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Development of a Practical Route for the Manufacture of *N*-[5-(3-Imidazol-1-yl-4-methanesulfonyl-phenyl)-4-methyl-thiazol-2-yl]acetamide

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Abstract:

An efficient synthesis of a potent candidate in our respiratory program is described. The synthesis based on a key Darzens condensation−α,β-epoxide rearrangement circumvented the toxicity and safety issues encountered in the original synthesis route. Subsequent functionalization and formation of an heterocyclic moiety is presented with a particular emphasis on the practicality, robustness, and streamlining of the process.

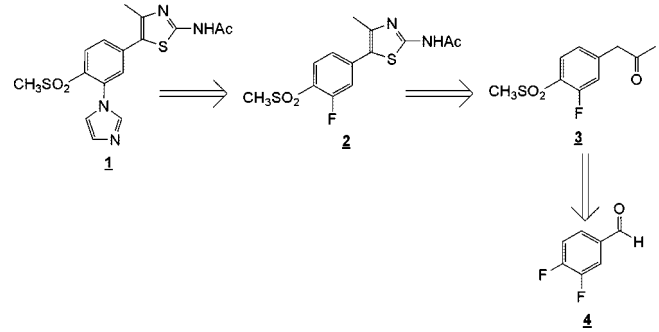
Introduction

Asthma is a chronic inflammatory disease characterized by recurrent attacks of breathlessness and wheezing, responsible for over 255,000 deaths in 2005 according to the World Health Organization (WHO).[1] If no urgent action is taken, WHO predicts an alarming increase of almost 20% in the next 10 years. Today, although more than 300 million people have been diagnosed as suffering from asthma, it is still considered to be under-diagnosed and under-treated, creating a substantial burden to individuals and families and possibly restricting individuals' activities for a lifetime. Although asthma cannot be cured, appropriate management could control the disorder and enable people to enjoy a better quality of life.

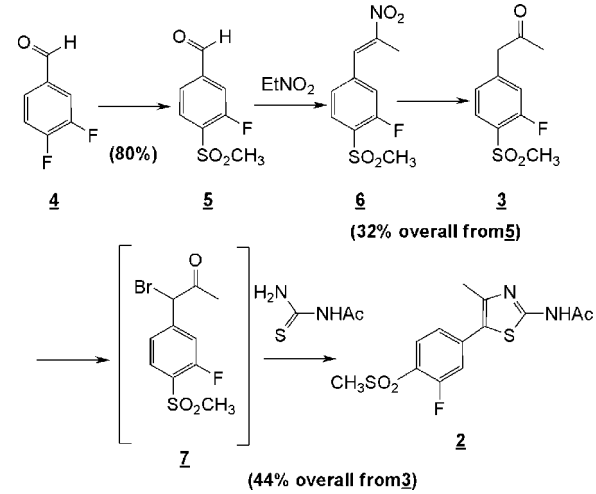
In the course of our respiratory program, a potent candidate (**1**) was discovered.[2] In the mild-persistent to moderate asthma patient segment, the introduction of a successful nonsteroidal oral therapy would offer numerous benefits for the patients. Multikilogram quantities of the drug substance were needed for the development of **1**. The present paper describes the evolution of the synthetic approach from the early route to the long-term development route.

In a retrosynthetic plan, a sequential approach was designed where the imidazole would be introduced last via an S_NAr on the activated aryl fluoride **2** (see Scheme 1). The thiazole subunit could come from the keto intermediate **3** and thiourea after α-halogenation and condensation. Compound **3** could in turn come from an S_NAr reaction of 3,4-difluorobenzaldehyde **4** with sodium thiomethoxide or more directly with the corresponding sulfinate anion, followed by Henry condensation with nitroethane and subsequent reduction of the nitro compound. These disconnections offered us the advantage to define compound **2** as a very advanced API starting material, which would facilitate our outsourcing strategy.

