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Practical routes to the triarylsulfonyl chloride intermediate of a β_3 adrenergic receptor agonist

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Abstract—A β_3 adrenergic receptor agonist was prepared on a multi-kilogram scale in high yield and purity via a convergent synthesis. A key intermediate in this synthesis was an arylthiazolylbenzenesulfonyl chloride. The triaryl segment of this sulfonyl chloride was assembled at the thiazole ring via coupling of α-haloketone and thiobenzamide precursors (Hantzsch synthesis). Three strategies for introducing the *para*-sulfonyl chloride moiety were developed and evaluated. The sulfonation/chlorination and diazotization/chlorosulfonylation routes were found the most efficient.

1. Introduction

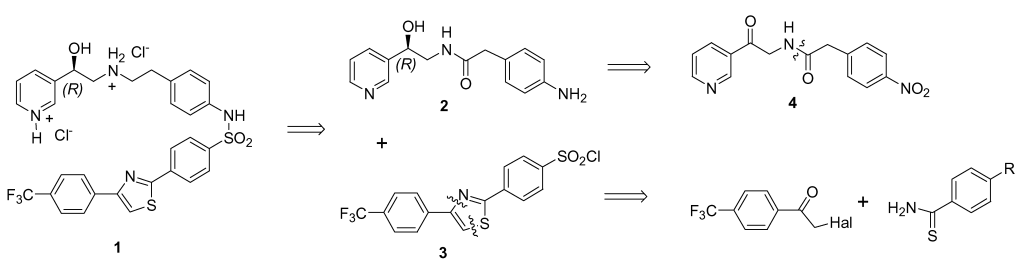
Agonists for the β_3 adrenergic receptors on the surface of adipocytes have been pursued as a potential treatment for obesity at Merck. Stimulation of this receptor elevates the metabolic rate and increases energy utilization, leading to weight loss.[1] The pyridylethanolamine compound **1** containing a substituted thiazole benzenesulfonamide pharmacophore was found to be a potent and selective human β_3 agonist and this compound was chosen for clinical development.[2] A practical, scalable synthesis of **1** was therefore needed to support the safety assessment and clinical testing program.

A more convergent synthesis of **1** than the previous linear synthesis[2] would entail coupling of the upper chiral aniline segment **2** with a preformed lower triarylsulfonylchloride segment **3** (Scheme 1). Introduction of the amide functionality in **2** guaranteed chemoselectivity in the reaction with the sulfonyl chloride. Moreover, this suggested the use of ketoamide precursor **4**, which can be prepared from 4-nitrophenylacetic acid and a 3-pyridyl aminomethyl ketal.[3] An efficient synthesis of **2** using a highly enantioselective yeast-mediated reduction of **4** has been reported and was used in this work.[3] This paper highlights three different strategies to assemble the lower triaryl segment **3** and its coupling with **2** and further conversion to target **1**.

2. Results and discussion

2.1. Synthesis of sulfonyl chloride 3

The three different approaches to triaryl segment **3** are all based on a convergent Hantsch disconnection of the central thiazole ring.[4] They differ in their strategy to introduce the desired sulfonyl halide functionality regioselectively. In the initial strategy, bromide **14** was transformed to **3** via a metalation/sulfination/chlorination sequence. Subsequently, a direct sulfonation reaction followed by chlorination was found to provide the sulfonyl chloride in a more economical approach. Finally, a practical diazotization/



Scheme 1.

Keywords: β_3 agonist; synthesis; sulfonyl chloride.

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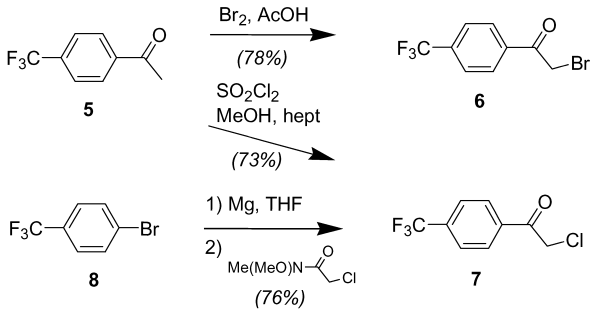


Scheme 2.

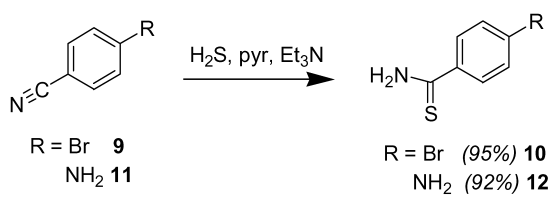
chlorosulfonation strategy was investigated and successfully demonstrated on multi-Kg scale.

The required α-haloketone precursor was prepared by two approaches (Scheme 2). Commercially available acetophenone **5** was treated with an equimolar quantity of bromine in acetic acid to provide a 32:2:1 mixture of desired bromide **6**, a corresponding dibromide and unreacted **5**. Slow addition of water to this mixture induced the crystallization of the product. Some starting material and dibromide were also present in the isolated material but did not pose a problem in the next step since they do not react with thioamides.

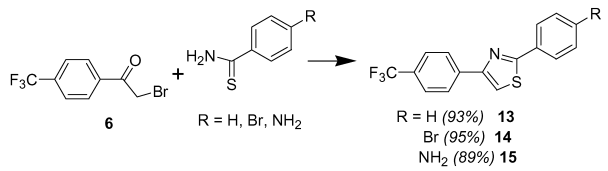
Alternatively, ketone **5** was chlorinated with sulfuryl chloride in heptane–methanol to afford **7** in good yield.[5] Chloroketone **7** could also be prepared by reacting the Grignard reagent derived from **8** with the Weinreb amide prepared from chloroacetylchloride.[6]

The thioamide precursors for the Hantzsch synthesis were either commercially available or were readily prepared from the corresponding nitriles (Scheme 3). Thus, addition of 1.5–2 equiv. of hydrogen sulfide to a concentrated solution of **9** in pyridine and triethylamine readily afforded the bromothiobenzamide **10** which was crystallized by addition of water and isolated in 95% yield. Conversion of nitrile **11** to aminothiobenzamide **12** was markedly slower (2 days using 6 equiv. of H_2S). However, moderate heating in a sealed tube accelerated the reaction (45°C, 16 h, 1.5 equiv. of H_2S) and **12** was obtained in 92% yield.

Thiazoles **13**–**15** readily formed when stoichiometric amounts of the respective thioamides were reacted with either **6** or **7** in warm ethanol.[4] The products crystallized directly from the reaction mixtures and were simply filtered to provide pure thiazoles in high yields. Aniline **15** was isolated either as the hydrochloride or hydrobromide salt, depending on which haloketone was used (Scheme 4).



Scheme 3.



