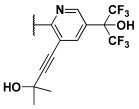
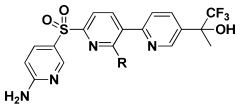
Table 2. SAR of Pyridyl C-ring Analogues

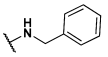


Cmpd No.	R	hGK-hGKRP AlphaScreen IC_{50} (μM)[a]	Rat Translocation EC_{50} (μM)	RLM CL_{int} (μL/min/mg)[b]
12		0.358 ± 0.094	NT[c]	<14
20		1.885 ± 0.551	NT[c]	18
21		4.506 ± 0.778	NT[c]	<14
22		0.796 ± 0.303	NT[c]	27
23		0.084 ± 0.026	3.55	177
24		0.065 ± 0.004	0.60	36
25		0.021 ± 0.005	0.76	>399
26		0.042 ± 0.007	0.83	29
27		0.211 ± 0.045	NT[c]	<14

[a]Data reported as the mean and SD where $n \geq 3$. [b]In vitro rat microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM. [c]NT = not tested.

Table 3. SAR of Pyridyl B-ring Analogues



Cmpd No.[a]	R	hGK-hGKRP AlphaScreen IC_{50} (μM)[b]	Rat Translocation EC_{50} (μM)	RLM CL_{int} (μL/min/mg)[c]
34		0.140 ± 0.036	NT[d]	21
35		0.152 ± 0.022	NT[d]	42
36		0.288 ± 0.092	NT[d]	62
37		0.238 ± 0.101	NT[d]	43
38		0.099 ± 0.025	0.66	280
39		0.007 ± 0.002	0.19	100
40		0.233 ± 0.053	NT[d]	114
45		6.021 ± 1.260	NT[d]	213
46		0.015 ± 0.004	0.16	252
47		0.038 ± 0.007	0.74	142
48		0.120 ± 0.034	NT[d]	130

[a]Racemic mixtures. [b]Data reported as the mean and SD where $n \geq 3$. [c]In vitro rat microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM. [d]NT = not tested.

(R = NH*i*Pr) ≈ **37**, (R = NH*c*Pr)]. However, this trend did not extend to the bulky cyclohexyl analogue **38**, which exhibited improved activity (IC_{50} = 99 nM) probably due to an increase in van der Waals contacts with the protein. Further improvements in potency were achieved when the planarity of the substituent at this position was increased. An aniline at this position (**39**) gave the best result, with a single-digit nanomolar IC_{50} in the biochemical assay. Both the amino cyclohexyl derivative **38** and the aniline analogue **39** had improved cellular activities with EC_{50} values of 0.66 and 0.19 μM respectively; however, they were quickly cleared in rat liver microsomal preparations. Extending the projection of the substituent with a *N*-benzyl group (**40**) or changing the nature of the linkage of the substituent to the B-ring (oxygen vs nitrogen) to form ether **45** were detrimental for activity. The result with ether **45** (IC_{50} = 6 μM) supports our hypothesis that the amino group helps to anchor the B- and C-ring at an optimal planar torsional angle. The X-ray cocrystal structure of **39** (Figure 4) bound to hGKRP shows that the compound binds as predicted and confirmed the postulated intramolecular hydrogen bond interaction between the amino group on the B-ring and the pyridyl nitrogen of the C-ring.

Encouraged by the result obtained with analogue **39**, we replaced the phenyl group with the three regioisomeric pyridines (**46**–**48**) with the goal of decreasing the log *P* and possibly reducing the cell shift observed for **39** (>25-fold). Unfortunately, the incorporation of the nitrogen atoms was detrimental to the biochemical activity with IC_{50} values 2- to 15-fold higher than the parent phenyl derivative, **39**. However, introduction of a polar pyridine substituent did reduce the cell shift in the case of analogue **46** (only 10-fold).

Having optimized the biochemical and cellular potencies of this set of analogues, we turned our attention to modifications of the central B-ring. The goal was to improve biochemical potency without a substantial increase in MW, lipophilicity, or polar surface area that could impact cell shift and the PKDM profile of these compounds. We examined a small set of analogues that contained replacement of the central 6-membered aromatic group by 5-membered heterocycles (B-ring). To help in the

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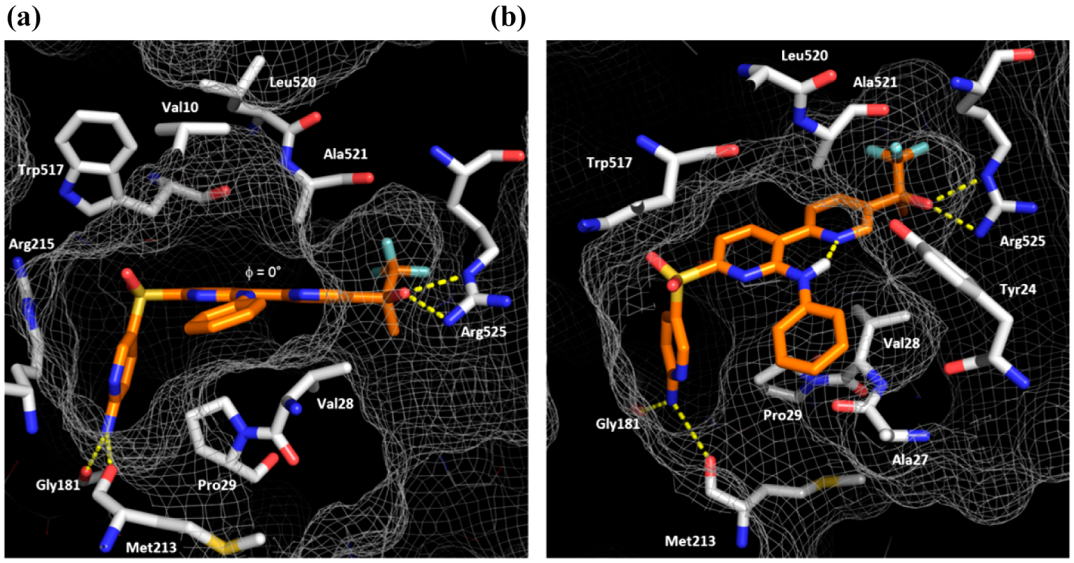

Figure 4. Top (a) and side (b) views of X-ray crystal structure of compound **39** bound to hGKRP. The hydrogen bonds to Gly181, Met213, and Arg525 are depicted in yellow.[12]

design of novel GK-GKRP disruptors, we analyzed the dihedral angle profiles of biaryl sulfones having a thiophene, thiazole, and *N*-methyl imidazole as the central B-ring. In the case of these 5,6-heterocyclic ring systems, there were two dihedral angles that influenced the overall conformation of these derivatives: the angle between the 5-membered B-ring and the six-membered C-ring (Figure 5) and the angle between the aryl sulfone A-ring and the 5-membered B-ring (Figure 6).

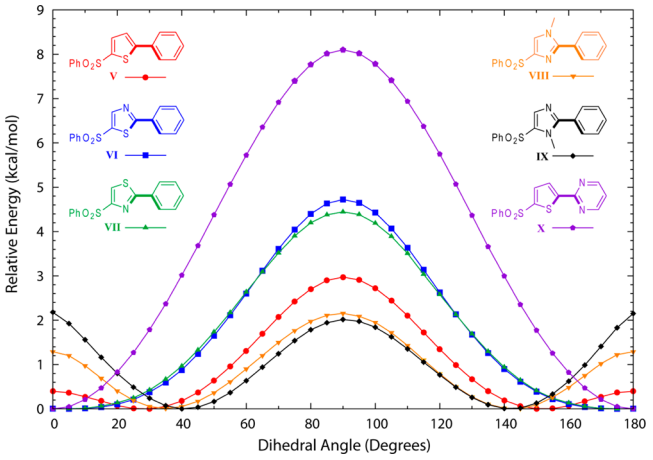

Figure 5. SCRF-B3LYP/6-31G* dihedral profile of (5,6)-biarylsulfone structures (B- and C-rings). The scanned dihedral is depicted in bold.

Figure 5 shows that the 5,6-heterocyclic B−C-ring systems that can adopt low energy conformations near the optimal coplanar geometry are thiophenes (structures V and X) and thiazoles (structures VI and VII). On the other hand the *N*-methyl imidazole scaffolds (structures VIII and IX) were predicted to possess a disfavorable orientation of the B−C-ring system, with a minimum at ∼30−40° and having a 1−2 kcal/mol coplanarization penalty compared to other more favorable 5-membered heterocyclic B-rings. Next we examined the dihedral angle between the A- and B-rings (Figure 6). The optimal dihedral angle in the binding conformation between the A- and B-rings is found to be approximately 90° (Figure 2b). This

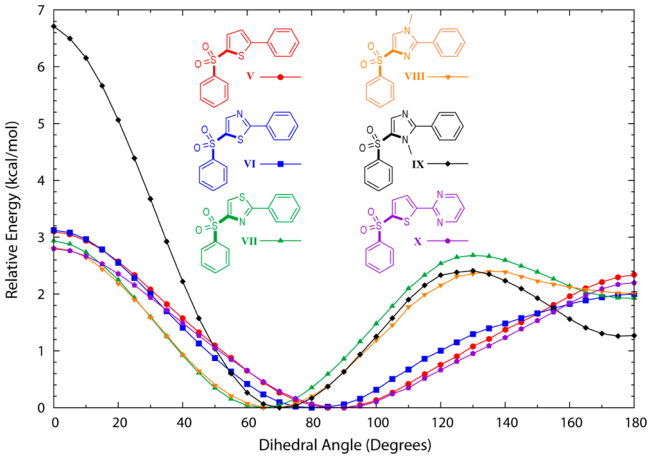

Figure 6. SCRF-B3LYP/6-31G* dihedral profile of (5,6)-biarylsulfone structures (A- and B-rings). The scanned dihedral is depicted in bold.

conformation predisposes the amino on the pyridine A-ring for optimal hydrogen bond interactions with Gly181 and Met213. Figure 6 shows that the two thiophenes (structures V and X) and one of the thiazoles (structure VI) had minima near the optimal 90° orientation, whereas thiazole VII and *N*-methyl imidazoles VIII and IX had minima at nonoptimal orientations of ∼60−70°. The repulsive interactions between either the *N*-methyl substituent (in structure IX) or the in-plane nitrogen lone pair (in structures VII and VIII) and the sulfonic oxygen may give rise to a significant energy penalty for adoption of the required ∼90° binding conformation.

From the analysis of these two dihedral angles we would predict that the thiophene-phenyl (V), thiazole-phenyl (VI), and thiophene-pyrimidine (X) ring systems would provide the most potent analogues and the thiazole-phenyl (VII) and *N*-methyl imidazoles (VIII and IX) would be less favorable. To test this hypothesis the derivatives shown in Table 4 were prepared and evaluated. The results obtained in the biochemical assay were in agreement with the quantum mechanical predictions (i.e., **58**, **65**, and **86** were the most potent while **99**, **105**, and **110** were significantly less active). Specifically, substitution of the phenyl

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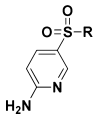
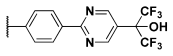
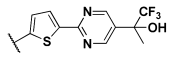
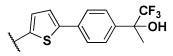
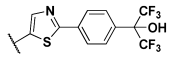
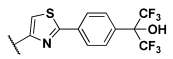
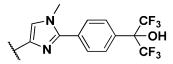
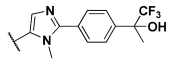
Table 4. SAR of Unsubstituted 5,6-Biaryl Sulfone Analogues



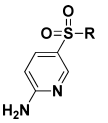
Cmpd No.	R	hGK-hGKRP AlphaScreen IC_{50} (μM)[b]	RLM CL_{int} (μL/min/mg)[c]
13		0.104 ± 0.037	<14
58[a]		0.480 ± 0.048	<14
65[a]		1.930 ± 1.050	<14
86		0.534 ± 0.052	<14
99		>33	<14
105		>33	<14
110[a]		>33	<14

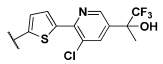
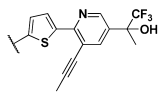
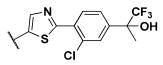
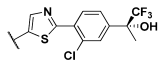
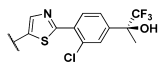
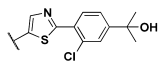
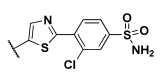
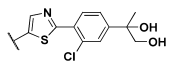
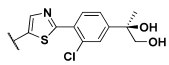
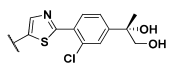
[a]Racemic mixtures. [b]Data reported as the mean and SD where $n \geq 3$. [c]In vitro rat microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM.