Scheme 1. **Retrosynthetic analysis**



Scheme 2. **Original manufacturing of 2**[a]



[a] Reagent and conditions: (a) CH_3SO_2Na, DMSO, 75 °C, 3 h; (b) $EtNO_2$, NH_4OAc, 105 °C, 6 h; (c) Fe, AcOH, 100 °C, 2 h; (d) Br_2, dioxane, 10 °C, 2.5 h; (e) *N*-acetyl-thiourea, 5-ethyl-2-methyl-pyridine, CH_3CN, 50 °C, 1 h then 80 °C, 2.5 h.

The original synthesis started from the readily available 3,4-difluorobenzaldehyde (**4**), which was reacted with a slight excess of sodium methylsulfinate in dimethyl sulfoxide in an S_NAr process (see Scheme 2). A rapid temperature study and optimization of the amount of sodium methylsulfinate showed that formation of the bis-sulfonylated product **8** was the major process impurity (see Figure 1). It could be minimized to below 6% by reducing the reaction temperature to ca. 75 °C and using 1.1 equiv of sodium methylsulfinate. A single recrystallization from DMSO/water then allowed for isolation of the desired product **5** in 80% yield and purity higher than 98%. Interestingly, the quality of sodium methylsulfinate appeared to be critical for the robustness of the reaction. Various supplies with supposedly nearly identical purity

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(1) See World Health Organization asthma web page at http://www.who.int/mediacentre/factsheets/fs307/en/.

(2) Bruce, I.; Cuenoud, B.; Keller, T. H.; Pilgrim, G. E.; Press, N.; Le Grand, D. M.; Ritchie, C.; Valade, B.; Hayler, J.; Budd, E. PCT Int. Appl. (**2004**) WO 2004096797.

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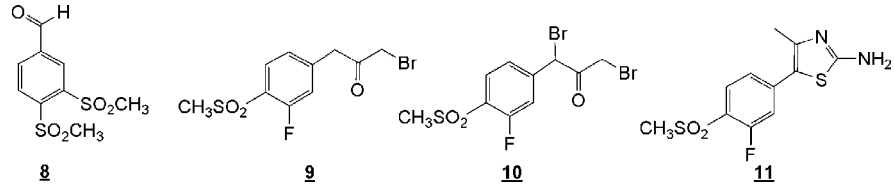

8 **9** **10** **11**

Figure 1. **By-products in 7 and 2.**

levels indeed resulted in significant variations in the yield and amount of bis-sulfonylated product **8**.

The key keto intermediate **3** was then prepared in a two-step process. Nitroethane was first reacted with the aldehyde **5** at 105 °C to generate the nitro alkene product **6**,[3] reduced to the corresponding enamine and hydrolyzed to ketone **3**.[4] Several critical process issues became apparent from this sequence. The addition of nitroethane to the aldehyde **5** was carried out at elevated temperature (more than 100 °C), and an important exothermic decomposition (>3000 J/g) was observed with a relatively low onset temperature (ca. 159 °C) compared to the reaction temperature. Our concern with this relatively low safety margin was further reinforced when the nitro alkene intermediate **6** was found to be Ames positive. A cumbersome process therefore had to be designed to minimize contact with the mutagenic intermediate **6**. In addition, although the chemical yield for this transformation had proven robust, the crude product required column chromatography to provide an acceptable quality of product **6**. The subsequent reduction step was carried out with iron in acetic acid at 40 °C. An endothermic decomposition with low onset temperature was again observed (ca. 95 °C), although with a moderate enthalpy of decomposition as observed by DSC of the reaction mixture. The purification process also proved tedious, requiring both column chromatography and recrystallization to obtain high quality material with no metal contamination. The overall isolated yield for these two steps was therefore low (32% overall).