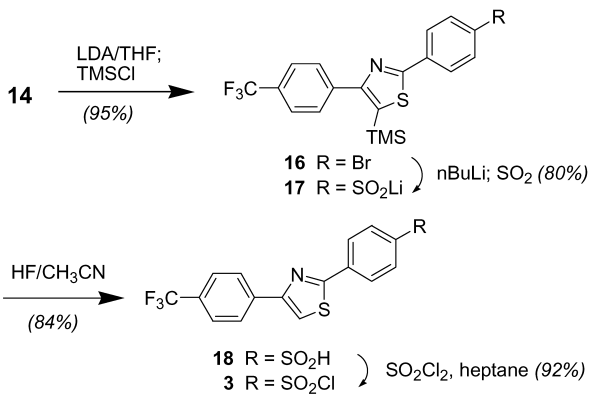
Scheme 4.

Thiazoles **13**–**15** were then converted to sulfonyl chloride **3** via three different approaches.

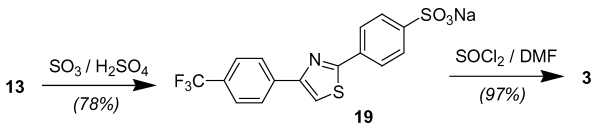
2.1.1. Lithiation/sulfination route. The reaction of an aryllithium with sulfur dioxide to provide the corresponding lithium sulfinate followed by chlorination has been reported as an effective route to arylsulfonyl chlorides.[7] The regiochemical control that this approach ensured was attractive. However, implementation using compound **14** was problematic due to the relatively acidic C-5 hydrogen attached to the thiazole ring.[8] Halogen–metal exchange of **14** with *n*-butyllithium followed by deuterium quench afforded deuterium incorporation at both the *para*-position of the phenyl group and the thiazole ring. Formation of a Grignard reagent followed by deuterium quench also showed deuterium incorporation on the thiazole ring.

This problem was resolved by using a TMS protecting group (Scheme 5). Thus, deprotonation of **14** with LDA in THF followed by reaction with trimethylsilyl chloride provided the C-5 TMS intermediate **16** in 95% yield after crystallization. Addition of 1.1 equiv. of *n*-butyllithium to the latter followed by quenching with sulfur dioxide provided the expected **17**, which could be crystallized from heptane/THF. Desilylation with aqueous HF in acetonitrile provided the sulfinic acid **18**, which directly crystallized from the reaction mixture. Filtration and chlorination with sulfuryl chloride afforded sulfonyl chloride **3**. Thorough drying of the sulfinic acid intermediate proved to be critical since the presence of residual acetonitrile led to chlorination at C-5 of the thiazole ring in the subsequent reaction. In the fully optimized four step operation, aryl bromide **14** could be transformed into sulfonyl chloride **3** in 59% overall yield.

The need for a temporary blocking group in the thiazole ring, the use of a low temperature halogen–metal exchange (<−70°C) and corrosive aqueous hydrogen fluoride, and the relatively large number of operations made this initial



Scheme 5.



Scheme 6.

approach less than practical and not conducive to scale up. Therefore, two other strategies towards introduction of the sulfonyl chloride functionality were investigated.

2.1.2. Sulfonation route. A second approach to sulfonyl chloride **3** is based on the direct sulfonation of phenylthiazole **13** with neat fuming sulfuric acid (oleum) as shown in Scheme 6.[9] Not surprisingly, this reaction affords a mixture of the desired *para*-sulfonic acid and the undesired *meta*-isomer.

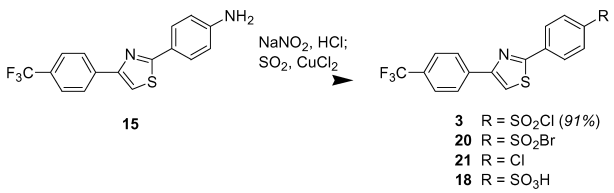
For these studies (see Table 1), the lower strength oleums (20 and 25% SO_3 in H_2SO_4) were used because they are less corrosive and hazardous to use. In addition, an effort was made to keep reagent volumes at a minimum (3–5 mL/g **13** or 5.4–9.1 equiv. SO_3) in order to avoid quenching large excesses of the reagent after the reaction. Useful selectivities were observed under these conditions. The selectivity increased slightly with increasing potency and excess of the oleum (entry 3 vs 7 and entry 1 vs 2, respectively). Lowering the temperature also increased the selectivity (entry 2 vs 3 vs 4). The use of low temperatures with 25% oleum was a safety concern due to its high freezing point (14°C). As a result, 20% oleum (freezing point 1°C) was preferred and the conditions of entry 7 provided an acceptable rate of reaction and selectivity.

An exceedingly convenient procedure to isolate the product directly from the reaction mixture was discovered, avoiding the need for neutralizing large amounts of strong acid. Dilution of the reaction mixture with water followed by addition of THF or acetonitrile resulted in a homogeneous solution. When solid sodium chloride was added to this solution, the sodium sulfonate **19** crystallized as a readily filterable solid. Most importantly, this crystallization largely removed the undesired *meta* isomer. A recrystallization afforded pure **19** with <0.1% of the *meta* isomer in 78% overall isolated yield. Chlorination of **19** with thionyl chloride in acetonitrile in the presence of a catalytic amount of DMF provided sulfonyl chloride **3** in 97% yield.

Even though the above sulfonation/chlorination approach was more efficient (overall yield 75%) and practical than the

Table 1. Effect of oleum strength and volume used as well as reaction temperature on the *para*/*meta* selectivity and reaction time

Entry	Oleum (%), vol (mL/g), equiv. SO_3	Temperature (°C)	*Para*/*meta*	Rxn time (h)
1	25%, 3 mL/g, 5.4	0 to 5	7.8/1	1.5
2	25%, 5 mL/g, 9.1	0 to 5	8.7/1	0.5
3	25%, 5 mL/g, 9.1	−4 to −1	9.3/1	1
4	25%, 5 mL/g, 9.1	−10 to −8	9.7/1	1
5	25%, 4 mL/g, 7.2	−11 to −9	9.0/1	3
6	20%, 4 mL/g, 5.8	−6 to −3	8.0/1	8
7	20%, 5 mL/g, 7.2	−5 to −1	8.5/1	4



Scheme 7.

lithiation/sulfination approach described in Section 2.1.1, the need to recrystallize **19** one or more times to afford the very low levels of the *meta* isomer which are acceptable to us prompted us to develop a third synthesis of sulfonyl chloride **3**.

2.1.3. Diazotization/chlorosulfonylation route. Conversion of anilines to sulfonyl chlorides via their diazonium salts is a known but little used reaction.[10] The diazonium salt is allowed to react with sulfur dioxide and HCl in the presence of copper(I) or (II) salts to afford the sulfonyl chloride directly. This process was attractive because it offered one-pot access to our desired sulfonyl chloride **3** with complete regiochemical control starting from the readily available **15** (Scheme 7).

