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Practical Synthesis and Molecular Structure of a Potent Broad-Spectrum Antibacterial Isothiazoloquinolone

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Abstract:

We report the synthesis of the new 2-sulfonylquinolone ethyl 1-cyclopropyl-6,7-difluoro-2-methanesulfonyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (5). Sulfone 5 is a key intermediate used in the optimized synthesis of the isothiazoloquinolone 9-cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpyridin-4-yl)-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (1), a potent broad-spectrum antibacterial agent that is effective against clinically important resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). Our synthetic method is free of chromatographic purification and amenable to large-scale synthesis. The molecular structures of 1, 9-cyclopropyl-6,7-difluoro-8-methoxy-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (4), 5, and ethyl 2-cyclopropylamino-6,7-difluoro-8-methoxy-4-oxo-4*H*-thiochromene-3-carboxylate (10) were established unambiguously using multinuclear NMR spectroscopy and X-ray crystallography.

Introduction

Isothiazoloquinolones (ITQs) are a class of potent antibacterial agents that, like the related fluoroquinolones, act by inhibiting type II bacterial topoisomerases.[1−3] Recently, we reported ITQs containing functionalized aryls and heteroaryls at the 7-position of various 6- and 8-substituted cores (Figure 1).[4−7] Several of these compounds demonstrated (i) excellent in vitro antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), (ii) good selectivity for bacterial enzymes over human topoisomerase II, and (iii) desirable in vitro toxicity profiles. Compound **1**[6,7] (Figure 1) exhibited the most desirable balance of antibacterial activity (e.g, MRSA $MIC_{90} = 0.5\ \mu g/mL$), enzyme selectivity (e.g., *S. aureus* topoisomerase IV $IC_{50} = 0.7\ \mu M$ vs human topoisomerase II $EC_2 = 100\ \mu M$), and cytotoxicity (e.g., rat hepatocyte $CC_{50} > 100\ \mu M$). ITQ **1** also demonstrated good efficacy in an in vivo murine thigh model of infection employing MRSA. Our original synthesis[6] of **1**, however, was impractical for the preparation of large quantities of material necessary for preclinical development because it required multiple chromatographic purifications and unsuitable reaction conditions (e.g., the use of potentially dangerous reagents). Here, we describe a practical synthesis of **1** that takes advantage of a new 2-sulfonylquinolone intermediate. The synthesis is improved using this intermediate because (i) a potentially dangerous oxidant (*m*-chloroperbenzoic acid[8]) is no longer required, (ii) the new oxidant (Oxone, potassium peroxymonosulfate) does not require stoichiometric control, and (iii) chromatographic purification is not required.

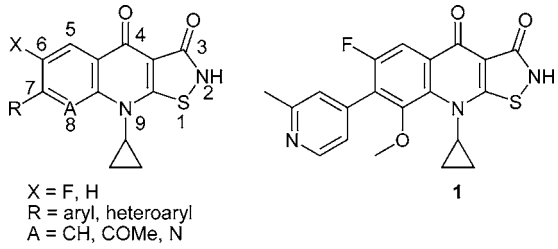

Figure 1. **Structures and numbering scheme of isothiazoloquinolones.**

Results and Discussion

We devised a strategy for the synthesis of **1** (Scheme 1) that relied on Suzuki−Miyaura cross coupling of boronic acid **2** with 7-bromo ITQ **3** to form the necessary biphenyl linkage.[6] We elected to prepare the requisite 7-bromo ITQ **3** from the corresponding 7-fluoro analogue **4**, using a Sandmeyer-type transformation, rather than directly from 2,5-difluoro-4-bromo-3-methoxybenzoic acid because the starting acid for **4**, 2,4,5-trifluoro-3-methoxybenzoic acid, is readily available from several commercial suppliers. ITQ **4** was

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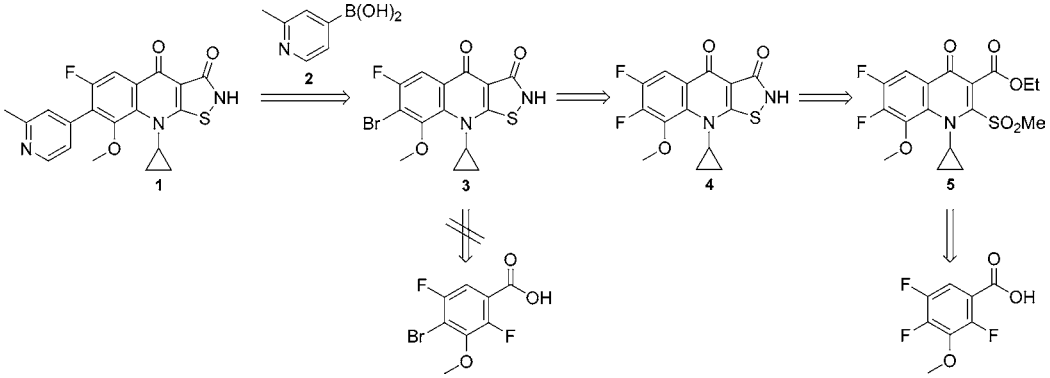
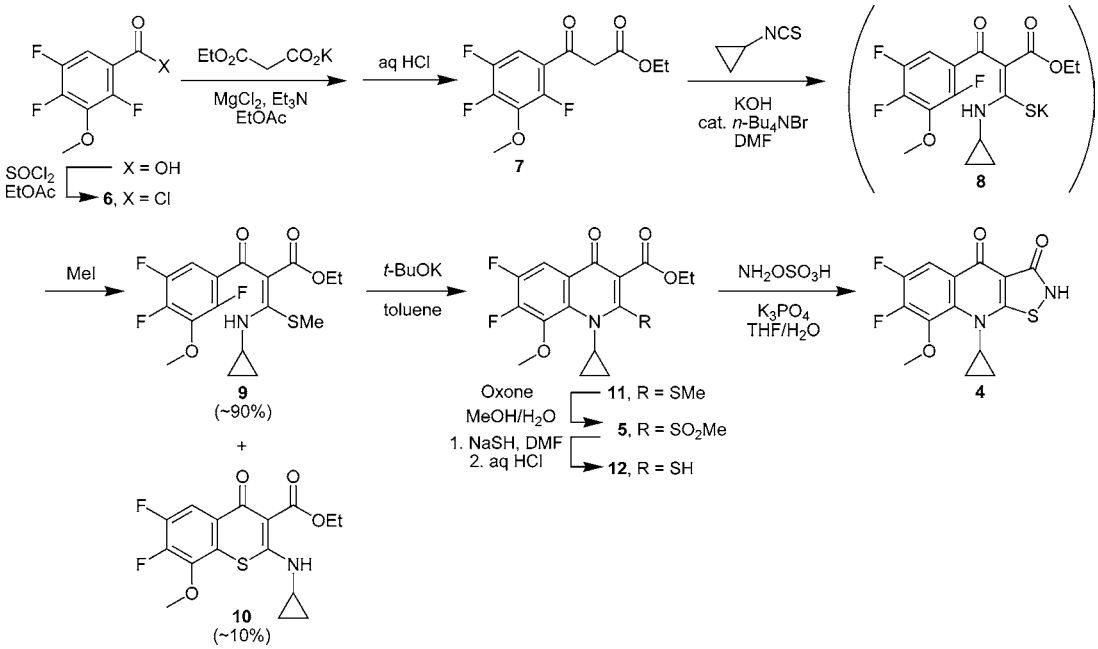
Scheme 1



Scheme 2



prepared as outlined in Scheme 2. This optimized sequence of transformations overcomes the limitations of previous syntheses of **1**[6] and related ITQs[9,10] that require several chromatographic purifications and reagents (e.g., *m*-chloroperbenzoic acid) not amenable to large-scale synthesis. Most importantly, the improved synthesis described in this report deviates from previous methods that do not exploit the benefits of the novel sulfone **5** (vide infra).