B-ring on **13** by a thiophene, a standard bioisostere of a phenyl group, gave sulfone **58**, that was 5-fold less potent. This loss in potency may be due to a decrease in van der Waals interactions between the central ring and the protein, or to the slight change in trajectory versus a six-membered B-ring (structure X, Figure 5). A more dramatic loss in potency was observed when the pyrimidine C-ring was substituted with a phenyl ring (**65**). Compound **65** had an IC_{50} value of 1.93 μM, similar to the original 6,6-biphenyl sulfone **4**. The next set of derivatives contained two heteroatoms within the 5-membered heterocyclic core, two isomeric thiazoles (**86** and **99**) and two isomeric *N*-methyl imidazoles (**105** and **110**). As mentioned above, the imidazole analogues **105** and **110** are highly disfavored and these analogues did not show any significant activity in the GK-GKRP biochemical assay. In contrast, there was a clear difference in potency between the two isomeric thiazoles: the 2,5-disubstituted thiazole **86** was more than 50-fold more potent than the 2,4-disubstituted thiazole **99** (IC_{50} value of 534 nM vs >33 μM).

We focused our continued efforts on improving the biochemical potency in the thiophene (**58**) and 2,5-thiazole series (**86**). An initial set of compounds was prepared to investigate the effect of accessing the shelf region from the ortho position of the C-ring on the thiophene series (Table 5). Substitution of one of the pyrimidyl nitrogens on the C-ring of **58** by a C−Cl (**59**) or C-propyne (**60**) resulted in a greater than 5-fold improvement in biochemical potency; however, the metabolic stability of **60**, the most potent thiophene analogue, was very poor, and also a large cell shift was observed in the rat hepatocyte assay. The X-ray cocrystal structure of **59** bound to hGKRP is depicted in Figure 7.

Table 5. SAR of Substituted 5,6-Biaryl Sulfones



Cmpd No.[a]	R	hGK-hGKRP AlphaScreen IC_{50} (μM)[b]	Rat Translocation EC_{50} (μM)	RLM CL_{int} (μL/min/mg)[c]
59		0.129 ± 0.030	NT[d]	<14
60		0.051 ± 0.015	1.20	>399
87		0.023 ± 0.006	NT[d]	<14
88[e]		0.037 ± 0.017	0.14	<14
89[e]		0.018 ± 0.006	0.98	<14
90		0.015 ± 0.002	0.56	17
91		0.257 ± 0.087	NT[d]	107
92		0.010 ± 0.003	NT[d]	<14
93[e]		0.006 ± 0.002	0.10	<14
94[e]		0.061 ± 0.012	0.42	<14

[a]All the compounds are racemic mixture unless stated. [b]Data reported as the mean and SD where $n \geq 3$. [c]In vitro rat microsomal stability measurements were conducted in the presence of NADPH at 37 °C for 30 min at a final compound concentration of 1 μM. [d]NT = Not tested. [e]The stereochemistry at carbinol carbon was assigned arbitrarily.

Visual inspection of the complex structure revealed that **59** binds to hGKRP in a conformation other than its global minimum. This conformation, possessing a syn orientation of the chloro substituent with respect to the thiophene sulfur, allows the chlorine atom to occupy the more spatially tolerant shelf region. As a consequence, the thiophene sulfur and pyridine nitrogen of the biaryl system are required to adopt a disfavored anti conformation, rather than the preferred S−N syn-locked orientation which would maximize the stabilizing interaction between these heteroatoms.[23−25]

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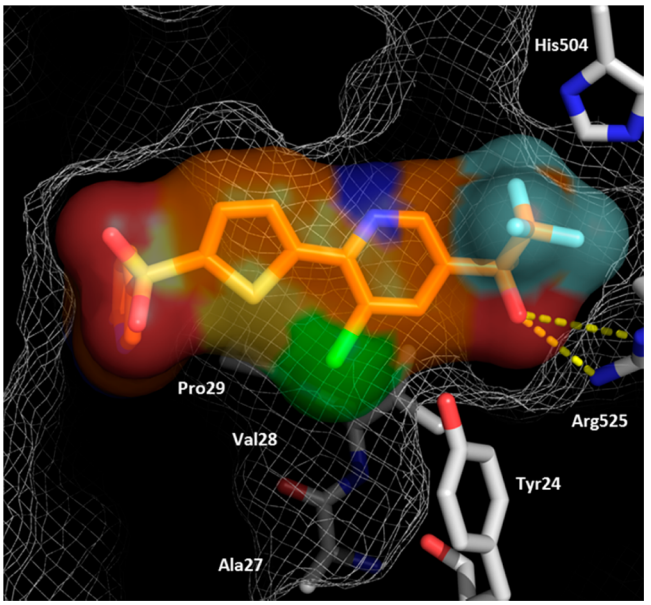

Figure 7. Top view of X-ray cocrystal structure of thiophene **59** bound to hGKRP. Shape complementary of the ligand and hGKRP binding pocket depicted by transparent and mesh surfaces, respectively.[12]

Figure 8 depicts the computed dihedral profile for both the thiophene-chloropyridine moiety present in **59** (structure XI)

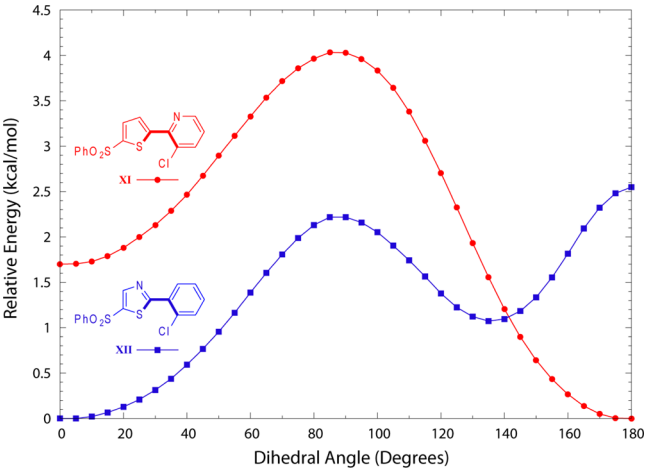

Figure 8. PCM-B3LYP/6-31G* dihedral profile for thiophene-chloropyridine and thiazole-chlorophenyl moieties. The 0° orientation is depicted above each of the respective curves.

and that of a proposed, regioisomeric thiazole-chlorophenyl ring system (structure XII). The S−Cl syn, S−N anti conformation (ϕ = 0°) for bound **59** (structure XI) is predicted to lie ∼1.6 kcal/mol higher in energy above its 180° minimum (Figure 8). Conversely, the thiazole regioisomer (XII) would enrich the population of binding conformer (0°) via elimination of the S−N syn form, which is less suitable for binding (ϕ = 180°; Figure 8). This species (where S−Cl is syn) should instead bind hGKRP in its minimum energy conformation, while still allowing access to the shelf region by the ortho-chloro substituent.[26] Therefore, thiazole analogue **87** was prepared and found to be over 5-fold more potent than its thiophene counterpart **59** (Table 5), in addition this compound was found to be stable in rat liver microsomes. Chiral separation of **87** by supercritical fluid chromatography (SFC) afforded **88** and **89**[27] yielding biochemical IC_{50} values of 37 and 18 nM, respectively, and good activities were obtained in the rat cellular hepatocyte assay.

At this point, attention was turned to the tail piece, the tertiary hydroxyl group on the C-ring, with the goal of optimizing the physicochemical properties of the compound (clogP, PSA, and MW), potentially leading to lower cell shift and consequently higher cellular activity.[10] The hydroxyl group forms a key hydrogen-bond interaction with the side chain guanidine of Arg525 (Figure 2). This hydrophilic residue facilitated incorporation of polarity into the molecule and the surrounding hydrophobic region accommodated the bulky trifluoromethyl group. The gem-dimethyl alcohol, **90** (Table 5), which had a lower clogP and molecular weight compared to **89**, had an IC_{50} in the AlphaScreen similar to the chiral trifluoromethyl alcohol **89** and showed a small improvement in the translocation assay (EC_{50} = 0.56 μM). To further decrease the lipophilicity of the compound, sulfonamide **91** was prepared. Sulfonamides have previously shown to be acceptable substitutions for the benzylic alcohol as a tail group;[10] however, **91** showed significantly lower biochemical potency (IC_{50} = 257 nM). We hypothesized that in the biaryl sulfone series the sulfonamide tail piece did not have the optimal trajectory to completely satisfy the Arg525 hydrogen bond as we have previously seen in the original piperazine series. Incorporation of additional polarity at the tail in the form of a diol (**92**) gave, not only one of the most potent analogues in this series, but also the one with the higher binding efficiency (BE = 0.4).[28] In order to further profile this compound, the two stereoisomers were separated by chiral SFC (**93** and **94**)[27] and tested in the biochemical and cellular assays. The more potent enantiomer **93** not only showed single-digit nanomolar potency in the AlphaScreen but was also the most potent analogue from this series in the rat hepatocyte GK translocation assay (EC_{50} = 0.10 μM).

On the basis of its in vitro properties, sulfone **93** was selected for pharmacokinetic (PK) studies in Sprague−Dawley rats (Table 6). Pharmacokinetic parameters from the intravenous (iv) route indicated a very low plasma clearance of 0.033 L/h/kg, a V_{ss} of 0.18 L/kg, and a terminal half-life of 4.7 h. Following a single oral dose of 10 mg/kg, maximal plasma concentration of compound **93** (57.6 μM total and 0.43 μM free drug) was reached 4 h post dosing and slowly declined over time. The oral bioavailability of compound **93** was estimated to be over 80%. These results allowed for in vivo coverage of the in vitro cellular EC_{50} (0.10 μM) for over 12 h, allowing for evaluation in a PD experiment where the compound was dosed orally at 10 and 100 mg/kg in Sprague−Dawley rats. In this experiment, liver GK translocation from the cell nucleus was monitored by

Table 6. Rat in Vivo PK Properties of Biaryl Sulfone 93

Cmpd No.	$t_{1/2}$[a] (h)	V_{ss}[a] (L/kg)	CL[a] (L/h/kg)	C_{max}[b] (μM)	AUC[b] (μM·h)	F[b] (%)	f_u[c]
93	4.7	0.18	0.033	57.6	568	82	0.0075

[a]2 mg/kg intravenous dose (100% DMSO). [b]10 mg/kg oral dose (1% Tween 80, 2% HPMC, 97% water). [c]Fraction unbound, determined via rapid equilibrium dialysis.

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immunohistochemistry (IHC) at 6 and 24 h post oral dose (Figure 9). An IHC score of four represented no pharmacodynamic (PD) response, while a score of zero indicated complete nuclear translocation of GK. As shown in Figure 9, the 100 mg/kg dose of compound **93** showed complete translocation of GK to the cytoplasm at the 6-h time point and a significant PD effect remained for 24 h. The 10 mg/kg showed more than 60% GK translocation at 6 h. At this dose and time point the mean free drug concentration was 0.19 μM (Figure 9), which approximates the rat hepatocyte cellular EC_{50} of 0.10 μM.

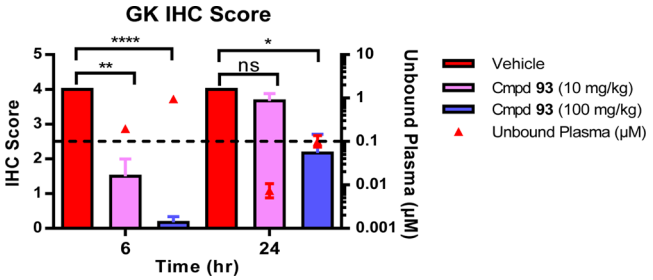

Figure 9. In vivo GK translocation (colored bars, left *y* axis) and unbound plasma concentrations (red triangles, right *y* axis) in rats following oral administration of **93** (10, 100 mg/kg, 6 and 12 h postdose). The statistical significance of the measurements were based on comparison to the individual vehicle control groups ($n = 6$; * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$). The dotted line represents the GK translocation EC_{50} (0.10 μM) in rat primary hepatocytes.

CONCLUSION

In summary, a new series of biaryl sulfones based on our previously disclosed aryl piperazines GK-GKRP disruptors was designed and prepared. Analysis of the X-ray crystal structure of original biaryl sulfone **4** bound to hGKRP, coupled with conformational analysis and SAR studies, led initially to the discovery of unsubstituted biarylsulfones possessing good in vitro activity but lacking cellular activity in rat hepatocytes. Potency was further increased by accessing a previously described hydrophobic shelf region from either the B- or C-rings. Optimization of this series culminated in the discovery of thiazole sulfone **93**. This new sulfone, possessing a lipophilicity-lowering, Arg525-engaging diol moiety, demonstrated single-digit nanomolar potency as a GK-GKRP disruptor in a biochemical assay and was also able to modulate the translocation of nuclear GK in rat hepatocytes. Pharmacokinetic data indicated that **93** exhibited low clearance and high oral bioavailability, and in vivo pharmacological studies showed that **93** was able to increase liver GK translocation to the cytoplasm following a single oral dose. Taken together, the present work represents an encouraging entry into a novel series of potent in vitro and in vivo active GK-GKRP disruptors.