Thus, treatment of the hydrobromide salt of aniline **15** with sodium nitrite in a mixture of glacial acetic acid and aqueous hydrochloric acid afforded the corresponding diazonium salt. Treatment of the resulting slurry with sulfur dioxide and copper salts afforded a mixture of sulfonyl halides **3** and **20**, which crystallized directly from the reaction mixture. Some undesired aryl chloride **21** and bromide **14** (via a Sandmeyer reaction)[11] as well as sulfonic acid **18** were also generated, but these were all removed in the crystallization.

Further optimization of these conditions was pursued to ensure that this process can be performed safely.

Diazotization of **15** occurs rapidly to afford a bright, yellow diazonium salt, much of which is out of solution. Thermal analyses of these solids showed their potential for extremely rapid, exothermic decomposition. In contrast, in solution, only slow and low energy decompositions were observed. Thus, a process was developed in which all of the diazonium salt remained in solution and in which the chlorosulfonylation reaction was executed at or below room temperature. The solubility of the diazonium salt in several water miscible organic solvents was found to decrease in the following order: DMF>THF, acetonitrile>acetone>dioxane. Further evaluation demonstrated that acetonitrile was the best solvent for our process.

For the chlorosulfonylation step, both copper(I) and copper(II) salts (chlorides, bromides, acetates and triflates) were effective in catalyzing the reaction with sulfur dioxide. With copper(I) salts the reaction was generally faster and more vigorous than with copper(II) salts. The latter were preferred since they allowed better control of temperature and foaming, which is caused by the liberation of nitrogen during this step. Aryl chloride **21** and sulfonic acid **18** are the principal side products in this reaction. Optimization

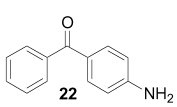
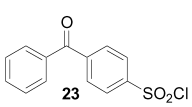
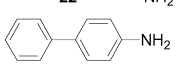
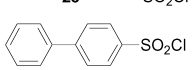
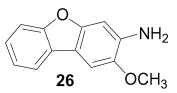
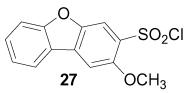
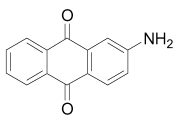
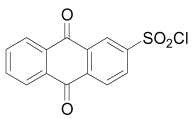
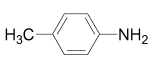
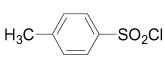
Table 2. Chlorosulfonylation of **15** free-base in 7.5:1:1 acetonitrile/acetic acid/conc HCl using 1 equiv. $CuCl_2$ at room temperature

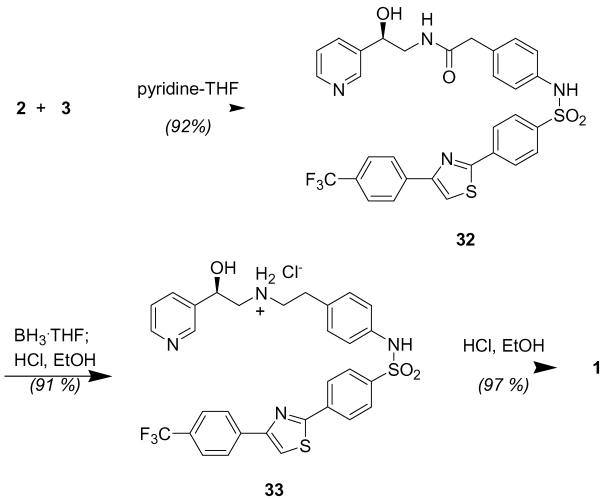
Entry	Equiv. SO_2	Rxn time (h)	**3** vs **21**	**3** yield, A% purity
1	2.2	23	4/1	75%, 94.9 A%
2	10	7	13/1	90%, 97.8 A%
3	16	3	18/1	92%, 98.2 A%
4	32	3	36/1	93%, 99.1 A%

studies showed that minimizing the amount of water and increasing the SO_2 concentration reduces the formation of **18** and **21**, respectively (Table 2). The reaction rate, yield and purity of the product increased as more SO_2 was used. On the other hand, it is also important to keep the excess of corrosive SO_2 to a minimum. Thus, we arrived at an optimum charge of ~20 equiv. of SO_2. The gas can be introduced by either adding a 30% solution in acetic acid (saturated) or by passing gaseous SO_2 into the reaction mixture directly. On larger scale condensation of the gas can be conveniently achieved by introduction into a closed vessel at a pressure of 5 psig at 5°C. Emission of SO_2 can be controlled by using a caustic scrubber in the venting lines of the reaction vessel and water for the bay scrubber.

Under optimum conditions, a mixture of **3** and **20** was produced in a 2.6:1 ratio and 84% overall yield starting with the HBr salt of aniline **15**, which was prepared from readily available bromoketone **6**. The use of a mixture of sulfonyl halides was inconsequential for the next step. Pure sulfonyl chloride could be prepared by using either the HCl salt of **15** (prepared from chloroketone **7**) or its free base. Pure sulfonyl bromide **20** could be prepared by running the reaction with concentrated HBr instead of concentrated HCl. Detailed hazard evaluation showed that our optimum process was operationally safe. Subsequent reaction of aniline free base **15** on multi-kg scale afforded sulfonyl chloride **3** in a reproducible 90% overall yield and excellent purity.

Table 3. Diazotization: acetonitrile, acetic, HCl, 1.2 equiv. $NaNO_2$, 5°C Chlorosulfonylation: 21–33 equiv. SO_2, 1.26 equiv. $CuCl_2$, RT age

Substrate	Product	Yield (%)
 **22**	 **23**	94
 **24**	 **25**	80
 **26**	 **27**	84
 **28**	 **29**	84
 **30**	 **31**	99



Scheme 8.

In an effort to demonstrate the scope of our newly developed diazotization/chlorosulfonylation procedure we examined five other anilines (Table 3). In each case, corresponding sulfonyl chloride was isolated in high yield and purity (>98%) after filtration of the crude reaction mixtures. Impurities were rejected to the acetonitrile-rich mother liquors and recrystallization of the products was not necessary. The procedure is most likely safe in these cases too since all diazonium salts were completely solubilized. In the case of aniline **28** some diazonium salt was out of solution. It is projected that some additional development on a case-by-case basis can circumvent this potential problem.

In conclusion the diazotization/chlorosulfonation reaction outlined above provides the most practical and economic approach to sulfonyl chloride **3**. All operations are performed in the 5–25°C range, and inexpensive and readily available reagents are used. The desired product can be isolated directly from the crude reaction mixture via a simple filtration. Importantly, starting with regioisomerically pure aniline **15** guarantees the production of pure sulfonyl chloride **3**. It should be noted that solubilization of the diazonium salt intermediate significantly reduces the potential hazard of working with this high-energy species. Indeed, this process has been safely scaled up to prepare multi-kg quantities of sulfonyl chloride **3** in high yield and purity.