The synthesis of **4** began with conversion of commercially available 2,4,5-trifluoro-3-methoxybenzoic acid to the corresponding acid chloride **6** using thionyl chloride (Scheme 2). Conversion of an acid chloride to a β-keto ester is accomplished typically via treatment with monoethyl malonate in the presence of >2 equiv of *n*-butyllithium.[11] Unlike our previous synthesis,[6] we opted for a more process-friendly method that eliminated the use of *n*-butyllithium, the formation of butane gas, and the need for low-temperature conditions: compound **6** was treated with ethyl potassium malonate in the presence of magnesium chloride and triethylamine to generate β-keto ester **7** after acidic workup. Compound **7** was purified readily by recrystallization, avoiding column chromatography, to give the desired product in high yield (77% yield from the starting acid). β-Keto ester **7** was then reacted with potassium hydroxide and cyclopropyl isothiocyanate in dimethylformamide under phase-transfer conditions (using tetrabutylammonium bromide as catalyst) to afford thiolate **8**, rather than under the anhydrous conditions used in our original synthesis[6] that employed sodium hydride and generated hydrogen gas. Thiolate **8** was not isolated but methylated in situ to give **9** and byproduct **10**, the latter of which formed via intramolecular displacement of the C-2 fluoride of **8** by its thiolate anion.[10] Using $\geq$1.5 equiv of cyclopropyl isothiocyanate in this two-step transformation suppressed the formation of byproduct **10** to ~10%. The molecular structure of **10** was determined via X-ray crystallography (Figure 2).

After aqueous workup, product **9** (containing ~10% **10**) was refluxed in toluene with potassium *tert*-butoxide, avoiding the use of hydrogen-forming sodium hydride used in our original synthesis,[6] to furnish quinolone intermediate **11**. Sulfide **11** was next oxidized using Oxone in a methanol−

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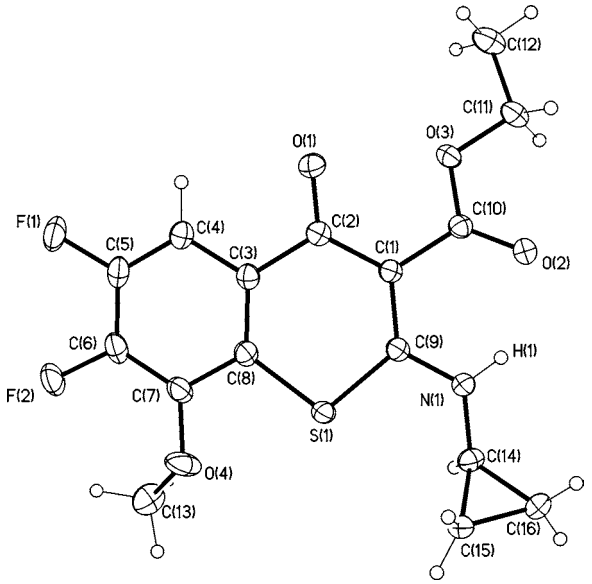

Figure 2. **Structure of thiochromone 10 as determined by X-ray diffraction. ORTEP view showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability. Intramolecular bonding exists between O(2) and amino proton H(1) forming a six-membered ring that possesses a mean planar deviation of 0.047 Å. The interatomic distances are 1.93 and 2.61 Å for H(1)···O(2) and N(1)···O(2), respectively, and the N(1)−H(1)···O(2) angle is 139.0°. The molecular rings are coplanar with a total mean deviation of 0.06 Å for S(1)−C(1−9). Selected bond lengths (Å) and angles (deg) with estimated standard deviations for 10: N(1)−H(1), 0.82(2); S(1)−C(8), 1.7413(19); S(1)−C(9), 1.7458(17); N(1)−C(9), 1.334(2); N(1)−C(14), 1.433(2); C(1)−C(9), 1.401(2); C(1)−C(10), 1.480(2); O(2)−C(10), 1.2233(19); O(3)−C(10), 1.335(2); C(1)−C(2), 1.449(2); O(1)−C(2), 1.228(2); C(2)−C(3), 1.495(2); C(3)−C(8), 1.386(3); C(8)−S(1)−C(9), 102.68(9); C(1)−C(9)−S(1), 125.05(12); C(9)−C(1)−C(2), 123.26(15); C(1)−C(2)−C(3), 119.37(15); C(8)−C(3)−C(2), 123.76(15); C(3)−C(8)−S(1), 124.45(13).**

water solvent system to generate sulfone **5**, which crystallized directly from the reaction mixture. We also found that urea hydrogen peroxide in formic acid effected the oxidation of **11** to generate **5**. CAUTION: *The latter reaction, however, was difficult to control (highly exothermic) and, therefore, was not suitable for large-scale synthesis.* The molecular structure of sulfone **5** was determined via X-ray diffraction (Figure 3A). Sulfone **5** crystallizes in the monoclinic space group $P2_1/c$ with two crystallographically independent, but chemically equivalent, molecules in the asymmetric unit and four molecules in the unit cell. As shown in Figure 3B, the two independent molecules possess different orientations of the peripheral sulfone, ester, methoxy, and cyclopropyl groups relative to the core (quinolone) two-ring system.

Development of the above process for the synthesis of sulfone **5** enabled the subsequent preparation of ITQ **4** in kilogram quantities. Sulfone **5** was next converted (Scheme 2) to the mildly air-sensitive thiol **12** upon treatment with excess sodium hydrosulfide hydrate. To prevent oxidative degradation, isolated **12** (unpurified) was reacted immediately with hydroxylamine-*O*-sulfonic acid under basic conditions (using potassium phosphate, avoiding the use of carbon dioxide forming sodium bicarbonate used in our original synthesis[6]) to afford **4** in high yield (51% overall from **7**

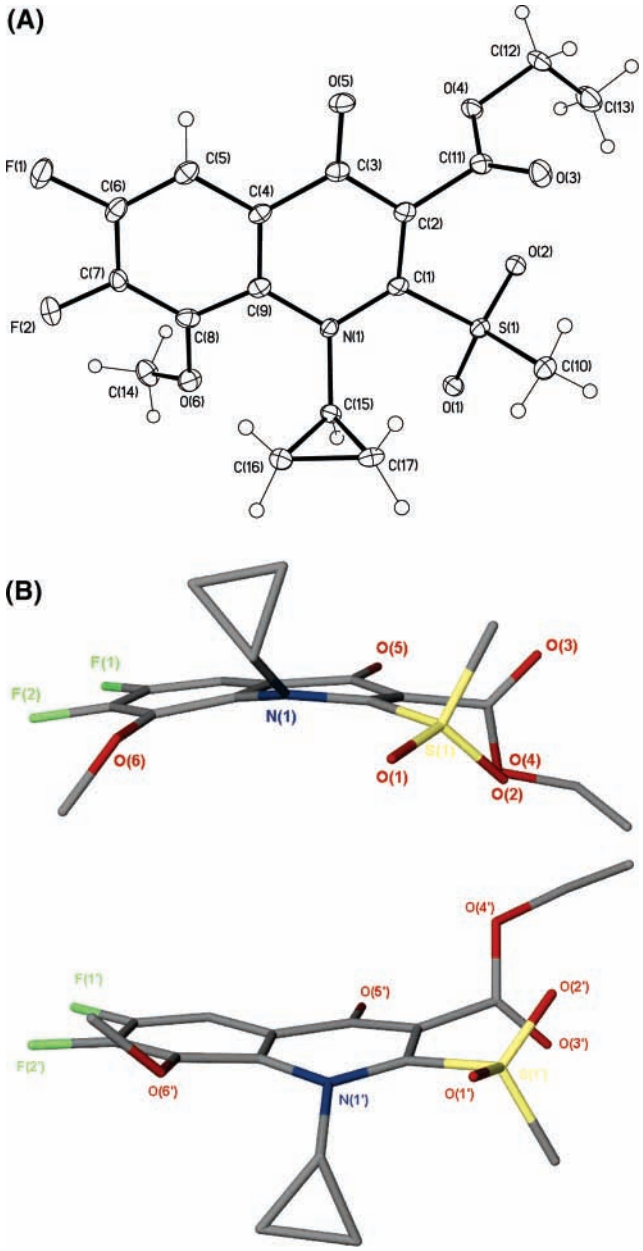

Figure 3. **Structure of sulfone 5 as determined by X-ray diffraction. ORTEP view of one of the two crystallographically independent molecules of 5 (molecule 1) showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability (A) and view of the two independent molecules (B). The molecular rings are coplanar with a total mean deviation of 0.08 Å for both N(1)−C(1−9) and N(1′)−C(1′−9′). There are no significant intermolecular contacts. Selected bond lengths (Å) and angles (deg) with estimated standard deviations for 5: C(1)−C(2), 1.351(5); C(1′)−C(2′), 1.365(5); S(1)−C(1), 1.822(4); S(1′)−C(1′), 1.818(4); O(3)−C(11), 1.193(4); O(3′)−C(11′), 1.203(4); O(4)−C(11), 1.348(4); O(4′)−C(11′), 1.338(4); C(2)−C(11), 1.520(5); C(2′)−C(11′), 1.510(5); C(2)−C(3), 1.451(5); C(2′)−C(3′), 1.453(5); O(5)−C(3), 1.233(4); O(5′)−C(3′), 1.225-(4); C(3)−C(4), 1.476(5); C(3′)−C(4′), 1.468(5); C(4)−C(9), 1.396(5); C(4′)−C(9′), 1.391(5); N(1)−C(9), 1.407(4); N(1′)−C(9′), 1.396(4); N(1)−C(1), 1.378(4); N(1′)−C(1′), 1.375(4); C(1)−N(1)−C(9), 117.2(3); C(1′)−N(1′)−C(9′), 118.2(3); C(2)−C(1)−N(1), 124.0(3); C(2′)−C(1′)−N(1′), 123.2(3); C(1)−C(2)−C(3), 120.8(3); C(1′)−C(2′)−C(3′), 120.2(3); C(2)−C(3)−C(4), 114.0(3); C(2′)−C(3′)−C(4′), 114.6(3).**

without any special handling or purification during the five-step transformation).