EXPERIMENTAL SECTION

Theoretical Methology and Conformational Analysis. All quantum mechanical calculations were performed with the *Gaussian 09* program system utilizing the B3LYP density functional, the 6-31G* basis, and the standard IEFPCM self-consistent reaction field (SCRF) implicit aqueous solvation model.[20] Dihedral scans were performed using a series of constrained optimizations, whereby the specified dihedral angle was kept frozen at a given value, with full optimization of the remaining geometric parameters subject to the given dihedral constraint. Total energies for a given system were then converted into relative energies (kcal/mol) for graphical depiction.

Biology. hGK–hGKRP AlphaScreen, GK translocation in rat hepatocytes, and in vivo PD studies in rats were performed as described previously.[8−11]

Chemistry. *General Procedures.* Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich, Acros, or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Microwave-assisted reactions were conducted with either an Initiator from Biotage, Uppsala, Sweden, or an Explorer from CEM, Matthews, NC. Silica gel chromatography was performed using either glass columns packed with silica gel (200–400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage or Redisep). NMR spectra were determined with a Bruker 400 or 300 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ units). All final compounds were purified to >95% purity as determined by LC–MS obtained on an Agilent 1100 spectrometer using the following methods: (A) Agilent SB-C18 column (50 × 3.0 mm, 2.5 μm) at 40 °C with a 1.5 mL/min flow rate using a 5–95% gradient of 0.1% TFA in CH_3CN in 0.1% TFA in water, over 3.5 min; (B) Phenomenex Gemini NX C18 column (50 × 3.0 mm, 3 μm) at 40 °C with a 1.5 mL/min flow rate using a 5–95% gradient of 0.1% formic acid in CH_3CN in 0.1% formic acid in water over 3.5 min. Low-resolution MS data were obtained at the same time as the purity determination on the LC–MS instrument using the ES ionization mode (positive).

*5-((4-Bromophenyl)sulfonyl)pyridin-2-amine (**7**).* A mixture of 2-chloro-5-iodopyridine (**5**) (1.12 g, 4.64 mmol), 4-bromothiophenol (**6**) (0.87 g, 4.64 mmol), CuI (44 mg, 0.23 mmol), K_2CO_3 (1.28 g, 9.29 mmol), and ethylene glycol (0.52 mL, 9.29 mmol) in IPA (10 mL) was heated under nitrogen at 80 °C for 16 h. The mixture was allowed to cool to room temperature and partitioned between water and CH_2Cl_2. The separated organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude product. The residue was purified by silica gel column chromatography (0–10% EtOAc/hexanes) to afford 5-((4-bromophenyl)thio)-2-chloropyridine (1.17 g, 84%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{11}H_7BrClNS$: 298; found 299 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 2.54 Hz, 1H), 7.81 (dd, J = 2.54, 8.41 Hz, 1H), 7.57–7.61 (m, 2H), 7.54 (d, J = 8.41 Hz, 1H), 7.30–7.35 (m, 2H).

To a solution of 5-((4-bromophenyl)thio)-2-chloropyridine (0.27 g, 0.91 mmol) in CH_2Cl_2 (5 mL) was added 3-chloroperoxybenzoic acid (0.41 g, 1.82 mmol). The reaction mixture was stirred at room temperature for 2 h and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0–20% EtOAc/hexanes) to afford 5-((4-bromophenyl)sulfonyl)-2-chloropyridine (0.10 g, 33%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{11}H_7BrClNO_2S$: 331; found 332 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (d, J = 2.54 Hz, 1H), 8.40 (dd, J = 2.64, 8.51 Hz, 1H), 7.93–8.02 (m, 2H), 7.84–7.91 (m, 2H), 7.79 (d, J = 8.41 Hz, 1H).

To a 25 mL glass resealable vial was added 5-((4-bromophenyl)-sulfonyl)-2-chloropyridine (98 mg, 0.29 mmol), aqueous NH_4OH (3 mL), and EtOH (3 mL). The vial was closed and heated at 120 °C for 18 h, the reaction was allowed to cool to room temperature, and the solvent was partially removed under reduced pressure. The white precipitate obtained was filtered, washed with water, and dried under reduced pressure. The title compound (75 mg, 81%) was obtained as a white solid and used without further purification. MS (ESI pos. ion): *m/z* calcd for $C_{11}H_9BrN_2O_2S$: 312; found 313 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, J = 2.54 Hz, 1H), 7.78–7.86 (m, 4H), 7.76 (dd, J = 2.54, 9.00 Hz, 1H), 7.15 (br s, 2H), 6.48 (d, J = 9.00 Hz, 1H).

*2-(4′-((6-Aminopyridin-3-yl)sulfonyl)-[1,1′-biphenyl]-4-yl)-1,1,1-trifluoropropan-2-ol (**4**).* A glass microwave reaction vessel was charged with **7** (71 mg, 0.23 mmol), 1,1,1-trifluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (**8**)[16] (86 mg, 0.27 mmol), $PdCl_2$(dppf) (18 mg, 0.02 mmol), Cs_2CO_3 (222 mg, 0.68 mmol), DME (1 mL), and water (0.1 mL). The vessel was closed and purged with

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nitrogen for several minutes. The reaction mixture was stirred and heated in a microwave reactor at 100 °C for 30 min. The organic layer was separated, and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (0−3% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (83 mg, 87%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{20}H_{17}F_3N_2O_3S$: 422; found 423 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 2.54 Hz, 1H), 7.94−8.02 (m, 2H), 7.90 (d, J = 8.61 Hz, 2H), 7.81 (dd, J = 2.54, 9.00 Hz, 1H), 7.73 (q, J = 8.61 Hz, 4H), 7.10 (br s, 2H), 6.67 (s, 1H), 6.51 (d, J = 9.00 Hz, 1H), 1.72 (s, 3H).

*5-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-sulfonyl)pyridin-2-amine (**9**).* A 25 mL glass resealable vial was charged with **7** (0.53 g, 1.69 mmol), bis(pinacolato)diboron (0.43 g, 1.69 mmol), $PdCl_2$(dppf) (69 mg, 0.08 mmol), KOAc (0.50 g, 5.1 mmol), and dioxane (8 mL). The vial was closed, purged with nitrogen for several minutes, and heated at 100 °C for 18 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite (diatomaceous earth), and the pad was washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to yield the title compound (0.61 g, 100%) as a brown solid that was used without further purification. MS (ESI pos. ion): m/z calcd for $C_{17}H_{21}BN_2O_4S$: 360; found 279 (M $-C_6H_{10}$).

*2-(6-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)pyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**12**).* A glass microwave reaction vessel was charged with **9** (0.38 g, 1.06 mmol), 2-(6-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (**10**)[10] (0.15 g, 0.53 mmol), $PdCl_2$(dppf) (22 mg, 0.03 mmol), Cs_2CO_3 (0.52 g, 1.59 mmol), DME (1.5 mL), and water (0.15 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated in a microwave at 100 °C for 30 min. The organic layer was separated and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (0−3% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (99 mg, 39%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{19}H_{13}F_6N_3O_3S$: 477; found 478 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.79 (s, 1H), 8.29 (d, J = 2.35 Hz, 1H), 8.13 (d, J = 8.80 Hz, 2H), 7.99−8.05 (m, 2H), 7.85 (d, J = 8.61 Hz, 2H), 7.62 (dd, J = 2.64, 8.90 Hz, 1H), 6.92 (s, 2H), 6.32 (d, J = 8.80 Hz, 1H).

*2-(2-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)pyrimidin-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**13**).* A glass microwave reaction vessel was charged with **9** (0.26 g, 0.73 mmol), 2-(2-chloropyrimidin-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**11**)[10] (0.10 g, 0.36 mmol), $PdCl_2$(dppf) (15 mg, 0.02 mmol), Cs_2CO_3 (0.36 g, 1.09 mmol), DME (1.5 mL), and water (0.15 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated in a microwave at 100 °C for 30 min. The organic layer was separated and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (0−3% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (56 mg, 32%) as a tan solid. MS (ESI pos. ion): m/z calcd for $C_{18}H_{12}F_6N_4O_3S$: 478; found 479 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (br s, 1H), 9.04 (s, 2H), 8.42 (d, J = 8.41 Hz, 2H), 8.31 (d, J = 2.74 Hz, 1H), 7.91 (d, J = 8.61 Hz, 2H), 7.63 (dd, J = 2.54, 9.00 Hz, 1H), 6.96 (s, 2H), 6.35 (s, 1H).

*5-((6-Chloropyridin-3-yl)thio)pyridin-2-amine (**15**).* To a stirred suspension of **5** (0.98 g, 4.11 mmol) and 6-aminopyridine-3-thiol (**14**) (0.52 g, 4.11 mmol) in IPA (7 mL) was added CuI (0.39 g, 2.05 mmol), K_2CO_3 (1.42 g, 10.26 mmol), and ethylene glycol (0.57 mL, 10.26 mmol). The reaction mixture was heated at 90 °C for 48 h. After cooling to room temperature, the mixture was filtered through a short pad of Celite. The filter cake was washed with EtOAc and CH_2Cl_2 (3 × 15 mL, each) and the combined organics were concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0−70% EtOAc/hexanes) to provide the title compound (0.45 g, 46%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{10}H_8ClN_3S$: 237; found 238 (M + H).

*2-(5′-((6-Aminopyridin-3-yl)sulfonyl)-[2,2′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**17**).* A stirred mixture of **15** (52 mg, 0.22 mmol), 1,1,1-trifluoro-2-(6-(trimethylstannanyl)-3-pyridinyl)-2-propanol (**16**)[16] (0.12 g, 0.33 mmol), Pd(PPh_3)$_4$ (13 mg, 11 μmol), and LiCl (46 mg, 1.1 mmol) in dioxane (2 mL) was heated at 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature and filtered through a short pad of Celite. The filter cake was washed with EtOAc (3 × 10 mL) and the combined organic phases were concentrated under reduced pressure to give the crude residue. The crude material was purified by silica gel chromatography (0−5% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the corresponding thioether intermediate as a light-yellow solid. This material was dissolved in dioxane (2 mL), and a solution of oxone (0.27 g, 0.44 mmol) in water (1 mL) was slowly added. The suspension was stirred at room temperature for 3 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give the crude material as an off-white solid. The crude material was purified by silica gel chromatography (0−5% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (9 mg, 10%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{18}H_{15}F_3N_4O_3S$: 424; found 425 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 9.15 (d, J = 1.76 Hz, 1H), 8.93 (s, 1H), 8.52−8.65 (m, 2H), 8.49 (d, J = 8.41 Hz, 1H), 8.41 (dd, J = 2.25, 8.51 Hz, 1H), 8.18 (dd, J = 1.76, 8.41 Hz, 1H), 7.90 (dd, J = 2.54, 9.00 Hz, 1H), 6.62 (d, J = 9.19 Hz, 1H), 1.83 (s, 3H).

*2-(6-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)-5-chloropyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**20**).* A glass microwave reaction vessel was charged with **9** (0.40 g, 1.12 mmol), 2-(5,6-dichloropyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**18**)[11] (0.10 g, 0.36 mmol), $PdCl_2$(dppf) (38 mg, 0.05 mmol), Cs_2CO_3 (0.91 g, 2.79 mmol), DME (3 mL), and water (0.3 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated in a microwave at 100 °C for 30 min. The organic layer was separated and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0−2% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (0.12 g, 68%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{19}H_{12}ClF_6N_3O_3S$: 511; found 512 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.90 (s, 1H), 8.49 (d, J = 2.54 Hz, 1H), 8.25 (s, 1H), 8.03 (d, J = 8.41 Hz, 2H), 7.95 (d, J = 8.41 Hz, 2H), 7.82 (dd, J = 2.54, 9.00 Hz, 1H), 7.13 (s, 2H), 6.52 (d, J = 9.00 Hz, 1H).

*2-(6-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)-5-methoxypyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**21**).* A glass microwave reaction vessel was charged with **9** (0.14 g, 0.38 mmol), 2-(6-chloro-5-methoxypyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**19**)[11] (78 mg, 0.25 mmol), $PdCl_2$(AmPhos)$_2$ (9 mg, 0.01 mmol), K_2CO_3 (0.10 g, 0.76 mmol), dioxane (1 mL), and water (0.1 mL). The vial was sealed and purged with nitrogen for several minutes. The reaction mixture was stirred and heated in a microwave at 140 °C for 40 min. The mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc and CH_2Cl_2 (3 × 10 mL each). The combined organic extracts were concentrated under reduced pressure and the crude material was purified by silica gel chromatography (0−7% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (57 mg, 45%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{20}H_{15}F_6N_3O_4S$: 507; found 508 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 8.53 (s, 1H), 8.47 (d, J = 2.54 Hz, 1H), 8.05−8.16 (m, 2H), 7.93−8.04 (m, 2H), 7.80 (dd, J = 2.54, 9.00 Hz, 1H), 7.73 (s, 1H), 7.10 (s, 2H), 6.51 (d, J = 9.00 Hz, 1H), 3.91 (s, 3H).