The thiazole ring was then built in a two-step process: regioselective benzylic bromination followed by reaction with *N*-acetyl-thiourea led to the desired heterocyclic moiety. The halogenation proved challenging, resulting in the terminal bromide **9**, dibrominated species **10**, and the back-reaction to **3** under acid catalysis from the released hydrobromic acid (see Figure 1).[5] After extensive screening, a preformed complex of bromine−dioxane used at low temperature (ca. 10 °C) was found to minimize the extent of side-reaction.[6] We also attempted to remove the hydrobromic acid generated in the process, to minimize the amount of back-reaction, by running the reaction under slight vacuum (150–200 mbar), and to our delight, a much improved chemical yield was obtained (from ca. 60% to ca. 85%). At completion, the reaction mixture was concentrated, diluted with acetonitrile, and heated in the presence of *N*-acetyl-thiourea for 3 h. A major side-reaction occurred once again promoted by the acid generated in the process, whereby the deacetylated compound (**11**) was indeed identified as a major side-product. The hydrobromic acid liberated in the course of the thiazole formation was therefore trapped with an acid scavenger, 5-ethyl-2-methylpyridine, to avoid an additional re-acetylation step. The product precipitated in the course of the reaction and was recrystallized from DMSO/water to provide material of high purity (>98%) in an overall 44% isolated yield for the two steps.

This initial approach allowed us to produce the first few hundred grams of material, but numerous process issues had been identified. The high cost of methylsulfinate and its varying quality, safety issues with the formation of the nitro alkene **6** and subsequent reduction, toxicological concerns with the mutagenic intermediate **6**, poor overall yield, and complex operations were major issues that prompted us to look for an alternative approach.

In an attempt to identify a more practical and scalable route, we turned our attention to the key intermediate ketone **3** and to an approach that utilized a Darzens condensation and subsequent α,β-epoxyester rearrangement.[7] This approach had the benefit over other proposals that it would afford the previously used key intermediate **3** and therefore it would not change our overall development strategy (same raw material and API starting material).

As previously, the readily available 3,4-difluorobenzaldehyde **4** was used as the precursor. It was first reacted with sodium thiomethoxide (21% in water) in an S_NAr reaction (see Scheme 3).[8] The mercaptan was used as a solution in water to minimize the discomfort caused by the malodorous reagent. The displacement proceeded almost quantitatively to **12** in 1 h. The crude reaction mixture was then used directly in the subsequent Darzens condensation with methyl-α-chloropropionate, which resulted in the formation of a diasteoisomeric mixture in more than 98% yield. The crude mixture was directly saponified, decarboxylated, and rearranged to the desired product **13** as a single product in high yield. Oxidation of the sulfide to the sulfone using the conditions developed by Noyori[9] led to the key intermediate **3** in an overall 75% yield. Interestingly, when the Darzens condensation−epoxide rearrangement sequence was attempted on 3-fluoro-4-methylsulfonebenzaldehyde, almost no Darzens condensation product was observed. We are currently investigating in more detail this electronic effect.

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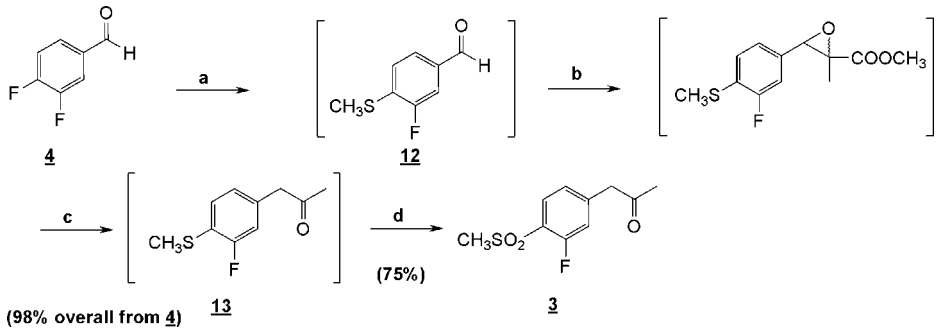
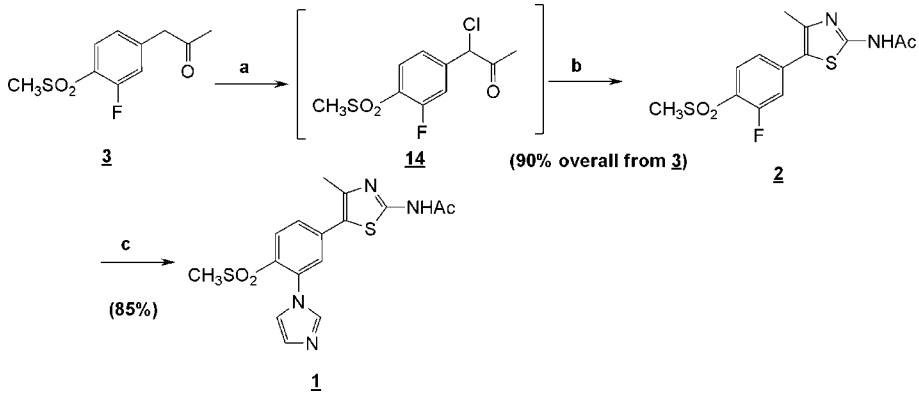
Scheme 3. **Manufacturing process of 3**[a]