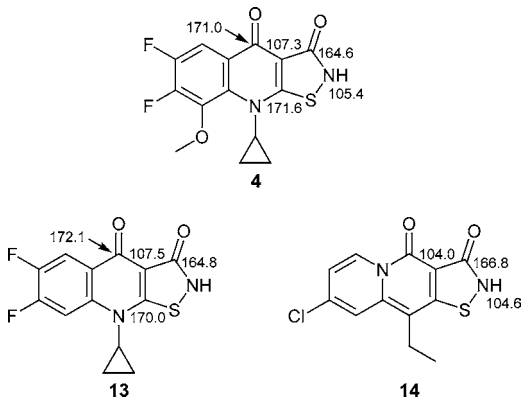

Figure 4. **Selected ^{13}C and ^{15}N NMR data of ITQ 4 and related compounds.**

For our initial synthesis of ITQ **4**,[6] we oxidized methyl sulfide **11** to the corresponding sulfoxide (not shown) using *m*-chloroperbenzoic acid following standard protocol.[9,10] This sulfoxide was then converted to **4** via treatment with anhydrous sodium hydrosulfide, followed by hydroxylamine-*O*-sulfonic acid. Our new methodology, using sulfone **5**, is critical for the practical synthesis of intermediate **4**, offering advantages over the previous sulfoxide method that precluded large-scale synthesis when considering the following. (i) Preparation of sulfone intermediate **5** avoids the use of *m*-chloroperbenzoic acid, which is potentially explosive and requires purification before use.[8] (ii) The process illustrated in Scheme 2 also eliminates the need for stoichiometric control of the oxidant. Oxone, the oxidant used to prepare **5**, may simply be used in excess. (iii) The need for chromatographic purification of the sulfoxide is eliminated as sulfone **5** crystallizes easily from the reaction mixture. (iv) The rate of reaction of the sulfone with sodium hydrosulfide (generating **12** en route to ITQ **4**) is greater (~3-fold) than that of the corresponding sulfoxide.

The HRMS and multinuclear NMR (^{1}H, ^{13}C, ^{15}N, and ^{19}F) spectroscopic data of ITQ **4** are fully consistent with its assigned structure. Specifically, the proton−carbon and carbon−carbon connectivities of **4**, based on COSY, HMQC, and HMBC experiments, are similar to those (unpublished) of the known ITQ **13**[9] (Figure 4). In addition, we labeled **4** with ^{15}N via reaction of **12** with [^{15}N]hydroxylamine-*O*-sulfonic acid.[12] The ^{13}C NMR spectrum of [2-^{15}N]-**4** is identical to that of **4** except the resonance of C-3 appears as a doublet ($J = 3.5$ Hz) rather than a singlet, indicating the ^{15}N-2-N/^{13}C-3-C coupling of the annelated isothiazolo ring. The ^{15}N NMR spectrum of [2-^{15}N]-**4** shows one resonance in the amido region at 105.4 ppm, consistent with the presence of the isothiazolo moiety. Both the ^{13}C and ^{15}N NMR spectroscopic data of **4** are also in excellent agreement with those of the structurally related isothiazolopyridone **14** (Figure 4) for which the solid-state structure was reported.[13] Furthermore, we confirmed the structure of **4** by X-ray diffraction (Figure 5). Slow evaporation of a solution of **4** in trifluoroacetic acid yielded crystals suitable for X-ray structural determination. ITQ **4** cocrystallizes with trifluoroacetic acid in a ratio of 1:2. The crystal lattice possesses an intricate hydrogen-bonding network as illustrated in Figure 5. Two adjacent ITQ molecules interact via N(1)−H(1)···O(1) hydrogen bonds with H(1)···O(1) distances of 1.89 Å. This interaction is reciprocated, and an eight-membered ring is formed. The cocrystallized solvent molecules are hydrogen bound to the two carbonyl groups via O(5)−H(5)···O(1) and O(7)−H(7)···O(2) interactions. H···O distances are 1.89 and 1.75 Å for H(5) and H(7), respectively.

We next converted fluoride **4** to bromide **3** (Scheme 3), which was necessary for the subsequent installation of the 7-pyridinyl group via Suzuki−Miyaura cross coupling. We performed a three-step conversion that followed our earlier method.[6] Unlike our previous method, however, we used 4-methoxybenzylamine rather than the cost-prohibitive 2,4-dimethoxybenzylamine to generate **15** via selective displacement of the C-7 fluoride. Compound **15** was then debenzylated with trifluoroacetic acid to give **16**, which was treated with *tert*-butyl nitrite in the presence of cupric bromide[14,15] to give **3** (45% yield based on **4**).

Finally, bromide **3** was reacted with commercially available boronic acid **2** under Suzuki−Miyaura cross-coupling conditions to generate **1** (Scheme 4). Using ≥2 equiv of **2** in the Suzuki−Miyaura reaction eliminates the competing debromination reaction of **3**. We found that tetrakis(triphenylphosphine)palladium(0) was a highly effective catalyst for cross coupling, whereas several commercially available polymer-supported palladium catalysts caused substantial debromination of **3** (40−80%). Initially, we relied on purification of **1** using preparative HPLC.[6] This method of purification, however, is not suitable for large-scale synthesis, and the palladium contamination of the purified material (~450 ppm) is unacceptable for a potential active pharmaceutical ingredient.[16] Instead, ITQ **1** was isolated by isoelectric precipitation at pH ~7, acidified, triturated, stirred in solution over activated charcoal and MP-TMT[17] (palladium-scavenging resin), and neutralized to afford analytically pure material (99% purity by HPLC with <40 ppm palladium detected by ICP-MS) in 49% yield. Overall, ITQ **1** was synthesized in 9% yield over 11 steps starting from 2,4,5-trifluoro-3-methoxybenzoic acid.

The assigned structure of ITQ **1** is consistent with multinuclear NMR (^{1}H, ^{13}C, and ^{19}F) spectroscopic data. Crystals of **1** suitable for X-ray crystallographic analysis (TFA salt) were obtained via recrystallization from aqueous ethanol. In contrast to ITQ **4** (Figure 5) and the related

