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Brief Article

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Identification and Characterization of 4-Chloro-*N*-(2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)benzamide (GSK3787), a Selective and Irreversible Peroxisome Proliferator-Activated Receptor δ (PPARδ) Antagonist

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4-Chloro-*N*-(2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)benzamide **3** (GSK3787) was identified as a potent and selective ligand for PPARδ with good pharmacokinetic properties. A detailed binding study using mass spectral analysis confirmed covalent binding to Cys249 within the PPARδ binding pocket. Gene expression studies showed that pyridylsulfone **3** antagonized the transcriptional activity of PPARδ and inhibited basal CPT1a gene transcription. Compound **3** is a PPARδ antagonist with utility as a tool to elucidate PPARδ cell biology and pharmacology.

Introduction

Nuclear receptors represent an important class of receptor targets for drug discovery. The peroxisome proliferator-activated receptors (PPARs[a]) are ligand activated transcription factors belonging to the nuclear receptor superfamily and play key roles in multiple physiological pathways. Three PPAR receptor subtypes with distinct tissue distributions, designated as PPARα, PPARγ, and PPARδ, have been identified. The PPARs are significantly involved in the control of fatty acid metabolism and represent attractive therapeutic targets.[1] PPARα is an important regulator of fatty acid catabolism in the liver and is the known target receptor for the fibrate class of lipid lowering drugs.[2] PPARγ activators are established insulin sensitizers and lower plasma glucose.[3] Rosiglitazone and pioglitazone are potent PPARγ agonists currently marketed for the treatment of type 2 diabetes.

There are currently no available drugs targeting PPARδ. While PPARδ remains the least understood subtype, it is now recognized as a regulator of genes involved in fatty acid oxidation, reverse cholesterol transport, and carbon substrate utilization in skeletal muscle.[4,5] Further evidence linking PPARδ to important roles in lipid homeostasis and glucose disposal is growing. For example, in rodent models of type 2 diabetes, the PPARδ agonist **1** (GW501516, Figure 1) improves insulin resistance and lowers plasma glucose. Agonist **1** has also been shown to correct the metabolic syndrome in obese primates. More significantly, PPARδ agonist **1** has recently been reported to reduce serum triglycerides and prevent the reduction of HDL-c and apo-A1 levels in sedentary human volunteers and increase muscle fatty acid oxidation in patients with insulin resistance.[6] These positive results collectively implicate PPARδ as a promising target for the novel treatment of metabolic disorders.

A number of PPARδ activating ligands have been disclosed, but there remains a need for additional small molecule regulators of PPARδ with a range of functional activity profiles to use as tools to further decipher the biological pathways regulated by PPARδ. Novo Nordisk recently reported a selective PPARδ partial agonist that corrected plasma lipid parameters and improved insulin sensitivity in a high fat fed transgenic mouse model highlighting the potential use of PPARδ partial agonists as novel agents for the treatment of dyslipidemia.[7] We identified a novel class of anthranilic acids as potent and selective PPARδ partial agonists with a distinct binding mode.[8] Compounds in this series act as potent partial activators on PPARδ target gene expression in human skeletal muscle cells.

Recently, we reported the identification of selective PPARδ antagonist **2** (GSK0660) which has utility as a tool for elucidating the biological role of PPARδ in vitro.[9] However, a limitation of antagonist **2** is that it lacks oral bioavailablilty. In this communication, we describe the identification and characterization of a chemically distinct PPARδ antagonist, 4-chloro-*N*-(2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)benzamide **3** (GSK3787, Figure 2), that was identified from our high-throughput screen of the GSK compound collection.

The pyridylsulfone **3** was identified as a potent and selective hPPARδ ligand ($pIC_{50} = 6.6$) with no measurable affinity for hPPARα or hPPARγ ($pIC_{50} < 5$) in our standard in vitro

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[a]Abbreviations: apo-A1, apolipoprotein A1; CPT1a, carnitine palmitoyltransferase 1a; Cys, cysteine; HCl, hydrogen chloride; HDLc, high density lipoprotein cholesterol; His, histidine; LCMS, liquid chromatography−mass spectrometry; *N*-Boc, *N*-*tert*-butoxycarbonyl; PDK4, pyruvate dehydrogenase kinase-4; PPAR, peroxisome proliferator-activated receptor; SAR, structure−activity relationship.