[a] Reagent and conditions: (a) $NaSCH_{3(aq)}$, CH_3CN, rt, 1 h; (b) methyl-α-chloropropionate, $NaOCH_3$, toluene, 0 °C to rt, 4 h; (c) NaOH; then HCl; (d) H_2O_2 30%, Na_2WO_4, *n*-BuOAc/H_2O, 50 °C, 12 h.

Scheme 4. **Manufacturing of the drug substance 1**[a]



[a] Reagent and conditions: (a) SO_2Cl_2, CH_3CN, 0–5 °C, 1 h; (b) *N*-acetyl-thiourea, 5-ethyl-2-methyl-pyridine, CH_3CN, 50 °C, 1 h then 80 °C, 3 h; (c) imidazole, K_2CO_3, NMP, 100 °C, then Ac_2O.

Further optimization of the process led to a more streamlined and practical process with a single purification throughout the sequence.

A more straightforward selective benzylic chlorination process was also identified as an alternative to the previously used bromination (see Scheme 4). The keto intermediate **3** was reacted with sulfuryl chloride in acetonitrile at ca. 0 °C for 1 h, concentrated, and directly submitted to the subsequent thiazole ring formation as previously developed.[10] The desired product **2** was isolated by crystallization from water in an overall 90% yield and purity higher than 95% after recrystallization from acetonitrile/water.

The original final S_NAr reaction proceeded smoothly in DMSO with cesium carbonate and gave the crude drug substance along with a significant amount of hydrolyzed amide. Both the base and solvent could be substituted by the more practical *N*-methylpyrrolidone and potassium carbonate with no impact on the outcome of the nucleophilic displacement. However, the amount of hydrolyzed amide remained above 15%. An in situ functionalization was therefore introduced as a second step. Eventually a one-pot protocol was designed wherein an excess of acetic anhydride was added at the end of the S_NAr to convert the amine back to the amide **1**. The crude material was then isolated by direct precipitation from *N*-methylpyrrolidone/water and recrystallized from DMSO/water to result in high quality material (>99%) and good overall yield (85%). Due to the potential autocatalytic decomposition of DMSO at elevated temperatures,[11] alternative solvent systems and conditions were evaluated. Direct slurry conversion at 60 °C was first attempted and proved sufficient to provide material of similar purity (>98%), high recovery (>95%) and good overall yield (85%). DMSO could eventually be completely removed and the recrystallization carried out in *N*-methylpyrrolidone/water. However, more dilute conditions were required to reject the process impurities and to meet the specifications. It followed that a slightly lower yield was achieved (ca. 80%, see Table 1).

Table 1. **Attempted purification of the drug substance 1**

solvent system	purity (%)	recovery (%)
DMSO/water (4:1), 100 °C	>98	ca. 95
N-methylpyrrolidone/water, 60 °C	>98	ca. 80
DMSO/water (4:1), 60 °C (slurry conversion)	>98	ca. 95

In summary, we have described here an efficient, practical and robust process to the target drug substance (**1**). The overall process was streamlined, and the overall yield for the sequence was improved from 7% to 45% from readily available 3,4-difluorobenzaldehyde **4** to the free base. The newly developed approach allowed us to circumvent the toxicity and safety issues originally encountered. In addition, it gave us the opportunity

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to develop a robust and practical protocol for the homologation of aromatic aldehydes after revisiting the Darzens condensation. Further efforts on the subject will be reported shortly.