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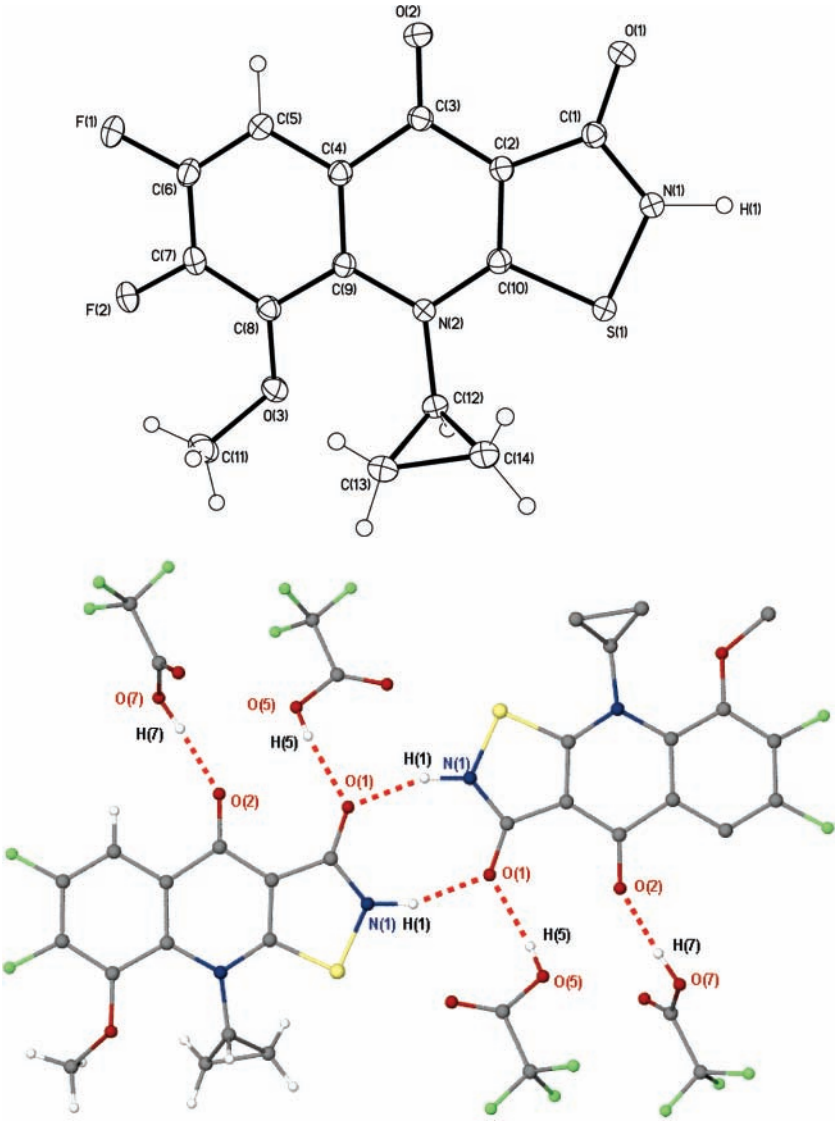
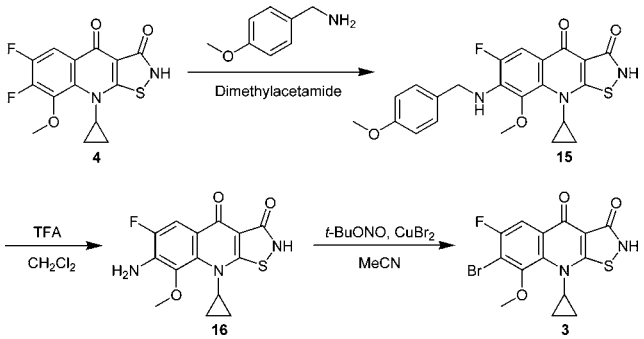
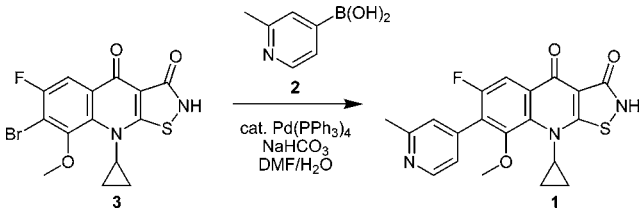


Figure 5. **Structure of ITQ 4 as determined by X-ray diffraction. ORTEP view showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability (top) and view of the hydrogen-bonding network in the crystal lattice (bottom). ITQ 4 cocrystallizes with TFA (solvent) in a ratio of 1:2. The molecular rings of 4 are coplanar with a total mean deviation of 0.07 Å for S(1)−N(1,2)−C(1−10). Selected bond lengths (Å) and angles (deg) with estimated standard deviations for 4·2TFA: O(5)−H(5), 0.78(2); O(7)−H(7), 0.86(2); N(1)−H(1), 1.05(2); C(2)−C(10), 1.3817(19); S(1)−C(10), 1.7245(16); S(1)−N(1), 1.6986(13); N(1)−C(1), 1.3521(19); O(1)−C(1), 1.2496(16); C(1)−C(2), 1.4508(19); C(2)−C(3), 1.429(2); O(2)−C(3), 1.2322(17); C(3)−C(4), 1.4715(19); C(4)−C(9), 1.4063(19); N(2)−C(9), 1.4115(19); N(2)−C(10), 1.3601(17); C(2)−C(10)−S(1), 112.94(11); N(1)−S(1)−C(10), 89.42(7); C(1)−N(1)−S(1), 116.65(10); N(1)−C(1)−C(2), 109.23(11); C(10)−C(2)−C(1), 111.74(13); C(10)−N(2)−C(9), 117.39(11); N(2)−C(10)−C(2), 125.30(14); C(10)−C(2)−C(3), 120.39(13); C(2)−C(3)−C(4), 114.34(12).**

Scheme 3



Scheme 4



isothiazolopyridone **14**,[13] salt **1** crystallizes as the enol rather than as the keto tautomer[18] (Figure 6). The central tricyclic ring system of **1** is planar with a total mean deviation of 0.08 Å for S(1)−N(1,2)−C(1−10). The torsion angle C(6)−C(7)−C(11)−C(15) is 48.0°. Hydrogen-bonding exists between the ion pair of salt **1** as illustrated in Figure 6. The interatomic distances for the hydroxyl hydrogen bond are

(18) For an overview of isothiazolones and their tautomers, see: (a) Taubert, K.; Kraus, S.; Schulze, B. *Sulfur Reports* **2002**, *23*, 79−121. (b) Siegemund, A.; Taubert, K.; Schulze, B. *Sulfur Reports* **2002**, *23*, 279−319.