2.2. Coupling and conversion to 1

The sulfonyl chloride **3** that was prepared by either of the three routes coupled readily with aniline alcohol **2** in THF using 1.1–1.5 equiv. of pyridine as the base to afford amide **32** in high yield (Scheme 8). Pyridine was preferred over triethylamine as the base, because with the latter significant *bis*-*N*-sulfonylation was observed. The coupling occurred readily at room temperature when the sulfonyl chloride/bromide mixture was used, because of the higher reactivity of the sulfonyl bromide. With pure sulfonyl chloride the coupling was slower and warming to 30–35°C was required.

Amide **32** could be reduced to the amine with BH_3–THF.

Slight warming at the end of the reaction was necessary to achieve a high conversion with a minimum excess of borane. However, typically some unconverted starting material (<2%) always remained at the end of reaction. It was found that removal of this impurity in a crystallization of the free base or the di-HCl salt of **1** was minimal. However, crystallization of mono-HCl salt **33** from ethanol completely rejected the unconverted **32**. Conversion of mono-HCl salt **33** to di-HCl salt **1** was readily achieved via addition of a second equivalent of dry HCl.

3. Summary

Three convergent syntheses of sulfonyl chloride **3** were developed. Introduction of the sulfonyl chloride functionality via a metalation/sulfination approach required protection of the thiazole and was found not to be very practical. In contrast, direct sulfonation of **13** with oleum was more practical and efficient. However, a mixture of regioisomers was obtained which required the separation of the unacceptable *meta*-isomer. A one-pot diazotization/chlorosulfonation reaction was operationally the simplest and afforded the sulfonyl chloride in 90% overall isolated yield. The choice of solvent ensured safe generation of the diazonium salt, and this process was successfully scaled up. Coupling of **3** with the chiral hydroxyaniline segment **2** followed by borane reduction yielded the β_3 agonist **1** in high yield and purity. Thus, β_3 adrenergic receptor agonist **1** was prepared efficiently on multi-kg scale in six steps starting from trifluoromethylacetophenone with overall yield of 50%.

4. Experimental

4.1. General remarks

Melting points are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. The product ratios in Tables 1 and 2 were determined from HPLC area% ratios at 254 nm (Zorbax RX-C8 column, 80:20 acetonitrile/0.25% $HClO_4$). Reactions were done under nitrogen and with mechanical stirring except with pressure vessels and smaller scale reactions (<100 mL) for which magnetic stirring were used. Reagents and solvents were added rapidly where addition times are not given. Purity values are %w/w vs pure standards.

4.2. Materials

4.2.1. 4-Trifluoromethylphenacyl bromide (6). Ketone **5** (93.2 g, 95% pure, 0.470 mol) was dissolved in 335 mL acetic acid and was cooled to 15°C. Conc. HBr catalyst (0.33 mL) was added, followed by bromine (25 mL, 0.48 mol) over 2 h. After 1.5 h age, water (670 mL) was then added to the reaction mixture over 5 h to form a slurry, which was cooled to 2°C. The solids were filtered, rinsed with water, and air-dried to afford bromoketone **6** (115 g, 86% pure, 78% yield). The bromoketone could be purified via recrystallization from heptane to afford a white solid: mp 59–60°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 5.00 (s, 2H), 7.90 (d, J=8.4 Hz, 2H), 8.18 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 34.6, 119.9, 122.6, 125.4, 126.1, 126.2, 128.1, 129.2, 129.9, 132.9, 133.2, 133.6, 133.9, 137.6, 191.5. Anal. Calcd for $C_9H_6BrF_3O$ (267.05): C, 40.48; H, 2.26; Br, 29.92; F, 21.34. Found: C, 40.64; H, 2.18; Br, 30.03; F, 21.11.

4.2.2. 4-Trifluoromethylphenacyl chloride (7). To Mg (0.38 g, 15.6 mmol) in 20 mL THF was added 4-bromobenzotrifluoride **8** (2.0 mL, 14.3 mmol), and the mixture was stirred 2 h with cooling. The resulting dark solution was cooled to −1°C, and a solution of chloroacetyl Weinreb amide (1.97 g, 14.3 mmol) in 20 mL THF was added over 15 min. The mixture was stirred 2 h and was warmed to room temperature. The mixture was cooled and was quenched with 20 mL 2N HCl solution. The aqueous layer was extracted twice with methyl *tert*-butyl ether (MTBE), and the combined organics were dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The residue was purified by silica gel chromatography (5% ethyl acetate/hexane) to afford chloroketone **7** (2.41 g, 76% yield). The product could be recrystallized from heptane to afford a white solid: mp 54–55°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 5.26 (s, 2H), 7.91 (d, J=8.2 Hz, 2H), 8.15 (d, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 48.2, 119.9, 122.7, 125.4, 126.1, 126.2, 128.1, 129.5, 129.8, 132.9, 133.2, 133.6, 133.9, 138.0, 191.6. Anal. Calcd for $C_9H_6ClF_3O$ (222.59): C, 48.56; H, 2.72; Cl, 15.93; F, 25.60. Found: C, 48.48; H, 2.66; Cl, 15.76; F, 25.57.

Alternative synthesis: ketone **5** (28.2 g, 95% pure, 142.5 mmol) was dissolved in 100 mL heptane and 9.1 mL methanol and cooled to 0–5°C. The solution of SO_2Cl_2 (14.5 mL, 180 mmol) in 50 mL heptane was added slowly over 75 min. The resulting mixture was stirred at this temperature for 25 min. Then, 200 mL 1 M $NaHCO_3$ was added over 10 min with cooling, followed by 500 mL heptane. The aqueous layer was extracted with 100 mL heptane, and the combined organic solution was concentrated to 50 mL to afford a slurry. This was cooled to 0–5°C and was filtered. The solids were rinsed with 20 mL cold heptane to afford after drying 23.2 g (73% yield) chloroketone **7**.

4.2.3. 4-Bromothiobenzamide (10). To a solution of 4-bromobenzonitrile **9** (30 g, 0.165 mol) in 100 mL pyridine was added triethylamine (23 mL, 0.165 mol). The solution was cooled to 10°C, and hydrogen sulfide gas was bubbled in for 15 min. The resulting green solution was stirred 6 h, and nitrogen was bubbled through the solution to remove the excess hydrogen sulfide. Water (100 mL) was added until the mixture became cloudy, and seed crystals of **10** were added. More water (370 mL) was added slowly, and the resulting slurry was stirred overnight. The solids were filtered, rinsed with water, and dried to afford 4-bromothiobenzamide **10** (33.7 g, 95% yield): mp 145–146°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.62 (d, J=8.6 Hz, 2H), 7.82 (d, J=8.6 Hz, 2H), 9.55 (s, 1H), 9.93 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 125.3, 129.7, 131.2, 138.8, 199.0. Anal. Calcd for C_7H_6BrNS (216.10): C, 38.91; H, 2.80; N, 6.48; Br, 36.98; S, 14.84. Found: C, 38.81; H, 2.62; N, 6.38; Br, 36.82; S, 14.92.