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ligand displacement assay.[10] Surprisingly, **3** failed to activate the receptor in a standard hPPARδ-GAL4 chimera cell-based reporter assay.[11] This result suggested that pyridylsulfone **3** might be a hPPARδ antagonist. To test this hypothesis, we measured the activity of pyridylsulfone **3** in a standard GAL4 chimera cell-based reporter antagonist assay in which an EC_{80} dose of the PPARδ agonist **1** was added to the cells.[12] Pyridylsulfone **3** completely antagonized the activity of agonist **1** with a pIC_{50} of 6.9 ($n = 2$). Compound **3** was inactive against hPPARα and hPPARγ in similar functional antagonist assays. Further screening in similar cell-based reported assays using the mouse PPARδ receptor showed pyridylsulfone **3** failed to activate the receptor and antagonized the activity of agonist **1** with a pIC_{50} of 6.9 and 94% maximal inhibition ($n = 2$). Thus, pyridylsulfone **3** is a selective PPARδ antagonist with equipotent species activity against the human and mouse receptor.

Chemistry

We initiated an effort to evaluate the developability of this new class of PPARδ antagonist. A series of compounds were synthesized to investigate the SAR and identify the key pharmacophore. We focused on three regions of the molecule: the pyridyl ring, the aliphatic linker, and the right-hand-side amide group. The synthesis of these compounds is detailed in Scheme 1. Sulfur alkylation of 2-mercaptopyridine **4** with *N*-Boc protected aminoalkyl bromide **5** in DMF provided 2-thiopyridine **6**. Oxidation of the sulfide to the sulfone **7** with potassium peroxymonosulfate followed by removal of the *N*-Boc protecting group with 4 N HCl in dioxane afforded aminosulfone **8**. Acylation of the primary amine with aroyl chlorides readily provided the final targets **3** and **9**−**20** in good overall yields.

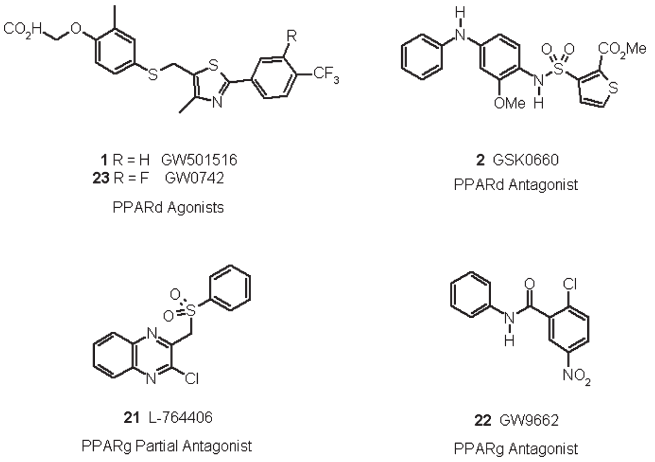

Figure 1. Structures of PPAR ligands.

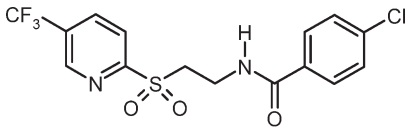

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Figure 2. Structure of pyridylsulfone **3** (GSK3787).