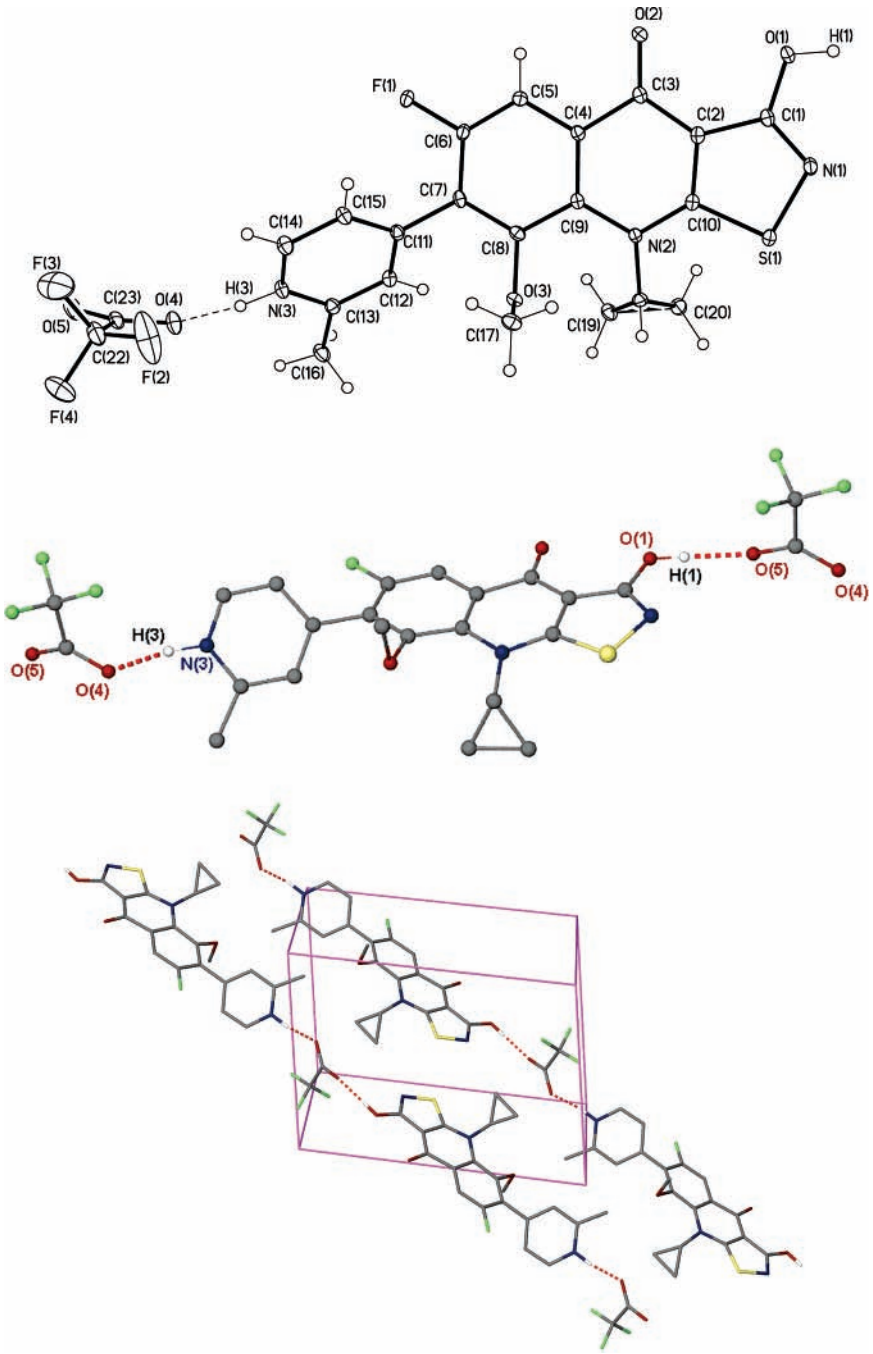


Figure 6. **Structure of ITQ 1 (TFA salt) as determined by X-ray diffraction. ORTEP view showing the atom-labeling scheme with thermal ellipsoids drawn at 30% probability (top), view of the hydrogen-bonding that exists between the ion pair (middle), and view of the hydrogen-bonded chains that propagate in the crystal lattice along the crystallographic *bc*-diagonal axis (bottom). Selected bond lengths (Å) and angles (deg) with estimated standard deviations for 1·TFA: N(3)−H(3), 0.97(3); O(1)−H(1), 0.89(3); C(2)−C(10), 1.388(3); S(1)−C(10), 1.717(2); S(1)−N(1), 1.6717(19); N(1)−C(1), 1.311(3); O(1)−C(1), 1.333(3); C(1)−C(2), 1.436(3); C(2)−C(3), 1.439(3); O(2)−C(3), 1.239(2); C(3)−C(4), 1.487(3); C(2)−C(10)−S(1), 110.19(15); N(1)−S(1)−C(10), 94.21(10); C(1)−N(1)−S(1), 109.78(15); N(1)−C(1)−C(2), 117.32(18); C(10)−C(2)−C(1), 108.49(18).**

1.76 and 2.62 Å for H(1)···O(5) and O(1)···O(5), respectively, and the O(1)−H(1)···O(5) angle is 163.3°. The interatomic distances for the amino hydrogen bond are 1.70 and 2.64 Å for H(3)···O(4) and N(3)···O(4), respectively, and the N(3)−H(3)···O(4) angle is 161.4°. These interactions form infinitely extending chains that propagate along the crystallographic *bc*-diagonal axis as illustrated in Figure 6 (bottom).

Conclusion

We described the synthesis and molecular structure of the new 2-sulfonylquinolone ethyl 1-cyclopropyl-6,7-difluoro-2-methanesulfonyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**5**). Sulfone **5** is a key intermediate used in the practical synthesis of the potent antibacterial ITQ **1**. Compound **1** was prepared in 9% yield over 11 steps. We characterized ITQs **1** and **4** thoroughly using several

techniques, which included the first ^{15}N NMR spectroscopic and X-ray crystallographic investigations. The synthesis of ITQ **1** via sulfone **5** is convenient, scaleable, and does not require chromatographic purification. The validity of the latter has been demonstrated especially in the final palladium-catalyzed cross-coupling step that produced high-purity **1** (99%) that contained <40 ppm of residual palladium.

Experimental Section

General Methods. All nonaqueous reactions were performed under an atmosphere of dry Ar (99.99%) using oven-dried glassware. Melting points were recorded on an Electrothermal Model IA9100 digital melting point apparatus; the reported values are the average of three measurements. NMR spectra were recorded at ambient temperature, unless noted otherwise, using either a Bruker Avance 300 spectrometer (^1H at 300.1 MHz, ^{13}C at 75.5 MHz, and ^{19}F at 282.4 MHz) or a Bruker Avance 500 spectrometer (^{15}N at 50.7 MHz). All ^{13}C, ^{15}N, and ^{19}F NMR spectra were broadband ^1H decoupled. The chemical shifts for ^1H and ^{13}C are reported in parts per million (δ) relative to external TMS and were referenced to signals of residual protons in the deuterated solvent. The chemical shifts for ^{15}N and ^{19}F are reported in parts per million (δ) relative to external liquid NH_3 and $CFCl_3$, respectively. ^1H and ^{13}C NMR data were assigned via two-dimensional correlation experiments ($^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC) and the usual principles of NMR spectroscopy (the magnitudes of coupling constants and chemical shifts). The purity of compounds was determined via HPLC-MS on a Waters X-bridge C18 150 mm × 4.6 mm 3.5 μm column using a 20-min gradient elution of increasing concentrations of CH_3CN in water (5−95%) containing 0.1% TFA with a flow rate of 1.0 mL/min and UV detection at 254 nm. Low-resolution mass spectra were recorded on a Thermo Finnigan Surveyor MSQ instrument (operating in APCI mode) equipped with a Gilson liquid chromatograph. High-resolution mass spectrometric analyses (ESI using NaI as internal standard) were performed at the W. M. Keck Foundation Biotechnology Resource Laboratory (Yale University, New Haven, CT); the reported exact masses are the average of five measurements. Elemental analyses were performed at Atlantic Microlab, Inc. (Norcross, GA). Determinations of trace quantities of residual Pd (ICP−MS) were performed at West Coast Analytical Service (Santa Fe Springs, CA).

Ethyl 3-Oxo-3-(2,4,5-trifluoro-3-methoxyphenyl)propionate (7). A mixture of 2,4,5-trifluoro-3-methoxybenzoic acid (20.7 g, 100 mmol), $SOCl_2$ (42.8 g, 360 mmol), and NaCl (~100 mg) in EtOAc (200 mL) was refluxed for 4 h, cooled to rt, and concentrated under reduced pressure. Toluene (50 mL) was added, and evaporated under reduced pressure; this procedure was repeated twice. The resulting residue was dried in vacuo for 18 h to give **6**. A mixture of potassium ethylmalonate (23.7 g, 139 mmol) and $MgCl_2$ (29.6 g, 312 mmol) in EtOAc (260 mL) was stirred for 30 min at rt. Et_3N (41.8 mL, 300 mmol) was then added, and the mixture continued to stir for 30 min. To this mixture, a solution of EtOAc (40 mL) containing acid chloride **6** (from above) was added slowly. The reaction mixture was refluxed for 2 h and then cooled to rt. To the reaction mixture was then added water (100 mL), and it was then acidified (pH ~1−2) with 6 N HCl and mixed vigorously. The organic layer was separated, and the aqueous layer was extracted with EtOAc (~20 mL), and then the organic layers were combined and evaporated. To the crude material was added EtOH (200 mL) and water (80 mL), and the mixture was heated (~50 °C) and then cooled. At 25−30 °C, a few seed crystals were added and stirred. The mixture was stirred at 20 °C for 30 min and then cooled to 10 °C and stirred for 30 min. The crystals that formed were collected and washed with 70% v/v aq EtOH (~100 mL) and dried to afford **7** (21.3 g, 77%, 2 steps). Mp 59−60 °C. Compound **7** existed as a ~10:1 keto/enol mixture of tautomers at room temperature in DMSO-d_6. ^1H NMR (DMSO-d_6): δ 1.18 (t, J_{H-H} = 7.0 Hz, keto $CO_2CH_2CH_3$), 4.02 (t, J_{H-F} = 1.0 Hz, keto OCH_3), 4.09 (d, J_{H-F} = 3.0 Hz, keto CH_2CO_2Et), 4.12 (q, J_{H-H} = 7.0 Hz, keto $CO_2CH_2CH_3$), 7.65 (ddd, J_{H-F} = 11.0 Hz, 8.5 Hz, 6.5 Hz, keto aromatic H-6). ^{19}F NMR (DMSO-d_6): δ −143.2 (dd, J_{F-F} = 22.0 Hz, 12.5 Hz, keto), −139.7 (dd, J_{F-F} = 22.0 Hz, 12.5 Hz, keto), −129.8 (apparent t, J_{F-F} = 12.5 Hz, keto). HRMS *m*/*z* calcd for $C_{12}H_{11}F_3NaO_4$ ($[M + Na]^+$), 299.0507; found, 299.0498. Anal. Calcd for $C_{12}H_{11}F_3O_4$: C, 52.18; H, 4.01; O, 23.17. Found: C, 52.44; H, 4.00; O, 23.27.