4.2.4. 4-Aminothiobenzamide (12). In a pressure tube a

solution of 4-aminobenzonitrile **11** (2.0 g, 16.9 mmol) in 4 mL pyridine and 2.5 mL triethylamine (17.9 mmol) was cooled, and hydrogen sulfide (0.84 g, 24.6 mmol) was bubbled in. The tube was sealed and heated to 60°C for 22 h. The reaction mixture was added slowly into 50 mL water containing seed crystals of **12**. The slurry was mixed 30 min at room temperature and was filtered. The solids were rinsed with water and dried to afford 4-aminothiobenzamide **12** (2.36 g, 92% yield): mp 194°C (d). ^{1}H NMR (400 MHz, d_6-DMSO): δ 5.80 (s, 2H), 6.49 (d, J=8.8 Hz, 2H), 7.78 (d, J=8.8 Hz, 2H), 8.92 (s, 1H), 9.15 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 112.3, 125.8, 130.1, 152.8, 198.3. Anal. Calcd for $C_7H_8N_2S$ (152.21): C, 55.24; H, 5.30; N, 18.40; S, 21.06. Found: C, 55.35; H, 5.18; N, 18.34; S, 21.28.

4.2.5. 2-(4-Bromo-phenyl)-4-(4-trifluoromethyl-phenyl)-thiazole (14). To a slurry of 4-bromothiobenzamide **10** (8.0 g, 37.0 mmol) in 92 mL ethanol was added bromoketone **6** (11.2 g, 88% pure, 37.0 mmol). The mixture was warmed to 45°C and continued to stir 4 h. The mixture was then cooled to 1°C, aged for 30 min, and then filtered. The solid was rinsed with 20 mL 3:1 ethanol/water and was dried to afford thiazole **14** (13.5 g, 95% yield): mp 150°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.70 (d, J=8.5 Hz, 2H), 7.80 (d, J=8.2 Hz, 2H), 7.94 (d, J=8.5 Hz, 2H), 8.22 (d, J=8.2 Hz, 2H), 8.39 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 117.9, 123.3, 124.2, 126.0, 126.1, 127.1, 128.2, 128.5, 128.9, 132.3, 132.6, 137.8, 154.0, 166.6. Anal. Calcd for $C_{16}H_9BrF_3NS$ (384.21): C, 50.02; H, 2.36; N, 3.65; Br, 20.80; S, 8.34. Found: C, 49.97; H, 2.31; N, 3.59; Br, 20.86; S, 8.38.

4.2.6. 2-(4-Bromo-phenyl)-4-(4-trifluoromethyl-phenyl)-5-trimethylsilyl thiazole (16). To a solution of thiazole **14** (20.0 g, 52.0 mmol) in 130 mL THF at −74°C was added LDA (1.45 M in cyclohexane, 46.7 mL, 67.7 mmol) over 12 min, and the mixture was stirred at −40°C for 40 min. TMSCl (8.6 mL, 68 mmol) was added over 6 min at −69°C, and the mixture was stirred 45 min at −50°C. The mixture was quenched with 200 mL saturated NH_4Cl and diluted with 100 mL water and 100 mL MTBE. After agitation, the organic layer was separated and evaporated to a concentrated liquid. Ethanol (150 mL) was added to form a slurry. To this was added 30 mL water over 30 min and the mixture was stirred overnight. The solids were filtered, rinsed with 3:1 ethanol/water and dried to afford silane **16** (22.5 g, 95% yield): mp 106–107°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 0.23 (s, 9H), 7.68 (d, J=8.6 Hz, 2H), 7.81 (q, 4H), 7.90 (d, J=8.6 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 0.9, 123.2, 124.2, 125.5, 125.6, 125.9, 128.6, 129.0, 129.3, 130.0, 130.5, 132.0, 132.6, 140.7, 161.1, 169.4. Anal. Calcd for $C_{19}H_{17}BrF_3NSSi$ (456.40): C, 50.00; H, 3.75; N, 3.07; Br, 17.51; S, 7.02. Found: C, 50.12; H, 3.71; N, 3.06; Br, 17.47; S, 6.76.

4.2.7. Lithium 4-[4-(4-trifluoromethyl-phenyhl)-5-trimethylsilyl-thiazol-2-yl]-benzenesulfinate (17). Silyl aryl bromide **16** (840 g, 1.84 mol) was dissolved in THF (9 L) and azeotropically dried via distillation to a total volume of 5 L volume. This solution was cooled to −74°C, and *n*-BuLi (2.4 M in heptane, 802 mL, 1.92 mol) was added over 30 min. The resulting solution was stirred for 40 min, and SO_2 gas (Caution! Hazardous gas) was passed over the liquid until the mixture turned from dark green to orange-red. The cooling bath was removed, and the reaction mixture was allowed to warm from −50°C to room temperature. The mixture was concentrated and the solvent composition was adjusted to 5:1 heptane/THF affording a viscous slurry, which was filtered under nitrogen. The solids were rinsed with heptane and dried under nitrogen to afford lithium sulfinate **17** (775 g, 85% pure, 80% yield), which was used directly for the next step. ^{1}H NMR (400 MHz, d_6-DMSO): δ 0.25 (s, 9H), 7.63 (d, J=8.2 Hz, 2H), 7.84 (q, 4H), 7.95 (d, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 0.9, 125.5, 125.6, 125.8, 126.0, 126.3, 128.9, 129.2, 129.6, 130.0, 132.2, 141.0, 161.0, 162.5, 170.9.

4.2.8. 4-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfinic acid (18). Lithium sulfinate salt **17** (728 g, 85% pure, 1.38 mol) was suspended in 4.4 L acetonitrile in a Nalgene vessel over an ice bath. A 48% HF solution (226 mL, 6.2 mol) (Caution! Hazardous liquid) was added resulting in a homogenous solution. The cooling bath was removed, and the mixture was stirred for 4 h during which solids formed. The slurry was cooled over an ice bath and was filtered. The solid cake was rinsed with cold acetonitrile and dried to afford sulfinic acid **18** (495 g, 86% pure, 84% yield), which was used directly for the next step. ^{1}H NMR (400 MHz, d_6-DMSO): δ 5.0 (br, 1H), 7.73 (d, J=8.2 Hz, 2H), 7.81 (d, J=8.2 Hz, 2H), 8.13 (d, J=8.2 Hz, 2H), 8.25 (d, J=8.2 Hz, 2H), 8.43 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 118.2, 123.3, 126.0, 126.1, 126.2, 126.9, 127.1, 128.5, 128.9, 137.9, 154.1, 166.9.