Results and Discussion

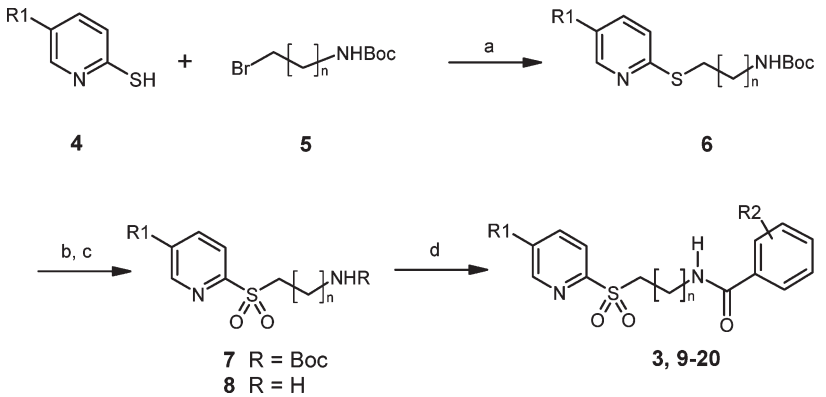
The ability of these compounds to bind to each of the PPAR subtypes was measured in vitro in a ligand displacement assay.[10] Functional PPARδ activity was measured in standard cell-based GAL4 chimera reporter assays using agonist[11] and antagonist formats.[12] These results are summarized in Table 1. Data for PPARδ antagonist **2** are included for comparison. Substitution of the arylamide ring did not have a significant effect on binding affinity. Replacement of the para chloro substitutent with a trifluoromethoxy group gave a

Table 1. Human PPARδ Binding and Functional Potency of Substituted Pyridylsulfones[a]

				hPPAR binding pIC_{50}			hPPARδ reporter	
compd	*n*	R1	R2	α	γ	δ	pIC_{50}	% inh
2				< 5	< 5	6.8	6.5	100
3	1	CF_3	4-Cl	< 5	< 5	6.7	6.9	100
9	1	CF_3	4-OCF_3	< 5	< 5	7.0	NT	
10	1	CF_3	4-Ph	< 5	< 5	6.7	6.6	100
11	1	CF_3	4-c-C_6H_{12}	< 5	< 5	6.0	NT	
12	1	CF_3	4-i-Bu	< 5	< 5	6.5	6.7	100
13	1	CF_3	2,4-diCl	< 5	< 5	6.8	6.7	100
14	1	CF_3	3-Br, 4-Cl	< 5	< 5	6.9	6.6	100
15	1	CF_3	3-Me, 4-Cl	< 5	< 5	6.9	6.6	100
16	1	CF_3	2-F, 4-Br	< 5	< 5	7.3	7.1	99
17	2	CF_3	4-Cl	< 5	< 5	< 5	NT	
18	2	CF_3	4-OCF_3	< 5	< 5	5.9	NT	
19	1	Me	4-Cl	< 5	< 5	< 5	NT	
20	1	H	4-Cl	< 5	< 5	< 5	NT	

[a] Values had a standard deviation of ≤10% ($n \geq 2$). Reported functional data are for the antagonist format of the hPPARδ-GAL4 chimera reporter assay. NT = not tested.

Scheme 1[a]



[a] (a) Et_3N, DMF, room temp; (b) potassium peroxymonosulfate, acetone−water, room temp; (c) 4 N HCl, dioxane, room temp; (d) ArCOCl, Et_3N, CH_2Cl_2, room temp.

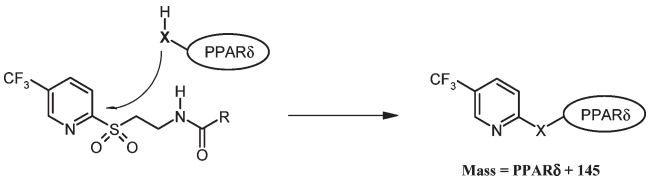


Figure 3. Proposed mechanism of covalent binding for 5-trifluoromethyl-2-pyridylsulfones.

small increase in binding potency (pIC_{50} = 7.0). However, substitution of the 4-chloro group with bulky lipophilic groups did not improve potency. The binding of the 4-phenyl analogue **10** was equipotent to pyridylsulfone **3**, while the bulkier lipophilic cyclohexyl analogue **11** was significantly weaker. The 4-isobutyl substituted analogue **12** exhibited similar potency and activity as pyridylsulfone **3**. Disubstitution of the arylamide ring did not increase binding or functional potency as evidenced by analogues **13**−**15**. One compound, however, that did show improved binding potency was the 2-fluoro-4-bromo analogue **16** (pIC_{50} = 7.3). All of the compounds tested for functional activity in the cell-based GAL4 chimera reporter assays profiled as antagonists.