*2-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)nicotinonitrile (**22**).* A glass microwave reaction vessel was charged with **20** (60 mg, 0.12 mmol), zinc cyanide (21 mg, 0.18 mmol), XPhos (5 mg, 0.01 mmol), $Pd_2(dba)_3$ (5 mg, 0.006 mmol), and DMF (0.5 mL). The vial was sealed and purged with nitrogen for several minutes. The reaction mixture was stirred and heated in a microwave reactor at 140 °C for 20 min. The mixture was passed through a short plug of Celite. The filter cake was washed with EtOAc (3 × 10 mL). The combined organic phases were concentrated under reduced pressure and the crude material was purified by silica gel chromatography (0−5% 1 M NH_3 in MeOH/CH_2Cl_2), followed by preparative silica gel TLC (3% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (10 mg, 17%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{20}H_{12}F_6N_4O_3S$: 502; found 503 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (br s, 1H), 8.67 (br s, 1H), 8.45 (br s, 1H), 8.03−

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8.17 (m, 4H), 7.91 (d, J = 9.00 Hz, 1H), 6.53 (d, J = 9.00 Hz, 1H), 5.09 (br s, 2H), 4.25 (br s, 1H).

*2-(6-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)-5-(prop-1-yn-1-yl)pyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**23**).* A sealable reaction vial was charged with **20** (98 mg, 0.19 mmol), XPhos palladium(II) phenethylamine chloride (7 mg, 10 μmol), Cs_2CO_3 (0.19 g, 0.57 mmol), 1-(trimethylsilyl)-1-propyne (0.14 mL, 0.96 mmol), and MeCN (2 mL). The vial was sealed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography (0−3% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (68 mg, 70%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{22}H_{15}F_6N_3O_3S$: 515; found 516 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (br s, 1H), 8.87 (br s, 1H), 8.48 (d, J = 2.35 Hz, 1H), 8.17 (d, J = 8.41 Hz, 2H), 8.12 (s, 1H), 8.02 (d, J = 8.41 Hz, 2H), 7.82 (dd, J = 2.45, 8.90 Hz, 1H), 7.13 (s, 2H), 6.52 (d, J = 9.00 Hz, 1H), 2.05 (s, 3H).

*3-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-2-propyn-1-ol (**24**).* A glass reaction vial was charged with **20** (73 mg, 0.14 mmol), XPhos palladium(II) phenethylamine chloride (5 mg, 7 μmol), K_2CO_3 (30 mg, 0.21 mmol), *tert*-butyl(dimethyl)(2-propyn-1-yloxy)silane (0.043 mL, 0.21 mmol), and DMA (2 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 110 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 × 10 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0−4% 2 M NH_3 in MeOH/CH_2Cl_2) to give 2-(6-(4-((6-amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-((*tert*-butyl(dimethyl)silyl)oxy)-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol as tan solid. This solid was dissolved in THF (3 mL) and tetra-*N*-butylammoniun fluoride (0.19 mL, 0.19 mmol, 1 M in THF) was added. The reaction mixture was stirred at room temperature for 2 h and then diluted with satd NH_4Cl (5 mL) and extracted with EtOAc (5 mL). The organic extract was washed with water (3 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give the crude material. The residue was purified by silica gel chromatography (5−7% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (43 mg, 58%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{22}H_{15}F_6N_3O_4S$: 531; found 532 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (br s, 1H), 8.94 (d, J = 1.37 Hz, 1H), 8.50 (d, J = 2.54 Hz, 1H), 8.14−8.28 (m, 3H), 8.03 (d, J = 8.61 Hz, 2H), 7.84 (dd, J = 2.64, 8.90 Hz, 1H), 7.17 (s, 2H), 6.53 (d, J = 9.00 Hz, 1H), 5.42 (t, J = 6.06 Hz, 1H), 4.31 (d, J = 6.06 Hz, 2H).

*2-(6-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(3-methoxy-1-propyn-1-yl)-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (**25**).* A 25 mL glass resealable vial was charged with **20** (0.10 g, 0.20 mmol), XPhos palladium(II) phenethylamine chloride (7 mg, 10 μmol), Cs_2CO_3 (0.20 g, 0.61 mmol), 3-methoxy-1-propyne (0.09 mL, 1.03 mmol), and MeCN (3 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography (4−7% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (83 mg, 76%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{17}F_6N_3O_4S$: 545; found 546 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (br s, 1H), 8.94 (s, 1H), 8.48 (s, 1H), 8.19 (br s, 1H), 8.13 (d, J = 7.43 Hz, 2H), 8.03 (d, J = 7.63 Hz, 2H), 7.82 (d, J = 8.41 Hz, 1H), 7.15 (br s, 2H), 6.52 (d, J = 8.61 Hz, 1H), 4.30 (br s, 2H), 3.13 (s, 3H).

*(2*R*)-4-(2-(4-((6-Amino-3-pyridinyl)sulfonyl)phenyl)-5-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-3-pyridinyl)-3-butyn-2-ol (**26**).* A 25 mL glass resealable vial was charged with **20** (98 mg, 0.19 mmol), XPhos palladium(II) phenethylamine chloride (7 mg, 10 μmol), K_2CO_3 (40 mg, 0.29 mmol), (2*R*)-3-butyn-2-ol (0.02 mL, 0.29 mmol), and DMA (2 mL). The vial was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 110 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the crude material. This material was purified by silica gel chromatography (2−5% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (66 mg, 64%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{17}F_6N_3O_4S$: 545; found 546 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (br s, 1H), 8.93 (d, J = 1.76 Hz, 1H), 8.49 (d, J = 2.15 Hz, 1H), 8.16−8.24 (m, 2H), 8.14 (d, J = 1.96 Hz, 1H), 7.99−8.09 (m, 2H), 7.83 (dd, J = 2.54, 9.00 Hz, 1H), 7.16 (s, 2H), 6.53 (d, J = 8.80 Hz, 1H), 5.54 (d, J = 5.48 Hz, 1H), 4.57 (quin, J = 6.31 Hz, 1H), 1.30 (d, J = 6.65 Hz, 3H).

*4-(2-(4-((6-Aminopyridin-3-yl)sulfonyl)phenyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)-2-methylbut-3-yn-2-ol (**27**).* A glass microwave reaction vessel was charged with **20** (105 mg, 0.20 mmol), XPhos palladium(II) phenethylamine chloride (7 mg, 10 μmol), Cs_2CO_3 (0.20 g, 0.61 mmol), 2-methylbut-3-yn-2-ol (0.10 mL, 1.02 mmol), and MeCN (3 mL). The vial was sealed and purged with nitrogen for several minutes. The reaction mixture was stirred and heated in a microwave reactor at 140 °C for 40 min. The reaction mixture was concentrated and purified by silica gel chromatography (4−7% 2 M NH_3 in MeOH/CH_2Cl_2) to give the title compound (4 mg, 4%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_{24}H_{19}F_6N_3O_4S$: 559; found 560 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.91 (d, J = 1.76 Hz, 1H), 8.50 (d, J = 2.15 Hz, 1H), 8.22 (d, J = 1.96 Hz, 1H), 8.12−8.17 (m, 2H), 8.04−8.08 (m, 2H), 7.86 (dd, J = 2.54, 9.00 Hz, 1H), 6.60 (d, J = 8.80 Hz, 1H), 1.43 (s, 6H).

*2-(2′,6′-Difluoro-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**30**).* A 25 mL round-bottomed flask was charged with 2-(6-bromopyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**29**)[10] (0.35 g, 1.30 mmol), 2,6-difluoropyridine-3-boronic acid (**28**) (0.22 g, 1.39 mmol), KOAc (0.14 g, 1.38 mmol), $PdCl_2(AmPhos)_2$ (40 mg, 0.056 mmol), dioxane (5 mL), and water (0.5 mL). The flask was closed and purged with nitrogen for several minutes. The reaction mixture was heated at 80 °C for 18 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10−40% EtOAc/hexanes) to give the title compound (0.25 g, 59%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{13}H_9F_5N_2O$: 304; found 305 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.73 (q, J = 8.30 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 2.7, 8.2 Hz, 1H), 1.87 (s, 3H).

*tert-Butyl (5-((2′-fluoro-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-[2,3′-bipyridin]-6′-yl)thio)pyridin-2-yl)carbamate (**32**).* A glass microwave reaction vessel was charged with **30** (2.70 g, 8.88 mmol), *tert*-butyl (5-mercaptopyridin-2-yl)carbamate (**31**)[16] (2.61 g, 11.54 mmol), K_2CO_3 (2.45 g, 17.75 mmol), and DMF (24 mL). The vial was sealed and purged with nitrogen for several minutes. The reaction mixture was stirred and heated in a microwave reactor at 80 °C for 15 min. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 15 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10−40% EtOAc/hexanes) to give the title compound (2.65g, 58%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{22}F_4N_4O_3S$: 510; found 533 (M + Na). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.17 (s, 1 H), 8.89 (d, J = 1.8 Hz, 1 H), 8.50−8.43 (m, 1 H), 8.39 (dd, J = 8.0, 9.9 Hz, 1 H), 8.10 (dd, J = 2.1, 8.4 Hz, 1 H), 8.05−7.92 (m, 2 H), 7.85 (d, J = 6.9 Hz, 1 H), 7.10 (dd, J = 1.8, 8.0 Hz, 1 H), 6.90 (s, 1 H), 1.76 (s, 3 H), 1.50 (s, 9 H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-fluoro-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**33**).* To a suspension of **32** (1.80 g, 4.39 mmol) in water (10 mL) at 0 °C was slowly added H_2SO_4 (11.7 mL, 219 mmol). After stirring for 5 min, sodium dichromate dihydrate (3.27 g, 10.97 mmol) was added and the cooling bath was removed. The reaction mixture was stirred at room temperature for 1.5 h, cooled to 0 °C, and quenched with ice (~7 g). The resulting mixture was basified to pH ~ 6 using 5 N NaOH and then extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (0.80 g,

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41%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{18}H_{14}F_4N_4O_3S$: 442; found 443 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (d, J = 1.9 Hz, 1H), 8.77 (dd, J = 7.8, 9.3 Hz, 1H), 8.45 (d, J = 2.3 Hz, 1H), 8.26−8.09 (m, 2H), 7.96 (dd, J = 1.7, 8.4 Hz, 1H), 7.81 (dd, J = 2.6, 8.9 Hz, 1H), 7.24 (s, 2H), 6.96 (s, 1H), 6.55 (d, J = 8.9 Hz, 1H), 1.77 (s, 3H).

General S_N2' Methods for the Preparation of Aminopyridines (34−40 and 42−44). *Method A.* To a solution of **33** (1 equiv) in DMSO was added the amine (2−11 equiv). The reaction mixture was stirred and heated in a microwave at 100 °C for 15 min. The reaction mixture was allowed to cool to room temperature then directly subjected to chromatographic purification or partitioned between water and an organic solvent (EtOAc or CH_2Cl_2). The combined organic phases were dried, filtered, concentrated under reduced pressure, and then purified by silica gel column chromatography.

Method B. To a solution of **32** or **33** (1 equiv) in THF at −50 °C was added KHMDS or LiHMDS (5−10 equiv) followed by the amine (2 equiv). The solution was stirred at 0 °C for 15 min and quenched by the addition of HCl (2 N). The reaction mixture was partitioned between water and EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography.