4.2.9. 4-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonyl chloride (3) (lithiation route). The sulfinic acid **18** (486 g, 86% pure, 1.13 mol) was suspended in 3.9 L acetonitrile with cooling over a salt ice bath. Sulfuryl chloride (103 mL, 1.24 mol) was added over 30 min while keeping the temperature below 2°C. After stirring 30 min, the slurry was filtered, rinsed with heptane, and dried to afford the sulfonyl chloride **3** (518 g, 81% pure, 92% yield).

4.2.10. 4-(4-Trifluoromethyl-phenyl)-2-phenyl-thiazole (13). A suspension of thiobenzamide (5.88 g, 42.9 mmol) in 80 mL isopropyl alcohol was cooled to 10°C, and bromoketone **6** (11.5 g, 42.9 mmol) was added. The mixture thinned, and the temperature rose to 27°C before a thick mixture of the product formed. The mixture was stirred for 2 h, then cooled to 1°C and filtered. The solids were rinsed with cold isopropyl alcohol and water and dried to afford **13** (12.2 g, 93% yield). The product could be recrystallized from ethanol to afford a white solid: mp 136°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.52 (m, 3H), 7.81 (d, J=8.1 Hz, 2H), 8.03 (m, 2H), 8.25 (d, J=8.1 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 117.5, 123.3, 126.0, 126.1, 126.2, 126.7, 127.1, 128.5, 128.8, 129.7, 130.9, 133.1, 138.0, 153.9, 167.9. Anal. Calcd for $C_{16}H_{10}F_3NS$ (305.32): C, 62.94; H, 3.30; N, 4.59; F, 18.67; S, 10.50. Found: C, 62.90; H, 3.33; N, 4.51; F, 18.67; S, 10.37.

4.2.11. Sodium 4-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonate (19). Oleum (20% SO_3/H_2SO_4; 150 mL) (Caution! Very corrosive liquid) was cooled to −5°C, and phenylthiazole **13** (30 g, 98.2 mmol) was added

over 30 min in six portions. The temperature of the reaction mixture was maintained below −1°C. The resulting viscous liquid was stirred for 4 h at −5°C, after which the reaction was complete. Water (70 mL) was added slowly to quench the mixture, keeping the temperature below 10°C. After conducting a small test run, the remaining 190 mL aliquot (73%) of this mixture was added to a mixture of 209 mL water and 152 mL THF. The mixture was heated to 54°C to form a clear solution to which 38 g of solid NaCl was added. A slurry formed, which was cooled over 1 h to 25°C and filtered. The solids were rinsed with water. This product (98.4% pure) was dissolved in 350 mL of a 1.5:1 mixture of water and THF at 60°C, and a solution of 2 mL of 50% NaOH in 10 mL water was added, followed by 130 mL of brine. The resulting slurry was cooled to 20°C and filtered. The solids were rinsed with water and dried to afford sulfonate salt **19** (23 g, 99.9% pure, 78% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.79 (d, J=8.1 Hz, 2H), 7.82 (d, J=8.1 Hz, 2H), 8.02 (d, J=8.1 Hz, 2H), 8.27 (d, J=8.1 Hz, 2H), 8.41 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 117.8, 123.3, 126.0, 126.1, 126.2, 126.9, 127.1, 128.5, 128.8, 133.1, 138.0, 150.4, 153.9, 167.4. Anal. Calcd for $C_{16}H_9F_3NNaO_3S_2$ (407.36): C, 47.18; H, 2.23; N, 3.44; F, 13.99; S, 15.74. Found: C, 46.81; H, 1.95; N, 3.16; F, 13.80; S, 15.89.

4.2.12. 4-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonyl chloride (3) (sulfonation/chlorination route). The sulfonate salt **19** (10.0 g, 24.5 mmol) was suspended in 50 mL acetonitrile at room temperature, and thionyl chloride (3.6 mL, 49 mmol) and 1.0 mL of DMF were added. The mixture was stirred for 3.5 h and then filtered. The solids were rinsed with acetonitrile and water, and dried to afford sulfonyl chloride **3** (9.64 g, 97% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.76 (d, J=8.2 Hz, 2H), 7.81 (d, J=8.2 Hz, 2H), 8.01 (d, J=8.2 Hz, 2H), 8.26 (d, J=8.2 Hz, 2H), 8.41 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 117.8, 123.3, 126.0, 126.1, 126.2, 126.9, 127.1, 128.5, 128.8, 133.1, 138.0, 150.3, 153.9, 167.4. Anal. Calcd for $C_{16}H_9ClF_3NO_2S_2$ (403.82): C, 47.59; H, 2.25; N, 3.47; Cl, 8.78; S, 15.88. Found: C, 47.44; H, 1.97; N, 3.36; Cl, 8.96; S, 15.77.

4.2.13. 4-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-phenylamine hydrobromide salt (15). Bromoketone **6** (77.3 g, 86% pure, 0.25 mol) was dissolved in 765 mL of isopropyl alcohol, and *p*-aminothiobenzamide **12** (37.9 g, 0.25 mol) was added. A thick slurry formed within a few minutes. The mixture was heated to 48°C, aged for 4 h and then cooled to 2°C. The slurry was filtered, rinsed cold isopropyl alcohol and dried to afford aniline **15** hydrobromide salt (89.2 g, 89% yield): mp 308°C (d). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.1 (br, 3H), 7.31 (d, J=8.5 Hz, 2H), 7.82 (d, J=8.2 Hz, 2H), 8.04 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.2 Hz, 2H), 8.37 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 117.3, 121.7, 123.3, 126.0, 126.1, 126.2, 127.1, 128.1, 128.4, 128.8, 129.6, 138.0, 138.7, 153.8, 167.2. Anal. Calcd for $C_{16}H_{12}BrF_3N_2S$ (401.24): C, 47.90; H, 3.01; N, 6.98; Br, 19.91; S, 7.99. Found: C, 47.62; H, 2.79; N, 6.86; Br, 19.73; S, 7.76.