The length of the aliphatic linker is critical for activity. Extension of the middle two-carbon chain of trifluoromethoxy **9** to the three-carbon linker analogue **18** significantly reduced binding affinity (pIC_{50} = 5.9). In addition, **17**, the one-carbon extended analogue of pyridylsulfone **3**, was not active. Substitution of the pyridine ring is also critical for activity. Removal of the trifluoromethyl substituent as in analogue **20** produced an inactive compound. Replacement of the trifluoromethyl group with a methyl substituent provided inactive **19**. In addition, the corresponding sulfide analogue of pyridylsulfone **3** fails to bind to PPARδ, indicating that the sulfur must be oxidized for activity (data not shown). These results suggest that a strong electron withdrawing group para to the sulfone group is required for activity.

On the basis of this SAR, we raised the question as to whether or not the para electron withdrawing group was facilitating a covalent binding interaction between the pyridyl ring and a nucleophilic residue within the receptor binding pocket that could lead to displacement of the sulfone group. Ligands binding irreversibly to the PPARs have been previously reported. For example, Merck published data showing that **21** (L-764406) was a PPARγ partial agonist that covalently bound within the ligand binding domain to a specific cysteine residue.[13] Compound **22** (GW9662) is a PPARγ antagonist structurally distinct from antagonist **21** that has also been shown to bind covalently to cysteine residues in the ligand binding pocket.[14]

To test our hypothesis, pyridylsulfones **3** and **9**, two analogues with different molecular weights, were independently incubated with PPARδ and the binding was monitored by mass spectra analysis. Both compounds gave the same exact mass equivalent to PPARδ + 145 mass units with complete conversion within 1 h of incubation. This suggested that both compounds covalently added the same fragment to the receptor. The common structural feature for these two antagonists that could add 145 mass units is the trifluoromethylpyridine group. On the basis of these results, the general mechanism in Figure 3 was proposed for covalent binding of this series of 5-trifluoromethyl-2-pyridylsulfones.

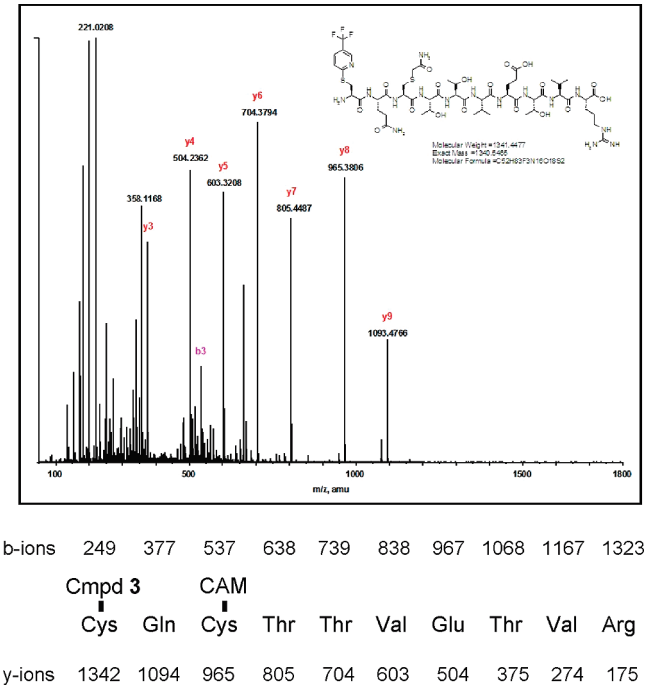


Figure 4. LC−MS/MS spectrum of peptide fragment generated from trypsin digestion of hPPARδ LBD−antagonist **3** complex.

To identify the exact site of covalent binding within the PPARδ binding pocket, a detailed binding study of pyridylsulfone **3** with PPARδ was undertaken. A sample of His-PPARδ (165−441) was incubated with pyridylsulfone **3** for 90 min. Routine LC/MS analysis of the protein sample showed a mass increase of 145 Da corresponding exactly to the additional mass of the 5-trifluoromethyl-2-pyridyl fragment from the ligand. Tryptic digestion was performed, and mass mapping of the digest identified a single peptide fragment with a mass size 145 Da greater than predicted. Rigorous analysis of the resulting m/z and product ion data for this fragment by LC−MS/MS identified Cys249, detected at 671.2 $[M + 2H]^{2+}$ as the site of covalent modification. This site was confirmed by a strong y ion series (Figure 4).