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(methylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol dihydrochloride (**34**).* This compound was prepared from **33** (17 mg, 0.038 mmol) and $MeNH_2$ (0.3 mL, 9.66 mmol, 40% solution) according to the general synthesis (method A). The product was isolated as a dihydrochloride salt and a yellow solid by treatment with HCl (20 μL, 4 N in dioxane) and filtration (18 mg, 52%). MS (ESI pos. ion): m/z calcd for $C_{19}H_{18}F_3N_5O_3S$: 453; found 454 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 1H), 8.54 (d, J = 2.20 Hz, 1H), 8.31 (d, J = 8.00 Hz, 1H), 8.20−8.12 (m, 1H), 8.12−8.03 (m, 1H), 7.31 (d, J = 7.80 Hz, 1H), 8.84 (d, J = 9.20 Hz, 1H), 2.90 (s, 3H), 1.78 (s, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(ethylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**35**).* This compound was prepared from **33** (21 mg, 0.05 mmol) and $EtNH_2$ (0.1 mL, 0.2 mmol, 2 M in THF) according to the general synthesis (method A). The title compound (13 mg, 56%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{20}H_{20}F_3N_5O_3S$: 467; found 468 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.75 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 2.5 Hz, 1H), 8.11−7.98 (m, 2H), 7.89−7.76 (m, 2H), 7.22 (d, J = 7.7 Hz, 1H), 6.51 (d, J = 8.9 Hz, 1H), 3.35 (q, J = 7.2 Hz, 2H), 1.69 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(isopropylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**36**).* This compound was prepared from **33** (70 mg, 0.16 mmol) and i-$PrNH_2$ (0.07 mL, 0.79 mmol) according to the general synthesis (method A). The title compound (56 mg, 73%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{21}H_{22}F_3N_5O_3S$: 481; found 482 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (d, J = 6.1 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.72 (d, J = 2.3 Hz, 1H), 8.06 (dd, J = 2.5, 8.8 Hz, 1H), 8.01 (dd, J = 2.3, 8.6 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 5.12 (s, 2H), 4.27−4.09 (m, 1H), 2.82 (br s, 1H), 1.87 (s, 3H), 1.21 (d, J = 6.6 Hz, 6H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(cyclopropylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**37**).* This compound was prepared from **33** (70 mg, 0.16 mmol) and cyclopropylamine (0.06 mL, 0.79 mmol) according to the general synthesis (method A). The title compound (58 mg, 76%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{21}H_{20}F_3N_5O_3S$: 479; found 480 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (br s, 1H), 8.79 (dd, J = 2.0, 8.3 Hz, 2H), 8.14 (dd, J = 2.3, 8.8 Hz, 1H), 8.02 (dd, J = 2.2, 8.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 6.54 (dd, J = 0.6, 8.8 Hz, 1H), 5.11 (s, 2H), 2.89−2.72 (m, 2H), 1.86 (s, 3H), 0.85−0.70 (m, 2H), 0.53−0.37 (m, 2H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(cyclohexylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**38**).* This compound was prepared from **33** (70 mg, 0.16 mmol) and cyclohexylamine (0.09 mL, 0.79 mmol) according to the general synthesis (method A). The title compound (62 mg, 75%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{24}H_{26}F_3N_5O_3S$: 521; found 522 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.34 (d, J = 6.0 Hz, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.08 (dd, J = 2.3, 8.8 Hz, 1H), 8.01 (dd, J = 2.4, 8.6 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 5.23 (s, 2H), 3.89 (dd, J = 3.9, 9.4 Hz, 1H), 2.70 (br s, 1H), 1.91 (d, J = 12.1 Hz, 2H), 1.87 (s, 3H), 1.80−1.58 (m, 3 H), 1.50−1.36 (m, 2H), 1.31−1.18 (m, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(phenylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**39**).* This compound was prepared from **33** (0.12 g, 0.28 mmol) and aniline (0.05 mL, 0.55 mmol) according to the general synthesis (method B). The title compound (43 mg, 29%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{24}H_{20}F_3N_5O_3S$: 515; found 516 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD): δ 8.94 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.14 (dd, J = 2.2, 8.5 Hz, 1H), 7.97−7.88 (m, 2H), 7.60−7.53 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 1.82 (s, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(benzylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**40**).* This compound was prepared from **33** (30 mg, 0.07 mmol) and benzylamine (80 mg, 0.75 mmol) according to the general synthesis (method A). The title compound (23 mg, 64%) was obtained as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{25}H_{22}F_3N_5O_3S$: 529; found 530 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.86 (s, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.71 (dd, J = 2.2, 8.9 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.31−7.19 (m, 5H), 6.46 (d, J = 9.0 Hz, 1H), 4.70 (s, 2H), 1.81 (s, 3H).

*tert-Butyl (5-((2′-phenoxy-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-[2,3′-bipyridin]-6′-yl)thio)pyridin-2-yl)carbamate (**41**).* To a 25 mL round-bottomed flask was added **32** (80 mg, 0.16 mmol), phenol (44 mg, 0.47 mmol), Cs_2CO_3 (0.26 g, 0.78 mmol), and DMSO (1 mL). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (10−40% acetone/hexanes) to give the title compound (65 mg, 71%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{29}H_{27}F_3N_4O_4S$: 584; found 585 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (d, J = 1.9 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.92 (dd, J = 2.3, 8.4 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.64−7.51 (m, 2H), 7.30 (s, 1H), 7.24 (s, 1H), 7.17−7.08 (m, 1H), 6.95 (d, J = 8.0 Hz, 3H), 2.53 (s, 1H), 1.85 (s, 3H), 1.59 (s, 9H).

*tert-Butyl (5-((2′-(pyridin-4-ylamino)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-[2,3′-bipyridin]-6′-yl)thio)pyridin-2-yl)carbamate (**42**).* This compound was prepared from **32** (0.10 g, 0.28 mmol) and 4-aminopyridine (0.09 g, 1.0 mmol) according to the general synthesis (method B). The title compound (80 mg, 70%) was obtained as a white solid. MS (ESI pos. ion): m/z calcd for $C_{28}H_{27}F_3N_6O_3S$: 584; found 585 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.78 (s, 1H), 10.25 (s, 1H), 9.01 (s, 1H), 8.48 (dd, J = 0.7, 2.2 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.19−8.07 (m, 4H), 8.07−7.93 (m, 2H), 7.30−7.20 (m, 2H), 6.99−6.90 (m, 2H), 1.78 (s, 3H), 1.52 (s, 9H).

*tert-Butyl (5-((2′-(pyridin-3-ylamino)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-[2,3′-bipyridin]-6′-yl)thio)pyridin-2-yl)carbamate (**43**).* This compound was prepared from **32** (70 mg, 0.14 mmol) and 3-aminopyridine (65 mg, 0.69 mmol) according to the general synthesis (method B). The title compound (60 mg, 75%) was obtained as a light-yellow solid. MS (ESI pos. ion): m/z calcd for $C_{28}H_{27}F_3N_6O_3S$: 584; found 585 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.61 (s, 1H), 10.18 (s, 1H), 9.01 (s, 1H), 8.58 (d, J = 2.5 Hz, 1H), 8.44 (dd, J = 0.8, 2.1 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 1.2 Hz, 2H), 8.07−8.01 (m, 1H), 8.00−7.91 (m, 2H), 7.84−7.74 (m, 1H), 6.99 (dd, J = 4.8, 8.4 Hz, 1H), 6.93 (s, 1H), 6.77 (d, J = 8.2 Hz, 1H), 1.78 (s, 3H), 1.52 (s, 9H).

*tert-Butyl (5-((2′-(pyridin-2-ylamino)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-[2,3′-bipyridin]-6′-yl)thio)pyridin-2-yl)carbamate (**44**).* This compound was prepared from **32** (70 mg, 0.14 mmol) and 2-aminopyridine (65 mg, 0.69 mmol) according to the general synthesis (method B). The title compound (62 mg, 77%) was obtained as a tan

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solid. MS (ESI pos. ion): m/z calcd for $C_{28}H_{27}F_3N_6O_3S$: 584; found 585 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.46 (s, 1H), 10.22 (s, 1H), 8.90 (d, J = 1.8 Hz, 1H), 8.48 (d, J = 1.6 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.20 (dd, J = 1.0, 4.8 Hz, 1H), 8.18−8.13 (m, 1H), 8.13−8.07 (m, 1H), 8.07−8.01 (m, 1H), 8.00−7.94 (m, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.33 (dt, J = 2.0, 7.9 Hz, 1H), 6.94 (s, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.85 (dt, J = 0.8, 6.0 Hz, 1H), 1.80 (s, 3H), 1.53 (s, 9H).

General Method for the Oxidation of Sulfides to Sulfones. To a suspension of **41**, **42**, **43**, or **44** (1 equiv) in water was added H_2SO_4 (40 equiv) and the solution was stirred at room temperature for 15 min. Then, $Na_2Cr_2O_7$ (2 equiv) was added, and the solution was stirred at room temperature for 2−3 h. The reaction mixture was quenched by the addition of NaOH (5 N) (pH ∼6) and partitioned between water and EtOAc. The organic extract was dried, filtered, concentrated under reduced pressure, and then purified by silica gel column chromatography.

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-phenoxy-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**45**).* This compound was prepared from **41** (75 mg, 0.13 mmol), according to the general oxidation method to afford the title compound (40 mg, 60%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{24}H_{19}F_3N_4O_4S$: 516; found 517 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (d, J = 1.8 Hz, 1H), 8.61 (d, J = 7.7 Hz, 1H), 8.28−8.06 (m, 3H), 7.91 (d, J = 7.7 Hz, 1H), 7.50−7.38 (m, 3H), 7.36−7.21 (m, 2H), 7.20−7.09 (m, 2H), 6.93 (br s, 1H), 6.42 (d, J = 8.9 Hz, 1H), 3.17 (s, 1H), 1.78 (s, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(pyridin-4-ylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**46**).* This compound was prepared from **42** (62 mg, 0.11 mmol) according to the general oxidation method to afford the title compound (17 mg, 31%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{19}F_3N_6O_3S$: 516; found 517 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.52 (s, 1H), 9.14 (s, 1H), 8.81 (d, J = 8.2 Hz, 1H), 8.65 (d, J = 7.2 Hz, 2H), 8.58 (d, J = 2.3 Hz, 1H), 8.34−8.26 (m, 2H), 8.22 (d, J = 7.2 Hz, 2H), 8.00−7.89 (m, 2H), 7.45 (br s, 1H), 7.09 (br s, 1H), 6.65 (d, J = 9.1 Hz, 1H), 1.81 (s, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(pyridin-3-ylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**47**).* This compound was prepared from **43** (56 mg, 0.12 mmol) according to the general oxidation method to afford the title compound (17 mg, 31%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{19}F_3N_6O_3S$: 516; found 517 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (s, 1H), 9.10 (s, 1H), 8.97 (d, J = 2.3 Hz, 1H), 8.65 (d, J = 8.2 Hz, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.36−8.13 (m, 4H), 7.81 (dd, J = 2.6, 8.9 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 4.9, 8.4 Hz, 1H), 7.19 (br s, 2H), 7.02 (s, 1H), 6.55 (d, J = 8.9 Hz, 1H), 1.80 (s, 3H).

*2-(6′-((6-Aminopyridin-3-yl)sulfonyl)-2′-(pyridin-2-ylamino)-[2,3′-bipyridin]-5-yl)-1,1,1-trifluoropropan-2-ol (**48**).* This compound was prepared from **44** (58 mg, 0.12 mmol) according to the general oxidation method to afford the title compound (25 mg, 40%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{23}H_{19}F_3N_6O_3S$: 516; found 517 (M + H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (s, 1H), 9.00 (s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.34−8.17 (m, 3H), 8.06 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 2.5, 8.9 Hz, 1H), 7.81−7.72 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.23 (br s, 2H), 7.10−6.96 (m, 2H), 6.58 (d, J = 8.9 Hz, 1H), 1.81 (s, 3H).

*2-(2-(5-Chlorothiophen-2-yl)pyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (**52**).* To a 100 mL round-bottomed flask was added 5-chloro-2-thienylboronic acid (**49**) (0.49 g, 3.02 mmol), 2-(2-chloro-5-pyrimidinyl)-1,1,1-trifluoro-2-propanol (**50**)[10] (0.46 g, 2.01 mmol), $PdCl_2$(dppf) (0.16 g, 0.20 mmol), Cs_2CO_3 (1.31 g, 4.03 mmol), and dioxane (10 mL). The reaction mixture was stirred at 90 °C for 18 h and allowed to cool to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10% EtOAc/CH_2Cl_2) to provide the title compound (0.20 g, 33%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{11}H_8ClF_3N_2OS$: 308; found 309 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 2H), 7.82 (d, J = 4.09 Hz, 1H), 7.26 (s, 1H), 6.98 (d, J = 3.95 Hz, 1H), 1.84 (d, J = 0.73 Hz, 3H).