4.2.14. 4-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonyl chloride (3). (diazotization/chlorosulfonylation route). From **15**·HBr salt: the aniline hydrobromide salt **15** (50 g, 0.125 mol) was suspended in 500 mL of acetonitrile and cooled over an ice bath. Concentrated HCl (200 mL) was added to afford a creamy mixture. A solution of $NaNO_2$ (10.3 g, 0.150 mol) in 25 mL of water was added via an addition funnel over 10 min. The temperature rose to 10°C during the addition, and an HPLC assay after 25 min showed complete conversion to the diazonium salt. A 30 wt% saturated solution of SO_2 in acetic acid (300 mL) was poured into the reaction mixture. Then, a solution of $CuCl_2 2H_2O$ (10.6 g) in 25 mL of water was added. In a few minutes, the dark solution yielded thick brown precipitates. Over time, tan solids of the sulfonyl chloride formed. After stirring for 2.5 h these solids were filtered and rinsed 250 mL of acetic acid, 200 mL 1:1 mixture of acetic acid/water and 800 mL of water. The solids were dried to afford sulfonyl chloride **3** (44 g, 92.5% pure, 81% yield) as a light yellow solid. This product was a 72:28 mixture of sulfonyl chloride and sulfonyl bromide, as determined by titration.

From **15** free base: in a glass pressure vessel, aniline free-base **15** (16.04 g, 50 mmol) was dissolved in 400 mL of acetonitrile at room temperature, and 40 mL of acetic acid was added. Concentrated HCl (40 mL) was added slowly over 2 min to afford a thick slurry, which was cooled to 5°C. A solution of $NaNO_2$ (4.14 g, 60 mmol) in 10 mL of water was added over 1 min, and the resulting solution was stirred for 20 min at 5°C. The vessel was pressurized over 35 min with SO_2 gas (88.7 g, 1.38 mol) from a cylinder to 5 psig, keeping the temperature at <10°C. Then, a solution of $CuCl_2 \cdot 2H_2O$ (8.52 g, 50 mmol) in 10 mL of water was added. The temperature was allowed to rise to 18°C over 10 min and the mixture was stirred for 4 h at room temperature. The slurry was filtered and rinsed sequentially with 50 mL of acetonitrile, 150 mL of water, and 50 mL of acetonitrile. The solids were vacuum dried overnight to afford sulfonyl chloride **3** (18.6 g, 99.5% pure, 91% yield).

4.2.15. 4-Benzoyl-benzenesulfonyl chloride (23) (representative procedure). 4-Aminobenzophenone **22** (3.94 g, 20.0 mmol) was dissolved in 160 mL of acetonitrile and after cooling to 0–5°C, 16 mL of acetic acid and 8 mL of concentrated HCl were added. To the mixture was added $NaNO_2$ (1.66 g, in 3 mL water) over 10 min at < 5°C. After stirring 20 min, SO_2 gas (42 g) was bubbled in over 40 min keeping the mixture <7°C. A solution of $CuCl_2$ (3.4 g, 25 mmol) in water (3 mL) was added and the mixture was allowed to warm and stir for 16 h at room temperature. The mixture was concentrated to 80 mL and was cooled to 0–5°C. The solids were filtered, washed with 20 mL of water, and dried to afford sulfonyl chloride **23** (5.27 g, 94% yield) as a pink solid; mp 96–97°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 2H), 7.66 (m, 1H), 7.82 (m, 2H), 8.00 (m, 2H), 8.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.0, 128.7, 130.1, 130.7, 133.6, 136.0, 143.5, 146.6, 194.5. Anal. Calcd for $C_{13}H_9ClO_3S$ (280.73): C, 55.62; H, 3.23; Cl, 12.63; S, 11.42. Found: C, 55.55; H, 3.23; Cl, 12.54; S, 11.25.

4.2.16. Biphenyl-4-sulfonyl chloride (25). 4-Aminobiphenyl **24** (3.38 g, 20.0 mmol) was processed to afford sulfonyl chloride **25** (4.05 g, 80% yield) as a yellow solid;

mp 118–119°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 3H), 7.63 (m, 2H), 7.82 (d, J=8.6 Hz, 2H), 8.11 (d, J=8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.9, 128.7, 130.1, 130.6, 133.6, 135.9, 143.4, 146.5. Anal. Calcd for $C_{12}H_9ClO_2S$ (252.72): C, 57.03; H, 3.59; Cl, 14.03; S, 12.69. Found: C, 56.80; H, 3.25; Cl, 14.10; S, 12.71.

4.2.17. 2-Methoxy-dibenzofuran-3-sulfonyl chloride (27). 3-Amino-2-methoxydibenzofuran **26** (4.26 g, 20.0 mmol) was processed to afford sulfonyl chloride **27** (4.97 g, 84% yield) as a purple solid; mp 197–198°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (s, 3H), 7.43 (m, 1H), 7.58–7.62 (m, 3H), 8.00 (d, J=7.8 Hz, 1H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.1, 104.1, 112.4, 113.2, 121.7, 122.6, 123.4, 129.6, 130.3, 131.8, 148.1, 153.8, 158.5. Anal. Calcd for $C_{13}H_9ClO_4S$ (296.73): C, 52.62; H, 3.06; Cl, 11.95; S, 10.81. Found: C, 52.65; H, 2.76; Cl, 12.18; S, 10.82.

4.2.18. 9,10-Dioxo-9,10-dihydro-anthracene-2-sulfonyl chloride (29). 2-Aminoanthraquinone **28** (4.46 g, 20.0 mmol was processed to afford sulfonyl chloride **29** (5.14 g, 84% yield) as a brown solid; mp 207–208°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.89 (m, 2H), 8.07 (m, 1H), 8.16 (m, 3H), 8.39 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 124.1, 127.1, 127.4, 131.6, 133.3, 133.5, 133.5, 134.9, 134.9, 153.9, 182.5, 182.7. Anal. Calcd for $C_{14}H_7ClO_4S$ (306.72): C, 54.82; H, 2.30; Cl, 11.56; S, 10.45. Found: C, 54.48; H, 2.01; Cl, 11.84; S, 10.35.

4.2.19. 4-Methylbenzenesulfonyl chloride (31). p-Toluidine **30** (2.14 g, 20.0 mmol) was processed to afford sulfonyl chloride **31** (3.92 g, 99% yield) as a white solid; mp 71–72°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 7.41 (d, J=8.1 Hz, 2H), 7.92 (dd, J=6.7, 1.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 126.9, 130.1, 141.6, 146.7. Anal. Calcd for $C_7H_7ClO_2S$ (190.65): C, 44.10; H, 3.70; Cl, 18.60; S, 16.82. Found: C, 44.00; H, 3.56; Cl, 18.63; S, 16.94.