Given that pyridylsulfone **3** has a reactive moiety, we sought to ascertain the potential of this compound for undesired nonselective reactivity. A semiquantitative experiment was undertaken to determine chemical reactivity wherein pyridylsulfone **3** (2 mg, 1 equiv) and *N*-acetylcysteine (10 mg, 12 equiv) were stirred in DMSO (0.6 mL) for 24 h at room temperature and then 8 h at 60 °C. LCMS was used to monitor the disappearance of pyridylsulfone **3** and the appearance of any new products. Analysis of the mixture after 24 h at room temperature and 8 h at 60 °C showed pyridylsulfone **3** remained without the appearance of any new products. Thus, pyridylsulfone **3** appears to be a chemically stable PPARδ antagonist.

Pyridylsulfone **3** was further studied for its effects on the expression of two key PPARδ regulated genes in human skeletal muscle cells as previously described.[9] The target genes CPT1a and PDK4 play an important role in energy homeostasis. CPT1a regulates fatty acid β-oxidation in skeletal muscle cells,[15] while PDK4 plays a key role in skeletal muscle metabolism by contributing to the regulation of glucose metabolism.[16] Compound **23** (GW0742) is a full PPARδ agonist that robustly induces target genes CPT1a and PDK4.[9] In our first experiment, 10 nM agonist **23** was added

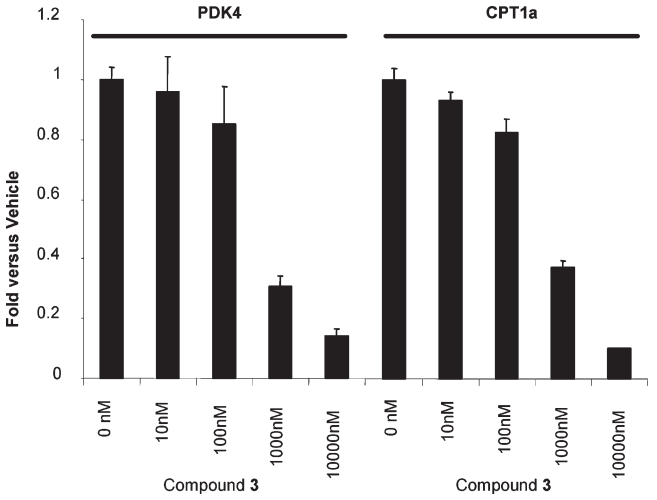


Figure 5. Antagonism of agonist **23** induced expression of target genes PDK4 and CPT1a by pyridylsulfone **3**.

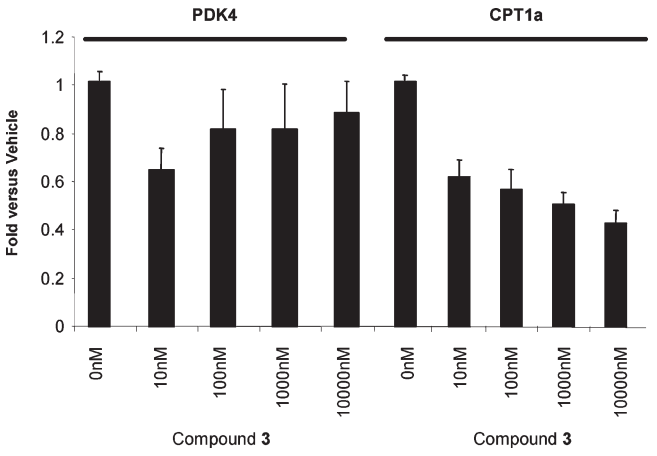


Figure 6. Antagonism of the basal expression of PPARδ target genes PDK4 and CPT1a by pyridylsulfone **3**.

to human skeletal muscle cells to stimulate the expression of target genes. Pyridylsulfone **3** was then tested at various doses for its ability to antagonize the agonist **23** stimulated transcription of CPT1a and PDK4 (Figure 5). Pyridylsulfone **3** effectively antagonized gene expression, suggesting that it can block the activated PPARδ receptor's activity.