*1,1,1-Trifluoro-2-(2-(5-mercaptothiophen-2-yl)pyrimidin-5-yl)-propan-2-ol (**54**).* To a 50 mL round-bottomed flask was added **52** (0.18 g, 0.58 mmol), 2-(diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine (32 mg, 0.06 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), sodium *tert*-butoxide (0.18 g, 1.73 mmol), (4-methoxyphenyl)methanethiol (0.096 mL, 0.69 mmol), and DME (3 mL). The reaction mixture was stirred at 90 °C for 18 h and allowed to cool to room temperature. The reaction mixture was diluted with saturated NH_4Cl (5 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30% EtOAc/hexanes) to provide 1,1,1-trifluoro-2-(2-(5-((4-methoxybenzyl)thio)thiophen-2-yl)pyrimidin-5-yl)propan-2-ol (0.17 g, 69%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{19}H_{17}F_3N_2O_2S_2$: 426; found 427 (M + H). The protected thiol was dissolved in TFA (3 mL) and stirred at 70 °C for 18 h. The solvent was removed under reduced pressure to provide the title compound (122 mg, 100%) as a yellow film. MS (ESI pos. ion): m/z calcd for $C_{11}H_9F_3N_2OS_2$ 306, found 307 (M + H).

*2-(2-(5-((6-Chloropyridin-3-yl)thio)thiophen-2-yl)pyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (**56**).* To a 25 mL round-bottomed flask was added **54** (0.13 g, 0.42 mmol), 2-chloro-5-iodopyridine (**5**) (0.10 g, 0.42 mmol), CuI (16 mg, 0.08 mmol), K_2CO_3 (0.18 g, 1.27 mmol), *N*,*N*-dimethyl-1,2-ethanediamine (0.02 mL, 0.17 mmol), and DMSO (3 mL). The reaction mixture was stirred at 90 °C for 3 h and allowed to cool to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (20% EtOAc/CH_2Cl_2) to provide the title compound (0.17 g, 69%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{16}H_{11}ClF_3N_3OS_2$: 417; found 418 (M + H).

*2-(2-(5-((6-Aminopyridin-3-yl)sulfonyl)thiophen-2-yl)pyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (**58**).* To a solution of **56** (72 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 3-chloroperoxybenzoic acid (60 mg, 0.34 mmol). The reaction mixture was stirred at 0 °C for 2 h and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (40% EtOAc/hexanes) to afford 2-(2-(5-((6-chloropyridin-3-yl)sulfonyl)thiophen-2-yl)pyrimidin-5-yl)-1,1,1-trifluoropropan-2-ol (72 mg, 95%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{16}H_{11}ClF_3N_3O_3S_2$: 449; found 450 (M + H). This material was dissolved in dioxane (2 mL) and NH_4OH (0.5 mL, 20% in water) was added. The reaction mixture was heated at 120 °C for 18 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (80% EtOAc/hexanes) to afford the title compound (54 mg, 78%). MS (ESI pos. ion): m/z calcd for $C_{16}H_{13}F_3N_4O_3S_2$: 430; found 431 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.98 (s, 2H), 8.51 (d, J = 2.19 Hz, 1H), 7.99 (d, J = 3.95 Hz, 1H), 7.89 (dd, J = 2.48, 8.92 Hz, 1H), 7.73 (d, J = 3.95 Hz, 1H), 6.63 (d, J = 9.06 Hz, 1H), 1.82 (s, 3H).

*2-(5-Chloro-6-(5-chlorothiophen-2-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**53**).* Following the procedure outlined above for compound **52**, the reaction of 2-(6-bromo-5-chloro-3-pyridinyl)-1,1,1-trifluoro-2-propanol (**51**)[11] and 5-chloro-2-thienylboronic acid (**49**) produced the title compound (22%) as a brown solid. MS (ESI pos. ion): m/z calcd for $C_{12}H_8Cl_2F_3NOS$: 341, found 342 (M + H).

*2-(5-Chloro-6-(5-mercaptothiophen-2-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**55**).* Following the procedure outlined for compound **54**, 2-(5-chloro-6-(5-chlorothiophen-2-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**53**) delivered the title compound (74%) as a brown oil. MS (ESI pos. ion): m/z calcd for $C_{12}H_9ClF_3NOS_2$: 339; found 340 (M + H).

*2-(5-Chloro-6-(5-((6-chloropyridin-3-yl)thio)thiophen-2-yl)-pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**57**).* Following the procedure outlined above for compound **56**, the reaction of 2-(5-chloro-6-(5-mercaptothiophen-2-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**55**) and 2-chloro-5-iodopyridine (**5**) produced the title compound (51%)

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as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{11}Cl_2F_3N_2OS_2$: 450; found 451 (M + H).

*2-(6-(5-((6-Aminopyridin-3-yl)sulfonyl)thiophen-2-yl)-5-chloropyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**59**).* Following the procedure outlined above for compound **58**, 2-(5-chloro-6-(5-((6-chloropyridin-3-yl)thio)thiophen-2-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**57**) delivered the title compound (87%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{13}ClF_3N_3O_3S_2$: 463; found 464 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.72 (br s, 1H), 8.51 (d, J = 2.05 Hz, 1H), 8.15 (d, J = 1.75 Hz, 1H), 8.11 (dd, J = 1.17, 4.09 Hz, 1H), 7.88 (dd, J = 2.56, 8.99 Hz, 1H), 7.71 (d, J = 4.09 Hz, 1H), 6.63 (dd, J = 0.58, 9.06 Hz, 1H), 1.80 (s, 3H).

*2-(6-(5-((6-Aminopyridin-3-yl)sulfonyl)thiophen-2-yl)-5-(prop-1-yn-1-yl)pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (**60**).* To a 50 mL round-bottomed flask was added **59** (41 mg, 0.09 mmol), XPhos palladium(II) phenethylamine chloride (6 mg, 9 μmol), Cs_2CO_3 (86 mg, 0.26 mmol), 1-(trimethylsilyl)propyne (0.07 mL, 0.44 mmol), and MeCN (2 mL). The reaction mixture was heated at 80 °C under a nitrogen atmosphere for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (80% EtOAc/hexanes) to provide the title compound (18 mg, 43%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{20}H_{16}F_3N_3O_3S_2$: 467; found 468 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.68 (d, J = 2.19 Hz, 1H), 8.51 (d, J = 2.05 Hz, 1H), 8.28 (d, J = 4.09 Hz, 1H), 8.06 (d, J = 2.05 Hz, 1H), 7.88 (dd, J = 2.56, 8.99 Hz, 1H), 7.69 (d, J = 4.09 Hz, 1H), 6.62 (dd, J = 0.51, 8.99 Hz, 1H), 2.22 (s, 1H), 1.78 (s, 1H).

*2-Chloro-5-((5-iodothiophen-2-yl)thio)pyridine (**63**).* To a 50 mL round-bottomed flask was added 2,5-diiodothiophene (**61**) (0.23 g, 0.68 mmol), 6-chloropyridine-3-thiol (**62**) (0.10 g, 0.68 mmol), CuI (26 mg, 0.14 mmol), K_2CO_3 (0.19 g, 1.37 mmol), *N*,*N*-dimethyl-1,2-ethanediamine (0.03 mL, 0.27 mmol), and DMSO (3 mL). The reaction mixture was stirred at 80 °C for 3 h and allowed to cool to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (10% EtOAc/hexanes) to provide the title compound (24 mg, 10%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_9H_5ClINS_2$: 353; found 354 (M + H).

*5-((5-Iodothiophen-2-yl)sulfonyl)pyridin-2-amine (**64**).* To a solution of **63** (24 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added 3-chloroperoxybenzoic acid (23 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 18 h and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (40% EtOAc/hexanes) to afford 2-chloro-5-((5-iodothiophen-2-yl)sulfonyl)pyridine (21 mg, 80%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_9H_5ClINO_2S_2$: 385; found 386 (M + H). This material was dissolved in dioxane (1 mL) and NH_4OH (0.2 mL, 20% in water). The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (70% EtOAc/hexanes) to afford the title compound (12 mg, 63%). MS (ESI pos. ion): m/z calcd for $C_9H_7IN_2O_2S_2$: 366; found 367 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 6.94 (d, J = 2.19 Hz, 1H), 6.31 (dd, J = 2.56, 8.99 Hz, 1H), 5.85 (s, 2H), 5.09 (d, J = 8.92 Hz, 1H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiophen-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**65**).* To a 25 mL round-bottomed flask was added **64** (12 mg, 0.03 mmol), 1,1,1-trifluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (**8**) (10 mg, 0.03 mmol), $PdCl_2$(dppf) (3 mg, 0.003 mmol), Cs_2CO_3 (21 mg, 0.07 mmol), dioxane (1 mL), and water (0.1 mL). The reaction mixture was stirred at 100 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (80% EtOAc/hexanes) to provide the title compound (7 mg, 50%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{18}H_{15}F_3N_2O_3S_2$: 428; found 429 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.49 (d, J = 1.90 Hz, 1H), 7.87 (dd, J = 2.56, 8.99 Hz, 1H), 7.63−7.73 (m, 5H), 7.46 (d, J = 3.95 Hz, 1H), 6.61 (dd, J = 0.58, 9.06 Hz, 1H), 1.22 (s, 3H).

*1,1,1,3,3,3-Hexafluoro-2-(4-(thiazol-2-yl)phenyl)propan-2-ol (**70**).* A 25 mL resealable glass vial was charged with 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**67**)[8] (1.41 g, 4.37 mmol), 2-(tributylstannanyl)-1,3-thiazole (**66**) (1.92 mL, 6.12 mmol), $PdCl_2(PPh_3)_2$ (0.15 g, 0.22 mmol), and DMF (5 mL). The vial was sealed, purged with nitrogen for several minutes, and heated at 90 °C for 2 h. After cooling to room temperature, the mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL). The organic layer was separated, washed with water (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude material was purified by silica gel chromatography (0−15% EtOAc/hexanes) to provide the title compound (0.43 g, 30%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{12}H_7F_6NOS$: 327; found 328 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 1H), 8.07−8.15 (m, 2H), 7.98 (d, J = 3.13 Hz, 1H), 7.87 (d, J = 3.13 Hz, 1H), 7.82 (d, J = 8.41 Hz, 2H).

*2-(4-(5-Bromothiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**76**).* A 25 mL round-bottomed flask was charged with **70** (0.31 g, 0.96 mmol), *N*-bromosuccinimide (0.26 g, 1.43 mmol), and DMF (4 mL). The reaction mixture was stirred at 70 °C for 3 h and was allowed to cool to room temperature. The reaction mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc. The organic extract was sequentially washed with water (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound (379 mg, 97%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{12}H_6F_6BrNOS$: 405; found 406 (M + H).

*2-(4-(5-((6-Chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**81**).* A glass microwave reaction vessel was charged **76** (0.22 g, 0.54 mmol), methyl 3-sulfanylpropanoate (0.06 mL, 0.60 mmol), $Pd_2(dba)_3$ (25 mg, 0.03 mmol), Xantphos (31 mg, 0.05 mmol), *N*,*N*-diisopropylethylamine (0.19 mL, 1.08 mmol), and dioxane (1.5 mL). The reaction mixture was purged with nitrogen for several minutes, and then stirred and heated in a microwave reactor at 120 °C for 30 min. The reaction mixture was diluted with water (3 mL) and extracted with CH_2Cl_2 (5 mL). The organic extract was washed sequentially with water (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude material was purified by silica gel chromatography (0−20% EtOAc/hexanes) to provide 3-((2-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1,3-thiazol-5-yl)sulfanyl)-propanoate (0.22 g, 92%) as a yellow oil. MS (ESI pos. ion): m/z calcd for $C_{16}H_{13}F_6NO_3S_2$: 445; found 446 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.93 (s, 1H), 8.04−8.13 (m, 2H), 7.98 (s, 1H), 7.84 (d, J = 8.22 Hz, 2H), 3.62 (s, 3H), 3.13 (t, J = 6.94 Hz, 2H), 2.70 (t, J = 6.85 Hz, 2H).

To a 25 mL round-bottomed flask was added 3-((2-(4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)phenyl)-1,3-thiazol-5-yl)-sulfanyl)propanoate (0.21 g, 0.47 mmol) and THF (3 mL). The reaction mixture was cooled to −78 °C, and under a nitrogen atmosphere, potassium *tert*-butoxide (0.57 mL, 0.57 mmol, 1 M in THF) was added. The reaction mixture was stirred at −78 °C for 1.5 h and at room temperature for 1.5 h. Removal of the solvent under reduced pressure provided potassium 2-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)thiazole-5-thiolate (0.17 g, 91%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{12}H_{17}F_6NOS_2$: 359; found 360.

To a 25 mL resealable glass vial was added potassium 2-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)thiazole-5-thiolate (0.17 g, 0.42 mmol), 2-chloro-5-iodopyridine (0.11 g, 0.47 mmol), CuI (5 mg, 0.02 mmol), K_2CO_3 (0.10 g, 0.71 mmol), ethylene glycol (0.05 mL, 0.94 mmol), and IPA (1.5 mL). The vial was sealed, purged with nitrogen for several minutes, and heated at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with

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water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0−25% EtOAc/hexanes) to provide the title compound (39 mg, 20%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_9ClF_6N_2OS_2$: 470; found 471 (M + H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**86**).* Following the procedure outlined above for compound **58**, 2-(4-(5-((6-chloropyridin-3-yl)thio)-thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**81**) delivered the title compound (87%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{11}F_6N_3O_3S_2$: 483; found 484 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 8.49−8.55 (m, 2H), 8.16 (d, J = 8.61 Hz, 2H), 7.82−7.91 (m, 3H), 7.28 (s, 2H), 6.56 (d, J = 9.00 Hz, 1H).