Ethyl 3-Cyclopropylamino-3-methylsulfanyl-2-(2,4,5-trifluoro-3-methoxybenzoyl)acrylate (9). A mixture of **7** (30.0 g, 109 mmol), KOH (7.5 g, 85%), and *n*-Bu_4NBr (0.35 g, 1.09 mmol) in DMF (300 mL) was stirred for 30 min at rt. The mixture was then cooled to 0 °C, and to it was added *c*-PrNCS dropwise (15.2 mL, 164 mmol). After the mixture stirred for 16 h at rt, MeI (7.5 mL, 121 mmol) was then added to the reaction mixture, which continued to stir for 3 h. The reaction mixture was quenched with water (800 mL) and saturated aq NH_4Cl (270 mL) and extracted with EtOAc (2 × 400 mL). The combined organic layers were washed with water (60 mL) and brine (60 mL) and evaporated to dryness under reduced pressure. The residue was dissolved in toluene (50 mL) and evaporated; this process was repeated twice. The final residue was used in the next reaction without purification. An analytical sample (light yellow solid) was obtained via flash column chromatographic purification on silica gel (eluent: 0−20% v/v EtOAc in hexanes). Mp 46−47 °C. ^1H NMR (DMSO-d_6): δ 0.75 (m, 2H, *c*-Pr-CH_2), 0.90 (m, 5H, overlapping $CO_2CH_2CH_3$ and *c*-Pr-CH_2), 2.46 (s, 3H, SCH_3), 2.93 (br, 1H, *c*-Pr-CH), 3.83 (q, J_{H-H} = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.95 (s, 3H, OCH_3), 7.10 (ddd, J_{H-F} = 10.5 Hz, 8.5 Hz, 6.0 Hz, 1H, aromatic H-6), 10.87 (br, 1H). ^{19}F NMR (DMSO-d_6): δ −151.7 (br d, J_{F-F} = 22.0 Hz, 1F), −141.8 (dd, J_{F-F} = 22.0 Hz, 13.5 Hz, 1F), −135.9 (br, 1F). LRMS ($C_{17}H_{18}F_3NO_4S$) *m*/*z* (%) 390 ($[M + H]^+$, 96), 344 (100), 296 (42). Anal. Calcd for $C_{17}H_{18}F_3NO_4S$: C, 52.44; H, 4.66; N, 3.60. Found: C, 52.39; H, 4.62; N, 3.55.

Ethyl 2-Cyclopropylamino-6,7-difluoro-8-methoxy-4-oxo-4*H*-thiochromene-3-carboxylate (10). Byproduct **10** was obtained via flash column chromatographic separation from **9** (vide supra). ^1H NMR ($CDCl_3$): δ 0.84 (m, 2H, *c*-Pr-

CH_2), 1.05 (m, 2H, *c*-Pr-CH_2), 1.40 (t, J_{H-H} = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.72 (m, 1H, *c*-Pr-CH), 4.15 (d, J_{H-F} = 2.5 Hz, 3H, OCH_3), 4.37 (q, J_{H-H} = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 8.04 (dd, J_{H-F} = 11.0 Hz, 7.5 Hz, 1H, aromatic H-5), 10.33 (br, 1H). ^{19}F NMR ($CDCl_3$): δ −150.2 (d, J_{F-F} = 20.5 Hz, 1F), −135.8 (d, J_{F-F} = 20.5 Hz, 1F). LRMS ($C_{16}H_{15}F_2NO_4S$) *m*/*z* (%) 356 ([M + H]$^+$, 100), 310 (36).

Ethyl 1-Cyclopropyl-6,7-difluoro-8-methoxy-2-methylsulfanyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (11). *t*-BuOK (11.0 g, 98 mmol) was added to a solution of **9** (from above) in toluene (300 mL) at rt. The resulting reaction mixture was refluxed for 16 h, cooled to rt, and diluted with water (270 mL). The aqueous layer was separated and extracted with EtOAc (130 mL). The combined organic layers were washed with water (60 mL) and brine (60 mL) and evaporated to dryness. The remaining residue was used in the next step without further purification. An analytical sample (colorless solid) was obtained via flash column chromatographic purification on silica gel (eluent: 0−50% v/v EtOAc in hexanes). Mp 125 °C. ^{1}H NMR (DMF-d_7): δ 0.79 (m, 2H, *c*-Pr-CH_2), 1.20 (m, 2H, *c*-Pr-CH_2), 1.30 (t, J_{H-H} = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.75 (s, 3H, SCH_3), 3.97 (m, 1H, *c*-Pr-CH), 4.14 (d, J_{H-F} = 2.0 Hz, 3H, OCH_3), 4.29 (q, J_{H-H} = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 7.64 (dd, J_{H-F} = 10.0 Hz, 8.5 Hz, 1H, aromatic H-5). ^{13}C NMR (DMF-d_7): δ 11.7 (br, *c*-Pr-CH_2), 13.7 ($CO_2CH_2CH_3$), 17.7 (SCH_3), 37.2 (*c*-Pr-CH), 61.1 ($CO_2CH_2CH_3$), 62.3 (d, J_{C-F} = 6.0 Hz, OCH_3), 105.7 (d, J_{C-F} = 19.0 Hz, CH, C-5), 122.4, 124.3 (dd, J_{C-F} = 6.0 Hz, 2.0 Hz), 137.0 (dd, J_{C-F} = 4.0 Hz, 1.5 Hz), 140.8 (dd, J_{C-F} = 11.5 Hz, 1.5 Hz), 147.6 (dd, J_{C-F} = 251.0 Hz, 15.5 Hz), 148.7 (dd, J_{C-F} = 248.0 Hz, 12.5 Hz), 156.6, 165.2, 171.6 (d, J_{C-F} = 1.5 Hz). ^{19}F NMR (DMF-d_7): δ −148.7 (d, J_{F-F} = 21.5 Hz, 1F), −139.9 (d, J_{F-F} = 21.5 Hz, 1F). LRMS ($C_{17}H_{17}F_2NO_4S$) *m*/*z* (%) 370 ([M + H]$^+$, 100), 324 (20). Anal. Calcd for $C_{17}H_{17}F_2NO_4S$: C, 55.28; H, 4.64; N, 3.79. Found: C, 55.23; H, 4.60; N, 3.72.

Ethyl 1-Cyclopropyl-6,7-difluoro-2-methanesulfonyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (5). Water (240 mL), followed by Oxone (229 g, 373 mmol), was added to a suspension of **11** (from above) in MeOH (690 mL). The reaction mixture was heated with stirring at 55−60 °C for 3 h. The reaction mixture was cooled to rt, diluted with water (450 mL), and stirred at ∼5 °C (ice bath) for 30 min. The resulting crystals were collected by filtration, washed with water (2 × 150 mL), and dried in vacuo to afford **5** (24.0 g). This material was used in the next step without further purification. An analytical sample (colorless solid) was obtained via recrystallization from EtOAc/hexanes. Mp 177−178 °C. ^{1}H NMR (DMF-d_7): δ 0.62 (m, 1H, *c*-Pr-CH_2), 1.11 (m, 2H, *c*-Pr-CH_2), 1.29 (m, 1H, *c*-Pr-CH_2), 1.32 (t, J_{H-H} = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 3.76 (s, 3H, SO_2CH_3), 4.18 (m, 1H, *c*-Pr-CH), 4.21 (d, J_{H-F} = 2.0 Hz, 3H, OCH_3), 4.33 (q, J_{H-H} = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 7.64 (dd, J_{H-F} = 10.0 Hz, 8.5 Hz, 1H, aromatic H-5). ^{13}C NMR (DMF-d_7): δ 8.9 (*c*-Pr-CH_2), 12.5 (*c*-Pr-CH_2), 13.5 ($CO_2CH_2CH_3$), 37.3 (*c*-Pr-CH), 44.5 (SO_2CH_3), 61.9 ($CO_2CH_2CH_3$), 62.2 (d, J_{C-F} = 6.5 Hz, OCH_3), 105.4 (d, J_{C-F} = 19.5 Hz, CH, C-5), 123.0, 124.4 (dd, J_{C-F} = 6.5 Hz, 1.5 Hz), 136.1 (dd, J_{C-F} = 4.5 Hz, 1.5 Hz), 141.4 (dd, J_{C-F} = 10.0 Hz, 1.5 Hz), 148.3 (dd, J_{C-F} = 253.0 Hz, 16.0 Hz), 149.4 (dd, J_{C-F} = 249.0 Hz, 12.5 Hz), 153.6, 163.9, 175.0 (d, J_{C-F} = 2.0 Hz). ^{19}F NMR (DMF-d_7): δ −146.5 (d, J_{F-F} = 21.0 Hz, 1F), −138.3 (d, J_{F-F} = 21.0 Hz, 1F). LRMS ($C_{17}H_{17}F_2NO_6S$) *m*/*z* (%) 402 ([M + H]$^+$, 20), 356 (100). Anal. Calcd for $C_{17}H_{17}F_2NO_6S$: C, 50.87; H, 4.27; N, 3.49. Found: C, 50.73; H, 4.21; N, 3.43.