4.2.20. (*R*)-*N*-(2-Hydroxy-2-pyridin-3-yl-ethyl)-2-(4-{4-[4-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonylamino}-phenyl)-acetamide (32). The aniline **2** (5.43 g, 20.0 mmol) and sulfonyl chloride **3** (8.24 g, 20.4 mol) in 63 mL of THF and 7 mL of pyridine were stirred at 35°C for 3 h. The reaction mixture was diluted with 70 mL of ethyl acetate and extracted with 70 mL of 1N HCl. The organic layer was washed with 70 mL of 1N $NaHCO_3$, filtered, concentrated and flushed with 70 mL of ethyl acetate. The concentrated residue was dissolved in 200 mL of THF to afford a cloudy solution, which was filtered through Solka Floc (6 g) and rinsed with 100 mL THF to remove the sulfonic acid impurity. The filtrate was concentrated, flushed with 70 mL of ethyl acetate, and the residue was dissolved in 70 mL of ethyl acetate. A slurry formed in 15 min, which was stirred for two days and was then filtered. The solids were rinsed with 35 mL of ethyl acetate and dried to afford the amide **32** (12.2 g, 96% pure, 92% yield): mp 166°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 3.24 (t, J=6 Hz, 2H), 3.28 (s, 2H), 4.61 (m, 1H), 5.58 (d, J=4.5 Hz, 1H), 7.03 (1, 4H), 7.23 (dd, J=4.8, 7.8 Hz, 1H), 7.60 (dt, J=7.8, 1.8 Hz, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.89 (d, J=8.4 Hz, 2H), 8.03 (t, J=5.7 Hz, 1H), 8.19 (d, J=8.4 Hz, 2H), 8.25 (d, J=8.2 Hz, 2H), 8.40 (d, J=4.0 Hz, 2H), 8.46 (s, 1H), 8.49 (s, 1H), 10.32 (s, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 41.8, 46.6, 69.5, 119.1, 120.9, 123.5, 126.2, 127.2, 127.4, 128.1, 128.7, 129.0, 130.1, 132.9, 134.1, 135.9, 136.6, 137.7, 139.0, 141.2, 148.1, 148.6, 154.3, 165.9, 170.5. Anal. Calcd for $C_{31}H_{25}F_3N_4O_4S_2$ (638.68): C, 58.30; H, 3.95; N, 8.77; F, 8.92; S, 10.04. Found: C, 58.21; H, 3.93; N, 8.67; F, 8.91; S, 9.99.

4.2.21. (*R*)-*N*-{4-[2-(2-Hydroxy-2-pyridin-3-yl-ethyl-amino)-ethyl]-phenyl}-4-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonamide, hydrochloride (33). To a solution of amide **32** (6.74 g, 97% pure, 10.2 mmol) in 50 mL of THF was added 1 M BH_3THF (50 mL) and was stirred 6 h at 30°C. The reaction mixture was quenched by careful addition of 1 M H_2SO_4 solution (50 mL), and the resulting solution was heated at reflux for 2 h. The mixture was cooled to room temperature and was diluted with 50 mL of isopropyl acetate, and was adjusted to pH 8.2 with 50% NaOH (6.5 mL). The layers were separated, and the organic layer was washed with 50 mL of water. The organic layer was assayed for yield of **33** free base, evaporated, flushed with isopropyl acetate, and then with absolute ethanol. To the resulting slurry in ethanol (70 mL) was added a solution of dry HCl in ethanol (1.62N, 6.3 mL) and was warmed to 35°C to dissolve the solids. Cooling to to room temperature formed a slurry, which was and age overnight, and heptanes (70 mL) was added over 3 h. This slurry was aged overnight and was then filtered, rinsed with a 1:1 mixture of ethanol–heptanes (30 mL), and dried to afford mono-HCl salt **33** (6.15 g, 91% yield): mp 237–238°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.91 (m, 2H), 3.10 (m, 4H), 5.05 (d, J=9.7 Hz, 1H), 6.32 (br, 1H), 7.12 (q, 4H), 7.38 (dd, J=4.8, 7.8 Hz, 1H), 7.77 (dt, J=8.0 Hz, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H), 8.18 (d, J=8.5 Hz, 2H), 8.25 (d, J=8.2 Hz, 2H), 8.50 (m, 1H), 8.51 (s, 1H), 8.58 (s, 1H), 9.2 (vbr, 2H), 10.1 (vbr, 1H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 31.0, 48.2, 53.2, 66.6, 119.2, 121.1, 123.9, 126.2, 127.2, 127.3, 128.2, 129.8, 133.7, 134.2, 136.4, 136.6, 137.4, 137.7, 141.2, 148.0, 149.4, 154.3, 165.9. Anal. Calcd for $C_{31}H_{28}ClF_3N_4O_3S_2$ (677.16): C, 56.32; H, 4.27; N, 8.47; Cl, 5.36; F, 8.62; S, 9.70. Found: C, 56.32; H, 4.24; N, 8.35; Cl, 5.59; F, 8.67; S, 9.82.

4.2.22. (*R*)-*N*-{4-[2-(2-Hydroxy-2-pyridin-3-yl-ethyl-amino)-ethyl]-phenyl}-4-[4-(4-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulfonamide, dihydrochloride (1). To a suspension of the mono-HCl salt **33** (28.2 g, 42.6 mmol) in 110 mL of ethanol was added a solution of dry HCl in ethanol (1.48N, 30 mL, 44.8 mmol). The mixture was warmed to 31°C to dissolve the solids. The solution was filtered into a second flask with a hot ethanol rinse (21 mL). Seed crystals of the di-HCl salt (1.2 g) were added, and the resulting slurry was aged for 2 days. The slurry was cooled over an ice bath and was filtered. The solids were washed with ethanol and dried to afford the di-HCl salt **1** (28.8 g, 97% yield): mp 228–230°C. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.93 (t, 2H), 3.11 (br, 2H), 3.20 (br, 1H), 3.34 (br, 1H), 5.32 (dd, J=2.8, 8.6 Hz, 1H), 6.9 (vbr, 1H), 7.13 (t, 4H), 7.80 (d, J=8.3 Hz, 2H), 7.91 (d, J=8.3 Hz, 2H), 8.04 (t, 1H), 8.16 (d, J=8.3 Hz, 2H), 8.23 (d, J=8.2 Hz, 2H), 8.50 (s, 1H), 8.58 (d, J=8.0 Hz, 1H), 8.87 (br, 1H), 8.92 (br, 1H), 9.41 (br, 2H), 10.55 (s, 1H). ^{13}C NMR (100 MHz,

d_6-DMSO): δ 30.9, 48.2, 52.5, 65.7, 119.2, 121.2, 123.2, 125.9, 126.2, 127.1, 127.3, 128.2, 128.6, 128.9, 129.7, 133.7, 136.5, 137.7, 140.5, 141.2, 141.5, 141.6, 143.5, 154.3, 165.8. Anal. Calcd for $C_{31}H_{29}Cl_2F_3N_4O_3S_2$ (713.62): C, 53.37; H, 4.19; N, 8.03; Cl, 10.16; F, 8.17; S, 9.19. Found: C, 53.46; H, 4.15; N, 7.96; Cl, 10.15; F, 8.18; S, 9.37.

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