*1-(3-Chloro-4-(thiazol-2-yl)phenyl)ethanone (**71**).* Following the procedure outlined for compound **70**, the reaction of 2-(tributylstannanyl)-1,3-thiazole (**66**) and 1-(4-bromo-3-chlorophenyl)ethanone (**68**) produced the title compound (69%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{11}H_8ClNOS$: 237; found 238 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, J = 8.22 Hz, 1H), 8.17 (d, J = 1.76 Hz, 1H), 8.14 (d, J = 3.13 Hz, 1H), 8.09 (d, J = 3.33 Hz, 1H), 8.05 (dd, J = 1.76, 8.41 Hz, 1H), 2.67 (s, 3H).

*2-(3-Chloro-4-(thiazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**72**).* To a 100 mL round-bottomed flask was added **71** (2.08 g, 8.76 mmol), CsF (67 mg, 0.44 mmol), and DME (10 mL). The reaction mixture was cooled to 0 °C, and under a nitrogen atmosphere (trifluoromethyl)trimethylsilane (1.55 mL, 10.52 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 30 min. The reaction mixture was diluted with satd NH_4Cl (15 mL) and extracted with EtOAc (20 mL). The organic extract was washed with water (10 mL) and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give 2-(2-chloro-4-(1,1,1-trifluoro-2-((trimethylsilyl)oxy)propan-2-yl)phenyl)thiazole as a yellow oil that was used without further purification.

To a 100 mL round-bottomed flask was added 2-(2-chloro-4-(1,1,1-trifluoro-2-((trimethylsilyl)oxy)propan-2-yl)phenyl)thiazole (3.31 g, 8.72 mmol) and THF (15 mL). The reaction mixture was cooled to 0 °C, and tetra-*N*-butyl ammonium fluoride (5.82 mL, 8.72 mmol, 1 M in THF) was added. The reaction mixture was stirred at 0 °C for 20 min and allowed to warm to room temperature. The reaction mixture was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (20 mL). The organic extract was washed with water (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (2.68 g, 100%) as yellow oil. MS (ESI pos. ion): m/z calcd for $C_{12}H_9ClF_3NOS$: 307; found 308 (M + H).

*2-(4-(5-Bromothiazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoropropan-2-ol (**77**).* Following the procedure outlined for compound **76**, the reaction of 2-(3-chloro-4-(thiazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**72**) and *N*-bromosuccinimide produced the title compound (96%) as yellow oil. MS (ESI pos. ion): m/z calcd for $C_{12}H_8BrClF_3NOS$: 385; found 386 (M + H).

*2-(3-Chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**82**).* A glass microwave reaction vessel was charged with 77 (1.63 g, 4.22 mmol), potassium 6-chloropyridine-3-thiolate (0.75 g, 4.22 mmol), $Pd_2(dba)_3$ (0.39 g, 0.42 mmol), Xantphos (0.49 g, 0.84 mmol), and dioxane (12 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated in a microwave reactor at 120 °C for 40 min. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL). The organic extract was washed sequentially with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product. The crude material was purified by silica gel chromatography (0−25% EtOAc/hexanes) to give the title compound (0.83 g, 44%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{11}Cl_2F_3N_2OS_2$: 450; found 451 (M + H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoropropan-2-ol (**87**).* Following the procedure outlined for compound **86**, 2-(3-chloro-4-(5-((6-chloropyridin-3-yl)-thio)thiazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**82**) delivered the title compound (76%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{13}ClF_3N_3O_3S_2$: 463; found 464 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.53 (d, J = 2.54 Hz, 1H), 8.31 (d, J = 8.41 Hz, 1H), 7.84−7.92 (m, 2H), 7.74 (d, J = 8.61 Hz, 1H), 7.28 (br s, 2H), 6.98 (s, 1H), 6.55 (d, J = 9.00 Hz, 1H), 1.74 (s, 3H).

The individual enantiomers (**88** and **89**) were isolated using chiral SFC Chiralpak ADH column (21 × 250 mm, 5 μ) eluting with MeOH in supercritical CO_2 (total flow was 70 mL/min). The two enantiomers were isolated with enantiomeric excesses >98%.

*(R)-2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoropropan-2-ol (**88**).* MS (ESI pos. ion): m/z calcd for $C_{17}H_{13}ClF_3N_3O_3S_2$: 463; found 464 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.54 (d, J = 2.74 Hz, 1H), 8.32 (d, J = 8.41 Hz, 1H), 7.86−7.93 (m, 2H), 7.73−7.79 (m, J = 8.80 Hz, 1H), 7.31 (s, 2H), 7.00 (s, 1H), 6.56 (d, J = 9.00 Hz, 1H), 1.75 (s, 3H).

*(S)-2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoropropan-2-ol (**89**).* MS (ESI pos. ion): m/z calcd for $C_{17}H_{13}ClF_3N_3O_3S_2$: 463; found 464 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.54 (d, J = 2.54 Hz, 1H), 8.32 (d, J = 8.41 Hz, 1H), 7.86−7.93 (m, 2H), 7.75 (d, J = 8.61 Hz, 1H), 7.31 (s, 2H), 7.00 (s, 1H), 6.56 (d, J = 9.00 Hz, 1H), 1.75 (s, 3H).

*2-(3-Chloro-4-(thiazol-2-yl)phenyl)propan-2-ol (**73**).* To a stirred solution of **71** (0.36 g, 1.52 mmol) in THF (4 mL) at 0 °C was added MeMgBr (0.76 mL, 2.28 mmol, 3 M in ether). The reaction mixture was stirred at 0 °C for 1 h, quenched by the addition of HCl (10 mL, 1 N) and extracted with EtOAc (15 mL). The organic extract was sequentially washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound (0.28 g, 73%) as a yellow oil.

*2-(4-(5-Bromothiazol-2-yl)-3-chlorophenyl)propan-2-ol (**78**).* Following the procedure outlined above for compound **76**, the reaction of 2-(3-chloro-4-(thiazol-2-yl)phenyl)propan-2-ol (**73**) and *N*-bromosuccinimide produced the title compound (98%) as yellow oil. MS (ESI pos. ion): m/z calcd for $C_{12}H_{11}BrClNOS$: 331; found 332 (M + H).

*2-(3-Chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)-propan-2-ol (**83**).* Following the procedure outlined for compound **82**, the reaction of 2-(4-(5-bromothiazol-2-yl)-3-chlorophenyl)propan-2-ol (**78**) and potassium 6-chloropyridine-3-thiolate, produced the title compound (50%) as a yellow solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{14}Cl_2N_2OS_2$: 396; found 397 (M + H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)propan-2-ol (**90**).* To a solution of **83** (0.21 g, 0.54 mmol) in AcOH (2 mL) at 0 °C was added sodium tungstate (8 mg, 0.03 mmol), followed by hydrogen peroxide (0.16 mL, 1.62 mmol, 30% in water). The reaction mixture was stirred at 0 °C for 3 h and water (5 mL) was added. The yellow precipitate obtained was filtered, washed with water, and dried. This material was dissolved in EtOH (2 mL) and added NH_4OH (1.5 mL, 20% in water). The reaction mixture was heated at 100 °C for 18 h and cooled to room temperature, and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (0−7% 2 M NH_3 in MeOH/CH_2Cl_2) to provide the title compound (66 mg, 30%) as a light-yellow solid. MS (ESI pos. ion): m/z calcd for $C_{17}H_{16}ClN_3O_3S_2$: 409; found 410 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.51 (d, J = 2.54 Hz, 1H), 8.21 (d, J = 8.41 Hz, 1H), 7.87 (dd, J = 2.64, 8.90 Hz, 1H), 7.73 (d, J = 1.76 Hz, 1H), 7.60 (dd, J = 1.76, 8.22 Hz, 1H), 7.28 (s, 2H), 6.53 (d, J = 9.00 Hz, 1H), 5.35 (s, 1H), 1.44 (s, 6H).

*3-Chloro-4-(thiazol-2-yl)benzenesulfonamide (**74**).* Following the procedure outlined for compound **70**, the reaction of 2-(tributylstannanyl)-1,3-thiazole (**66**) and 4-bromo-3-chlorobenzenesulfonamide (**69**) produced the title compound (34%) as an off-white solid. MS (ESI pos. ion): m/z calcd for $C_9H_7ClN_2O_2S_2$: 274; found 275 (M + H).

*4-(5-Bromothiazol-2-yl)-3-chlorobenzenesulfonamide (**79**).* Following the procedure outlined for compound **76**, the reaction of 3-chloro-4-(thiazol-2-yl)benzenesulfonamide (**74**) and *N*-bromosuccinimide produced the title compound (60%) as a white solid. MS (ESI pos. ion): m/z calcd for $C_9H_6BrClN_2O_2S_2$: 352; found 353 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 8.41 Hz, 1H), 8.22 (s, 1H), 8.03 (d, J = 1.76 Hz, 1H), 7.91 (dd, J = 1.76, 8.41 Hz, 1H), 7.64 (s, 2H).

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*3-Chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)-benzenesulfonamide (**84**).* Following the procedure outlined above for compound **82**, the reaction of 4-(5-bromothiazol-2-yl)-3-chlorobenzenesulfonamide (**79**) and potassium 6-chloropyridine-3-thiolate produced the title compound (60%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{14}H_9Cl_2N_3O_2S_3$: 417; found 418 (M + H).

*4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorobenzenesulfonamide (**91**).* Following the procedure outlined for compound **90**, 3-chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)-benzenesulfonamide (**84**) delivered the title compound (58%) as an off-white solid. MS (ESI pos. ion): *m/z* calcd for $C_{14}H_{11}ClN_4O_4S_3$: 430; found 431 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.55 (d, *J* = 2.35 Hz, 1H), 8.42−8.51 (m, 1H), 8.06 (d, *J* = 1.37 Hz, 1H), 7.88−7.97 (m, 3H), 7.69 (br s, 2H), 7.38 (d, *J* = 5.28 Hz, 1H), 6.59 (d, *J* = 9.00 Hz, 1H).

*2-(3-Chloro-4-(thiazol-2-yl)phenyl)propane-1,2-diol (**75**).* To a stirred mixture of trimethylsulfoxonium iodide (0.85 g, 3.85 mmol) in DMSO (3 mL) was added potassium *tert*-butoxide (0.43 g, 3.85 mmol), and the suspension was stirred at room temperature for 1 h. This mixture was added via cannula to a suspension of **71** (0.61 g, 2.57 mmol) in DMSO (3 mL). The reaction mixture was stirred at room temperature for 3 h and quenched by the addition of ice-water. The precipitate obtained was isolated by filtration and dried under reduced pressure. The crude material was dissolved in THF (3 mL) and at 0 °C, HCl (3 mL, 1 N) was added. The reaction mixture was stirred at 0 °C for 1 h and diluted with EtOAc. The organic extract was washed sequentially with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound (0.49 g, 71%) as a light-yellow solid. MS (ESI pos. ion): *m/z* calcd for $C_{12}H_{12}ClNO_2S$: 269; found 270 (M + H).

*2-(4-(5-Bromothiazol-2-yl)-3-chlorophenyl)propane-1,2-diol (**80**).* Following the procedure outlined above for compound **76**, the reaction of 2-(3-chloro-4-(thiazol-2-yl)phenyl)propane-1,2-diol (**75**) and *N*-bromosuccinimide produced the title compound (100%) as a light-yellow solid. MS (ESI pos. ion): *m/z* calcd for $C_{12}H_{11}BrClNO_2S$: 347; found 348 (M + H).

*2-(3-Chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)-propane-1,2-diol (**85**).* Following the procedure outlined for compound **82**, the reaction of 2-(4-(5-bromothiazol-2-yl)-3-chlorophenyl)propane-1,2-diol (**80**) and potassium 6-chloropyridine-3-thiolate, produced the title compound (62%) as a light-yellow solid. MS (ESI pos. ion): *m/z* calcd for $C_{17}H_{14}Cl_2N_2O_2S_2$: 412; found 413 (M + H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)propane-1,2-diol (**92**).* Following the procedure outlined above for compound **90**, 2-(3-chloro-4-(5-((6-chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)propane-1,2-diol (**85**) delivered the title compound (28%) as a light-yellow solid. MS (ESI pos. ion): *m/z* calcd for $C_{17}H_{16}ClN_3O_4S_2$: 425; found 426 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.53 (d, *J* = 2.74 Hz, 1H), 8.22 (d, *J* = 8.22 Hz, 1H), 7.89 (dd, *J* = 2.54, 9.00 Hz, 1H), 7.73 (d, *J* = 1.57 Hz, 1H), 7.60 (dd, *J* = 1.57, 8.41 Hz, 1H), 7.30 (s, 2H), 6.56 (d, *J* = 9.00 Hz, 1H), 5.28 (s, 1H), 4.86 (t, *J* = 5.87 Hz, 1H), 3.39−3.54 (m, 2H), 3.18 (d, *J* = 5.28 Hz, 1H), 1.42 (s, 3H).