9-Cyclopropyl-6,7-difluoro-8-methoxy-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (4). $NaSH{\cdot}xH_2O$ (5.8 g, $x \approx 1.2$, Aldrich) was added to solution of **5** (24.0 g, 60 mmol) in DMF (240 mL). The resulting mixture was stirred at rt for 5 h, diluted with water (620 mL), acidified with 6 N HCl (to pH ∼1−2), and extracted with EtOAc (2 × 150 mL). *CAUTION: Toxic hydrogen sulfide gas is evolved. This procedure must be carried out in a well-ventilated hood with provisions for preventing loss of H_2S to the atmosphere (e.g., a trap containing 20% aq NaOH).* The combined organic layers were washed with water (60 mL) and brine (60 mL), dried over Na_2SO_4, and evaporated under reduced pressure. To prevent oxidative degradation, isolated thiol **12** was used directly without further purification. The residue containing **12** was dissolved in a mixture of THF (240 mL), water (240 mL), and K_3PO_4 (69.0 g, 300 mmol) at 0 °C. H_2NOSO_3H (28.0 g, 248 mmol) was then added portionwise, and the resulting mixture was stirred at rt overnight. THF was removed under reduced pressure, and the mixture was acidified with 6 N HCl to pH 2. The resulting precipitate was collected, washed with water (3 × 50 mL), washed (while stirring ∼10 min) with TBME (3 × 50 mL), and dried in vacuo to afford **4** (17.8 g, 51% yield from **7**) as a cream-colored solid. An analytical sample was obtained via recrystallization from DMF. Mp 250 °C (dec). ^{1}H NMR (DMF-d_7): δ 1.23 (m, 2H, *c*-Pr-CH_2), 1.31 (m, 2H, *c*-Pr-CH_2), 3.98 (m, 1H, *c*-Pr-CH), 4.16 (d, J_{H-F} = 1.5 Hz, 3H, OCH_3), 7.92 (dd, J_{H-F} = 10.5 Hz, 9.0 Hz, 1H, aromatic H-5). ^{13}C NMR (DMF-d_7): δ 11.1 (*c*-Pr-CH_2), 35.9 (*c*-Pr-CH), 63.0 (d, J_{C-F} = 6.0 Hz, OCH_3), 107.1 (d, J_{C-F} = 18.0 Hz, CH, C-5), 107.3 (C-3a), 123.1 (dd, J_{C-F} = 7.5 Hz, 5.5 Hz, C-4a), 133.9 (dd, J_{C-F} = 5.5 Hz, 4.0 Hz, C-8a), 140.0 (dd, J_{C-F} = 12.0 Hz, 1.0 Hz, *C*−OCH_3, C-8), 147.7 (dd, J_{C-F} = 247.0 Hz, 12.5 Hz, C-6 or C-7), 148.3 (dd, J_{C-F} = 251.0 Hz, 15.5 Hz, C-6 or C-7), 164.6 (C-3), 171.0 (d, J_{C-F} = 2.0 Hz, C-4), 171.6 (C-9a). ^{15}N NMR (DMF-d_7, −50 °C): δ −105.4 (s, N-2). ^{19}F NMR (DMF-d_7): δ −146.9 (d, J_{F-F} = 21.5 Hz, 1F), −141.2 (d, J_{F-F} = 21.5 Hz, 1F). LRMS ($C_{14}H_{10}F_2N_2O_3S$) *m*/*z* (%) 325 ([M + H]$^+$, 100). HRMS *m*/*z* calcd for $C_{14}H_{10}F_2N_2NaO_3S$ ([M + Na]$^+$), 347.0278; found, 347.0269. Anal. Calcd for $C_{14}H_{10}F_2N_2O_3S$: C, 51.85; H, 3.11; N, 8.64. Found: C, 51.83; H, 3.15; N, 8.65.

9-Cyclopropyl-7-(4-methoxybenzylamino)-6-fluoro-8-methoxy-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (15). To a stirred solution of **4** (11.1 g, 34.3 mmol) in dimethylacetamide (200 mL) was added 4-methoxybenzylamine (18 mL, 137 mmol). The reaction mixture was stirred at 90 °C for 18 h, cooled to rt, and diluted with EtOAc (460 mL). The organic layer was washed with 2 N HCl (4 × 200 mL) to remove excess 4-methoxybenzyl amine, washed with brine

Table 1. **Crystallographic data for compounds 1, 4, 5, and 10**

	1·CF_3CO_2H	**4**·$2CF_3CO_2H$	**5**	**10**
empirical formula	$C_{22}H_{17}F_4N_3O_5S$	$C_{18}H_{12}F_8N_2O_7S$	$C_{17}H_{17}F_2NO_6S$	$C_{16}H_{15}F_2NO_4S$
fw (g mol^{-1})	511.45	552.36	401.38	355.35
crystal dimenions (mm^3)	0.20 × 0.20 × 0.10	0.35 × 0.20 × 0.20	0.10 × 0.10 × 0.05	0.20 × 0.20 × 0.20
crystal system	triclinic	triclinic	monoclinic	triclinic
space group	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$P2_1/c$ (#14)	$P\bar{1}$ (#2)
a (Å)	8.2971(17)	8.6649(17)	24.528(5)	8.8361(18)
b (Å)	9.7116(19)	9.1625(18)	7.1340(14)	9.6639(19)
c (Å)	14.452(3)	14.151(3)	21.125(4)	10.439(2)
α (deg)	81.00(3)	79.77(3)	90	101.76(3)
β (deg)	81.81(3)	74.02(3)	114.89(3)	99.69(3)
γ (deg)	66.27(3)	74.16(3)	90	113.51(3)
V (Å^3)	1048.9(4)	1032.6(4)	3353.0(12)	768.7(3)
Z	2	2	8	2
ρ_{calcd} (g cm^{-3})	1.619	1.776	1.590	1.535
μ (Mo Kα) (cm^{-1})	2.33	2.76	2.52	2.54
temp (K)	123(2)	173(2)	123(2)	173(2)
total data collected	9166	8913	14 391	6440
no. of indep reflns	5529 (R_{int} = 0.0393)	5385 (R_{int} = 0.0368)	8698 (R_{int} = 0.0681)	3972 (R_{int} = 0.0317)
no. of data/restraints/parms	5529/0/324	5385/0/365	8698/0/487	3972/0/221
largest diff peak and hole (e Å^{-3})	0.524 and −0.510	0.566 and −0.435	1.860 and −0.606	0.636 and −0.549
R^a, R_w^b	0.0533, 0.1499	0.0598, 0.1858	0.0778, 0.2018	0.0507, 0.1581
GOF	1.067	1.262	1.042	1.089

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for all $I > 2\sigma(I)$. [b] $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

(2 × 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford **15** as a dark brown oil. This material was used in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ 0.84 (m, 2H), 1.11 (m, 2H), 3.61 (s, 3H), 3.67 (s, 3H), 3.76 (m, 1H), 4.48 (s, 2H), 6.83 (d, J_{H-H} = 8.5 Hz, 2H), 7.26 (d, J_{H-H} = 8.5 Hz, 2H), 7.51 (d, J_{H-F} = 13.0 Hz, 1H). LRMS ($C_{22}H_{20}FN_3O_4S$) *m*/*z* (%) 442 ([M + H]$^+$, 100).