In a second experiment, the effect of pyridylsulfone **3** on the expression of the same PPARδ regulated target genes in the absence of the agonist **23** was examined to determine the compound's ability to antagonize basal gene transcription. Pyridylsulfone **3** was administered to human skeletal muscle cells at various doses and found to effectively antagonize the gene expression of CPT1a but not PDK4 (Figure 6). This suggests that pyridylsulfone **3** may selectively block the basal activity of the receptor on some PPARδ target genes highlighting the potential utility of this compound as a useful tool for further elucidating the biological role of PPARδ.

PPARδ has been implicated in the cross-talk of signaling cascades involved in the progression of colorectal cancer.[17,18] Although PPARδ expression is elevated in most human colorectal cancers, the role of PPARδ in colon carcinogenesis remains controversial and highly debated because of conflicting experimental results reported in the literature.[19] It has been hypothesized that PPARδ antagonists may offer utility for the prevention and/or treatment of colorectal cancer.[17] In an effort to probe the role of PPARδ in the modulation of colon cancer, we tested the PPARδ antagonist **3** in a panel of colorectal cancer cell lines (SW480, HCT116, DLD1, RKO) and noncolorectal cell lines (A549, HEK293).[20] Antagonist **3** was incubated in each of these cell lines for 3 days at concentrations up to 10 μM. Staurosporine and actinomyocin D were included as positive controls. Antagonist **3** had no measurable effect on the inhibition of cell proliferation and was not significantly different from DMSO vehicle in all cell lines. These results do not support the hypothesis that inhibition of PPARδ may provide effective antiproliferative activity against colorectal cancer. However, these preliminary experimental results are based on a single tool compound and more detailed studies are required to fully understand the potential role of PPARδ inhibition in the etiology of cancer.

Finally, pharmacokinetic studies were conducted with pyridylsulfone **3** to determine if this antagonist has potential use as an in vivo tool compound. Pyridylsulfone **3** was administered intravenously (0.5 mg/kg) and orally (10 mg/kg) to male C57BL/6 mice. Mean clearance (CL) and volume of distribution at steady state (V_{ss}) following iv administration were 39 ± 11 (mL/min)/kg and 1.7 ± 0.4 L/kg, respectively. Following oral administration, good exposure (C_{max} = 881 ± 166 ng/mL, AUC_{inf} = 3343 ± 332 h·ng/mL), half-life (2.7 ± 1.1 h), and bioavailability (F = 77 ± 17%) were observed. Thus, pyridylsulfone **3** has pharmacokinetic properties suitable for use as an in vivo PPARδ antagonist tool compound in mice.

In this disclosure, we have described the identification of 4-chloro-*N*-(2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)-benzamide **3** as an irreversible antagonist of human and mouse PPARδ that covalently modifies Cys249 within the ligand binding pocket. Pyridylsulfone **3** has been shown to antagonize the induction of PPARδ-regulated target genes in skeletal muscle cells. In preliminary in vitro studies, we demonstrated that this PPARδ antagonist is not a regulator of colon cancer cell proliferation. Antagonist **3** has good oral pharmacokinetic properties and represents a new tool for use in the further elucidation of PPARδ biology.

Experimental Section

Solvents and reagents were reagent grade and used without purification. Reactions involving air or moisture sensitive reagents were carried out under a nitrogen atmosphere. All ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si) in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet, s; broad singlet, bs; doublet, d; triplet, t; quartet, q; multiplet, m. Coupling constants (J) are reported in hertz. LCMS analyses were conducted using a Waters Acquity UPLC system with UV detection performed from 210 to 350 nm with the MS detection performed on a Waters Acquity SQD spectrometer. Analytical thin layer chromatography (TLC) was used to monitor reactions. Plates (2.5 cm × 7.5 cm) precoated with silica gel 60 F_{254} of 250 μm thickness were supplied by EM Science. Combustion microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. Purities of key compounds were >95% as determined by ^{1}H NMR and combustion microanalysis.