The individual enantiomers (**93** and **94**) were isolated using chiral SFC Chiralpak ADH column (21 × 250 mm, 5 μ) eluting with MeOH in supercritical CO_2 (total flow was 70 mL/min). This produced the two enantiomers with enantiomeric excesses >98%.

*(R)-2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)propane-1,2-diol (**93**).* MS (ESI pos. ion): *m/z* calcd for $C_{17}H_{16}ClN_3O_4S_2$: 425; found 426 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.55 (d, *J* = 1.96 Hz, 1H), 8.39 (s, 1H), 8.27 (d, *J* = 8.41 Hz, 1H), 7.91 (dd, *J* = 2.64, 9.10 Hz, 1H), 7.76 (d, *J* = 1.56 Hz, 1H), 7.57 (dd, *J* = 1.76, 8.41 Hz, 1H), 6.63 (d, *J* = 9.00 Hz, 1H), 3.64 (q, *J* = 11.50 Hz, 2H), 1.53 (s, 1H).

*(S)-2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)-3-chlorophenyl)propane-1,2-diol (**94**).* MS (ESI pos. ion): *m/z* calcd for $C_{17}H_{16}ClN_3O_4S_2$: 425; found 426 (M + H). ^{1}H NMR (400 MHz, CD_3OD): δ 8.55 (br s, 1H), 8.39 (s, 1H), 8.27 (d, *J* = 8.41 Hz, 1H), 7.91 (dd, *J* = 2.45, 9.10 Hz, 1H), 7.76 (d, *J* = 1.76 Hz, 1H), 7.57 (dd, *J* = 1.66, 8.31 Hz, 1H), 6.63 (d, *J* = 9.00 Hz, 1H), 3.64 (q, *J* = 11.5 Hz, 2H), 1.53 (s, 3H).

*2-(4-(4-Bromothiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**97**).* A 25 mL glass resealable vial was charged with 2,4-dibromothiazole (**95**) (0.78 g, 3.21 mmol), 1,1,1,3,3,3-hexafluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (**96**)[16] (1.19 g, 3.21 mmol), $PdCl_2$(dppf) (0.13 g, 0.16 mmol), Cs_2CO_3 (3.14 g, 9.63 mmol), DME (6 mL), and water (0.5 mL). The vial was closed and purged with nitrogen for several minutes and then stirred and heated at 90 °C for 4 h. The reaction mixture was allowed to cool to room temperature, the organic layer was separated, and the solvent was removed under reduced pressure. The crude material was purified by silica gel chromatography (0−10% EtOAc/hexanes) to provide the title compound (0.83 g, 63%) as a colorless oil. MS (ESI pos. ion): *m/z* calcd for $C_{12}H_6BrF_6NOS$: 405; found 406 (M + H).

*2-(4-(4-((6-Chloropyridin-3-yl)thio)thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**98**).* Following the procedure outlined for compound **76**, 2-(4-(4-bromothiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**97**) delivered the title compound (20%) as white solid. MS (ESI pos. ion): *m/z* calcd for $C_{17}H_9ClF_6N_2OS_2$: 470; found 471 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.47 (d, *J* = 1.96 Hz, 1H), 8.10 (d, *J* = 8.61 Hz, 2H), 8.01 (s, 1H), 7.90 (dd, *J* = 2.74, 8.41 Hz, 1H), 7.84 (d, *J* = 8.41 Hz, 2H), 7.55 (dd, *J* = 0.60, 8.41 Hz, 1H).

*2-(4-(4-((6-Aminopyridin-3-yl)sulfonyl)thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**99**).* Following the procedure outlined above for compound **86**, 2-(4-(4-((6-chloropyridin-3-yl)thio)-thiazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**98**) delivered the title compound (69%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{17}H_{11}F_6N_3O_3S_2$: 483; found 484 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (br s, 1H), 8.64 (br s, 1H), 8.49 (br s, 1H), 8.08 (d, *J* = 7.04 Hz, 2H), 7.72−7.95 (m, 3H), 7.19 (br s, 2H), 6.54 (d, *J* = 8.22 Hz, 1H).

*2-Bromo-4-((4-methoxybenzyl)thio)-1-methyl-1H-imidazole (**101**).* To a 50 mL round-bottomed flask was added 2,4-dibromo-1-methyl-1*H*-imidazole (**100**) (0.47 g, 1.98 mmol), 2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (55 mg, 0.10 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), sodium *tert*-butoxide (0.38 g, 3.95 mmol), (4-methoxyphenyl)methanethiol (0.27 mL, 1.98 mmol), and DME (5 mL). The reaction mixture was stirred at 90 °C for 3 h and allowed to cool to room temperature. The reaction mixture was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30% EtOAc/hexanes) to provide the title compound (0.42 g, 67%) as a brown oil. MS (ESI pos. ion): *m/z* calcd for $C_{12}H_{13}BrN_2OS$: 312; found 313 (M + H).

*1,1,1,3,3,3-Hexafluoro-2-(4-(4-((4-methoxybenzyl)thio)-1-methyl-1H-imidazol-2-yl)phenyl)propan-2-ol (**102**).* To a 25 mL round-bottomed flask was added **101** (0.36 g, 1.14 mmol), 1,1,1,3,3,3-hexafluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-propan-2-ol (**8**) (0.42 g, 1.14 mmol), $PdCl_2$(dppf) (93 mg, 0.11 mmol), Cs_2CO_3 (0.74 g, 2.29 mmol), dioxane (6 mL), and water (0.6 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated at 100 °C for 5 h. The reaction mixture was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30% EtOAc/hexanes) to provide the title compound (0.26 g, 48%) as a colorless oil. MS (ESI pos. ion): *m/z* calcd for $C_{21}H_{18}F_6N_2O_2S$: 476; found 477 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.88 (m, 2H), 7.70 (d, *J* = 8.33 Hz, 2H), 7.20 (s, 1H), 7.05−7.12 (m, 2H), 6.79 (s, 2H), 4.19 (s, 2H), 3.78 (s, 3H), 3.31 (s, 3H).

*2-(4-(4-((6-Aminopyridin-3-yl)thio)-1-methyl-1H-imidazol-2-yl)-phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**104**).* To a 25 mL round-bottomed flask was added **102** (0.23 g, 0.47 mmol) and TFA (2 mL). The reaction mixture was stirred at 70 °C for 18 h. The solvent was removed under reduced pressure. The crude product was dissolved in DMSO (2 mL) and added 2-amino-5-iodopyridine (**103**) (0.10 g, 0.47

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mmol), CuI (18 mg, 0.09 mmol), K_2CO_3 (0.26 g, 1.90 mmol), and *N,N*-dimethyl-1,2-ethanediamine (0.021 mL, 0.19 mmol). The reaction mixture was stirred at 90 °C for 18 h and allowed to cool to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (EtOAc) to provide the title compound (65 mg, 31%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{18}H_{14}F_6N_4OS$: 448; found 449 (M + H).

*2-(4-(4-((6-Aminopyridin-3-yl)sulfonyl)-1-methyl-1H-imidazol-2-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**105**).* To a solution of **104** (41 mg, 0.09 mmol), in CH_2Cl_2 (2 mL) at 0 °C was added mCPBA (32 mg, 0.18 mmol). The reaction mixture was stirred at 0 °C for 1 h and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (15% MeOH/CH_2Cl_2) to afford the title compound (21 mg, 48%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{18}H_{14}F_6N_4O_3S$: 480; found 481 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 6.96 (d, *J* = 1.90 Hz, 1H), 6.27−6.38 (m, 3H), 6.24 (s, 2H), 6.09 (dd, *J* = 1.97, 8.99 Hz, 1H), 5.52−5.62 (m, 1H), 2.41 (s, 3H).

*2-(4-(5-Bromo-1-methyl-1H-imidazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**107**).* To a 25 mL round-bottomed flask was added 2,5-dibromo-1-methyl-1*H*-imidazole (**106**) (0.24 g, 1.00 mmol), 1,1,1-trifluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-propan-2-ol (**96**) (0.32 g, 1.00 mmol), $PdCl_2$(dppf) (82 mg, 0.10 mmol), Cs_2CO_3 (0.65 g, 2.00 mmol), dioxane (4 mL), and water (0.4 mL). The reaction mixture was purged with nitrogen for several minutes and then stirred and heated at 100 °C for 5 h. The reaction mixture was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (30% EtOAc/CH_2Cl_2) to provide the title compound (0.20 g, 58%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{13}H_{12}BrF_3N_2O$: 348; found 349 (M + H).

*1,1,1-Trifluoro-2-(4-(5-((4-methoxybenzyl)thio)-1-methyl-1H-imidazol-2-yl)phenyl)propan-2-ol (**108**).* Following the procedure outlined for compound **100**, the reaction of 2-(4-(5-bromo-1-methyl-1*H*-imidazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**107**) and (4-methoxyphenyl)methanethiol produced the title compound (80%) as a brown solid. MS (ESI pos. ion): *m/z* calcd for $C_{21}H_{21}F_3N_2O_2S$: 422; found 423 (M + H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.18 Hz, 2H), 7.28−7.38 (m, 2H), 7.18 (s, 1H), 7.05−7.13 (m, 2H), 6.73−6.86 (m, 2H), 4.19 (s, 2H), 3.78 (s, 3H), 3.27 (s, 3H), 1.82 (d, *J* = 0.73 Hz, 3H).

*2-(4-(5-((6-Aminopyridin-3-yl)thio)-1-methyl-1H-imidazol-2-yl)-phenyl)-1,1,1-trifluoropropan-2-ol (**109**).* Following the procedure outlined for compound **104**, 1,1,1-trifluoro-2-(4-(5-((4-methoxybenzyl)thio)-1-methyl-1*H*-imidazol-2-yl)phenyl)propan-2-ol (**108**) delivered the title compound (25%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{18}H_{17}F_3N_4OS$: 394; found 395 (M + H).

*2-(4-(5-((6-Aminopyridin-3-yl)sulfonyl)-1-methyl-1H-imidazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**110**).* Following the procedure outlined for compound **105**, the reaction of 2-(4-(5-((6-aminopyridin-3-yl)thio)-1-methyl-1*H*-imidazol-2-yl)phenyl)-1,1,1-trifluoropropan-2-ol (**109**) and mCPBA produced the title compound (40%) as a white solid. MS (ESI pos. ion): *m/z* calcd for $C_{18}H_{17}F_3N_4O_3S$: 426; found 427 (M + H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.44 (d, *J* = 1.90 Hz, 1H), 7.77 (d, *J* = 8.33 Hz, 2H), 7.58 (dd, *J* = 1.97, 8.99 Hz, 1H), 7.52 (d, *J* = 8.48 Hz, 2H), 7.28 (s, 1H), 7.10 (d, *J* = 9.06 Hz, 1H), 3.86 (s, 3H), 1.77 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

Syntheses of intermediates **8**, **16**, **31**, and **96**. The cocrystal structures of hGKRP + compounds **4**, **39**, and **59** have been deposited in the Protein DataBank with PDB codes: 4OP2, 4OP3, and 4OP1, respectively. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jm5018175.

■ AUTHOR INFORMATION

Corresponding Authors

*Phone: 805-447-8814. E-mail: ntamayo@amgen.com.
*Phone: 805-447-3446. E-mail: mbartber@amgen.com.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AlphaScreen, amplified luminescent proximity assay; AmPhos, 4-(dimethylamino)phenyl]bis(*tert*-butyl)phosphine; calcd, calculated; CL, clearance; DME, 1,2-dimethoxyethane; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; dppf, 1,1′-bis(diphenylphosphino)ferrocene; EC_{50}, effective concentration; GK, glucokinase; GKA, glucokinase activator; GKRP, glucokinase regulatory protein; IPA, isopropylalcohol; Josiphos, 2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine; mCPBA, 3-chloroperoxybenzoic acid; pos, positive; RLM, rat liver microsomes; IC_{50}, inhibitory concentration at half maximal effect; iv, intravenous; rt, room temperature; TBAF, tetra-*N*-butylammonium fluoride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; XPhos precatalyst, chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl)]palladium

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