7-Bromo-9-cyclopropyl-6-fluoro-8-methoxy-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (3). To a stirred solution of **15** (crude from above, 12.3 g, 28 mmol) in CH_2Cl_2 (100 mL) was added TFA (6 mL). The reaction mixture was stirred at rt for 4 h and concentrated under reduced pressure to give **16** (TFA salt) as a red oil. To a stirred solution of *t*-BuONO (12 mL, 100 mmol) and $CuBr_2$ (28 g, 123 mmol) in CH_3CN (170 mL) was added dropwise a mixture of the crude TFA salt of **16** (from above) in CH_3CN (50 mL) at 67 °C. After the addition was complete (∼10 min), the reaction mixture was cooled to rt, and saturated aq NH_4Cl was added. The product was extracted with $CHCl_3$ (2 × 400 mL). This organic layer was washed with brine (2 × 250 mL), dried over Na_2SO_4, and evaporated under reduced pressure. A mixture of the remaining oil in 10% v/v MeOH in EtOAc (300 mL) was refluxed for 20 min with stirring. The remaining solid was removed at rt by filtration and washed with 50% v/v EtOAc in hexanes (2 × 100 mL). The filtrate was evaporated under reduced pressure to give **3** as a red solid (5.9 g, 45% yield from **4**). An analytical sample was obtained via preparative HPLC purification.[4] ^{1}H NMR (DMF-d_7): δ 1.16 (m, 2H, *c*-Pr-CH_2), 1.27 (m, 2H, *c*-Pr-CH_2), 3.94 (m, 1H, *c*-Pr-CH), 3.97 (s, 3H, OCH_3), 7.89 (d, J_{H-F} = 8.5 Hz, 1H, H-5). ^{13}C NMR (DMF-d_7): δ 12.0 (*c*-Pr-CH_2), 36.0 (*c*-Pr-CH), 62.8 (OCH_3), 107.6 (d, J_{C-F} = 24.0 Hz, CH, C-5), 108.0 (C-3a), 112.9 (d, J_{C-F} = 22.0 Hz, C−Br, C-7), 132.6 (C-4a), 134.6 (d, J_{C-F} = 2.0 Hz, C-8a), 149.8 ($C-OCH_3$, C-8), 156.0 (d, J_{C-F} = 245.0 Hz, C−F, C-6), 165.2 (C-3), 171.6 (C-4), 172.3 (C-9a). ^{19}F NMR (DMF-d_7): δ −111.2 (s). LRMS ($C_{14}H_{10}BrFN_2O_3S$) *m*/*z* (%) 385 ([M + H]$^+$, 100). HRMS *m*/*z* calcd for $C_{14}H_{10}BrFN_2NaO_3S$ ([M + Na]$^+$), 406.9477; found, 406.9473. Anal. Calcd for $C_{14}H_{10}BrFN_2O_3S$·0.15TFA: C, 42.69; H, 2.54; N, 6.96. Found: C, 42.49; H, 2.68; N, 7.22. The stoichiometry of the TFA was confirmed by ^{19}F NMR spectroscopy.

9-Cyclopropyl-7-(2-methylpyridin-4-yl)-6-fluoro-8-methoxy-9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (1). Under an atmosphere of Ar, $Pd(PPh_3)_4$ (1.81 g, 1.6 mmol), 2-methyl-4-pyridinylboronic acid (**2**, 12.8 g, 93 mmol), and 1 M aq $NaHCO_3$ (400 mL) were added to a solution containing **3** (12.0 g, 32 mmol) and DMF (800 mL). The resulting mixture was heated at 110 °C for 18 h and evaporated to dryness under reduced pressure. The isolated dark brown solid was partially dissolved in water (120 mL) and neutralized with concd HCl. The remaining solid was collected by filtration and washed with water (240 mL). The solid was dissolved in TFA (24 mL) and concentrated under reduced pressure to give a brown residue. This residue was triturated with water (240 mL). The solid that formed was collected by filtration, washed with water (120 mL), and washed with EtOAc (2 × 120 mL). The collected solid was dissolved in a mixture of MeOH (240 mL) and concd HCl (12 mL) and stirred over activated charcoal (1.2 g) at rt for 1 h. The charcoal was removed by filtration, and a small aliquot was removed and concentrated under reduced pressure. The remaining residue contained 191 ppm (ICP−MS) of residual palladium. The filtrate from above was stirred consequently over MP-TMT resin (3.2 g, 0.96 mmol/g, Argonaut Technologies) at rt for 24 h. The resin was removed by filtration, and the filtrate was concentrated under reduced pressure. The remaining residue was partially dissolved in water (120 mL) and neutralized with 40% aq NaOH. The solid was collected

by filtration, washed with water (2 × 36 mL), and dried in vacuo to give **1** (6.1 g, 49%) as a tan solid. Mp 248−249 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.01 (m, 2H, *c*-Pr-CH_2), 1.10 (m, 2H, *c*-Pr-CH_2), 2.50 (s, 3H, pyridinyl CH_3), 3.37 (s, 3H, OCH_3), 3.76 (m, 1H, *c*-Pr-CH), 7.28 (d, J_{H-H} = 5.0 Hz, 1H, pyridinyl H-5), 7.35 (s, 1H, pyridinyl H-3), 7.75 (d, J_{H-F} = 9.5 Hz, 1H, ITQ H-5), 8.55 (d, J_{H-H} = 5.0 Hz, 1H, pyridinyl H-6). ^{13}C (DMSO-d_6, 70 °C): δ 10.8 (*c*-Pr-CH_2), 23.6 (pyridinyl CH_3), 35.0 (*c*-Pr-CH), 62.1 (OCH_3), 106.1 (d, J_{C-F} = 24.0 Hz, C-5), 106.8 (C-3a), 121.6 (d, J_{C-F} = 1.0 Hz, pyridinyl C-5), 123.5 (d, J_{C-F} = 1.0 Hz, pyridinyl C-3), 126.5 (d, J_{C-F} = 18.0 Hz, C-7), 128.0 (d, J_{C-F} = 8.0 Hz, C-4a), 132.7 (d, J_{C-F} = 2.0 Hz, C-8a), 138.5 (pyridinyl C-4), 148.5 (d, J_{C-F} = 4.5 Hz, C-8), 148.6 (pyridinyl C-6), 154.8 (d, J_{C-F} = 246.5 Hz, C-6), 157.7 (pyridinyl C-2), 163.8 (C-3), 170.3 (d, J_{C-F} = 2.5 Hz, C-4), 170.8 (C-9a). ^{19}F NMR (DMSO-d_6): δ −119.0 (s). LRMS ($C_{20}H_{16}FN_3O_3S$) *m*/*z* (%) 398 ([M + H]$^+$, 100). HRMS *m*/*z* calcd for $C_{20}H_{17}FN_3O_3S$ ([M + H]$^+$), 398.0975; found, 398.0964. Analytical HPLC: t_R 8.95 min (98.9% purity). Residual Pd (ICP−MS): 39.0 ppm. Anal. Calcd for $C_{20}H_{16}FN_3O_3S \cdot 0.5H_2O$: C, 59.10; H, 4.22; N, 10.34. Found: C, 59.21; H, 3.93; N, 10.30.

X-ray Crystallography. Crystals of **1** were obtained as follows. ITQ **1** was dissolved in TFA and concentrated under reduced pressure; the remaining solid was recrystallized from aq EtOH to give crystals of **1**·TFA. Crystals of **4**, **5**, and **10** were obtained by slow evaporation of solutions of TFA, formic acid, and EtOAc/hexanes, respectively. All measurements were made on a Nonius KappaCCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å), and intensity data were collected using the ω-scan mode. The data were corrected for Lorentz and polarization effects, and no absorption correction was applied. The structures were solved by direct methods and expanded using Fourier techniques (SHELXTL v.6.12 software package). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms, with exceptions noted below, were treated as idealized contributions. For ITQ **1**, protons H(1) and H(3) were located from the residual electron difference map and refined with isotropic displacement parameters. For ITQ **4** and thiochromone **10**, amino proton H(1) was located from the residual electron difference map and refined with isotropic displacement parameters. ITQ **4** cocrystallized with solvent (trifluoroacetic acid) in a ratio of 1:2. The hydroxyl protons H(5) and H(7) of the solvent molecules were located from the residual electron difference map and refined with isotropic displacement parameters. One of the solvent molecules possessed positional disorder of the CF_3 group. The disorder was effectively modeled using alternative sites for F(6−8) with an occupancy factor ratio of 65:35. All components of disorder were refined using anisotropic displacement parameters. Crystal data and structure refinement details for **1**, **4**, **5**, and **10** are given in Table 1.

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Supporting Information Available

X-ray crystallographic data for compounds **1**, **4**, **5**, and **10** in CIF format. This information is available free of charge via the Internet at http://pubs.acs.org.

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