General Procedure for the Preparation of Substituted 2-Thiopyridines 6. The procedure for 1,1-dimethylethyl (2-{[5-trifluoromethyl)-2-pyridyl]thio}ethylcarbamate (**6**, R^1 = CF_3, n = 1) is representative. To a stirred solution of 5-trifluoromethyl-2-mercaptopyridine (4.00 g, 22.3 mmol) in DMF (80 mL) was added Et_3N (5.81 g, 57.4 mmol) followed by a solution of 2-(*N*-Boc-amino)ethyl bromide (5.44 g, 24.3 mmol) in DMF (20 mL). After being stirred for 3 h, the mixture was

poured into EtOAc, washed with water, brine, and dried over Na_2SO_4. Solvent was removed under reduced pressure to give the desired pyridyl sulfide as a white solid (7.04 g, 98%) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (9H, s), 3.23 (4H, m), 7.06 (1H, br s), 7.54 (1H, d, J = 8.6 Hz), 7.99 (1H, dd, J = 8.6, 2.2 Hz), 8.78 (1H, s).

General Procedure for the Preparation of Substituted 2-Sulfonylpyridines 7. The procedure for 1,1-dimethylethyl (2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethylcarbamate (**7**, R^1 = CF_3, n = 1) is representative. To a stirred solution of pyridyl sulfide **6** (R^1 = CF_3, n = 1) (7.03 g, 21.8 mmol) in 4:1 acetone−water (20 mL) was added Oxone (29.6 g, 48.1 mmol). The mixture was stirred overnight and then evaporated under reduced pressure to remove the acetone. The remaining aqueous suspension was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure to give the desired pyridylsulfone as a white solid (5.75 g, 74%) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (9H, s), 3.30 (2H, q, J = 6.2 Hz), 3.67 (2H, t, J = 6.4 Hz), 6.81 (1H, t, J = 5.4 Hz), 8.24 (1H, d, J = 8.2 Hz), 8.63 (1H, dd, J = 8.2, 1.6 Hz), 9.24 (1H, s).

General Procedure for the Preparation of Substituted 2-Sulfonylpyridylamines 8. The procedure for (2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)amine (**8**, R^1 = CF_3, n = 1) is representative. 4 N HCl in dioxane (100 mL) was added to pyridylsulfone **7** (R^1 = CF_3, n = 1) (4.50 g, 12.7 mmol), and the mixture was stirred for 3 h. The resulting white suspension was diluted with Et_2O (100 mL) and stirred for 10 min. The white solid was collected, washed thoroughly with Et_2O, and dried in vacuo to give the hydrochloride salt of the desired aminosulfone (3.49 g, 95%). This material was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.21 (2H, m), 3.89 (2H, m), 8.11 (3H, bs), 8.30 (1H, d, J = 8.2 Hz), 8.65 (1H, dd, J = 8.2, 1.8 Hz), 9.27 (1H, s).

General Procedure for the Preparation of Substituted 2-Sulfonylpyridylbenzamides 3 and 9−20. The procedure for 4-chloro-*N*-(2-{[5-trifluoromethyl)-2-pyridyl]sulfonyl}ethyl)benzamide **3** is representative. To a stirred suspension of aminosulfone hydrochloride **8** (R^1 = CF_3, n = 1) (3.49 g, 12.0 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (5.74 g, 56.7 mmol). The mixture immediately became homogeneous. 4-Chlorobenzoyl chloride (2.20 g, 12.6 mmol) was added to the mixture, and stirring was continued overnight. The mixture was poured into 1 N aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The remaining solid was recrystallized from EtOAc−hexane to afford 5-trifluoromethyl-2-pyridylsulfone **3** (4.25 g, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.61 (2H, m), 3.87 (2H, m), 7.43 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 8.19 (1H, d, J = 8.2 Hz), 8.45 (1H, d, J = 8.2 Hz), 8.53 (1H, t, J = 5.3 Hz), 9.02 (1H, s). LRMS (ES) m/z 393 (M + 1). Anal. Calcd for $C_{15}H_{12}N_2O_3SClF_3$: C, 45.87; H, 3.08; N, 7.13; S, 8.16; Cl, 9.03. Found: C, 45.89; H, 3.02; N, 7.08; S, 8.05; Cl, 9.06.

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