Experimental Section

3-Fluoro-4-methylsulfanylbenzaldehyde (12). To a well-stirred solution of 3,4-difluorobenzaldehyde **4** (33.6 mL, 300.0 mmol) in acetonitrile (330 mL) at room temperature was added sodium methanethiolate solution (105.2 g, 315 mmol; 21% in water) over a period of 1 h. The suspension was stirred for an additional 1 h at room temperature. Saturated sodium hydrogen carbonate solution (120 mL) and water (120 mL) were added, and acetonitrile was removed under vacuum (≥100 mbar, ET 50 °C). The mixture was extracted with toluene (300 mL). The organic phase containing the product was washed once with water (150 mL) and partially concentrated under vacuum (to ca. 50% w/w; giving ca. 102 g) to afford a yellow-brown clear solution of **12** in toluene (103.7 g; concentration, ca. 50% w/w; purity, 98.8%; theoretical yield, 51.0 g, 300 mmol). The crude solution was used as such in the next step; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (d, J = 1.25 Hz, 1H), 8.11 (t, J = 7.5 Hz, 1H), 7.98–8.01 (m, 2H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 159.4, 158.9, 134.9, 134.0, 126.7, 126.2, 113.6, 13.1; HRMS (M + H) calcd 171.02016, obsd 171.02742.

1-(3-Fluoro-4-methylsulfanyl-phenyl)propan-2-one (13). To the solution of **12** in toluene (103.7 g, ca. 50% w/w, ca. 300 mmol) was added methyl-α-chloropropionate (45.5 g, 360 mmol) over 10 min at room temperature. The solution was cooled to 0–5 °C, and a solution of sodium methoxide in methanol (62.6 g, 30% w/w, 348 mmol) was added over 20 min (exothermic) at a rate such that the temperature remained below 10 °C. The resulting suspension was stirred for an additional 30 min at 0–5 °C and then warmed to room temperature. The yellow suspension was stirred at room temperature until reaction completion (4 h). The mixture was diluted with toluene (150 mL) and warmed to 35–40 °C. A 30% solution of sodium hydroxide (34.5 mL, 345 mmol) was added over 45 min, and the suspension was allowed to stir for 1 h. At completion of the hydrolysis, water (450 mL) was added, the mixture was cooled to room temperature, and the two phases were separated. The water phase containing the product was washed an additional time with toluene (150 mL). To the water phase was added toluene (180 mL). The resulting triphasic mixture was heated to 60 °C, and concentrated hydrochloric acid (ca. 32 mL, ca. 385 mmol, 37%) was added over 30 min, to reach pH 2.5 (exothermic; CO_2 evolution). The mixture was stirred for 1 h at 60 °C and for an additional 4 h at 95 °C. The colourless biphasic mixture was then cooled to room temperature, and the phases were separated. The organic phase was washed with water (150 mL) and partially concentrated under vacuum (ca. 50% w/w; ca. 120 g; at ca. 50 °C) to afford a yellow-grey clear solution of **13** in toluene (120.0 g; concentration, ca. 50% w/w; purity, 87.7%; theoretical yield, 59.5 g, 300 mmol). The crude solution was used as such in the next step; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (t, J = 7.53 Hz, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 3.41 (s, 3H), 3.22 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 160.3, 157.7, 142.1, 132.6, 130.3, 125.9, 117.3, 51.4, 43.9, 28.9.

1-(3-Fluoro-4-methanesulfonyl-phenyl)propan-2-one (3). Sodium tungstate dihydrate (0.25 g, 0.75 mmol) and phenylphosphonic acid (0.12 g, 0.75 mmol) were added to water (15 mL) at room temperature and stirred until a clear solution was formed. To this solution were added methyltrioctylammonium hydrogen sulfate (0.37 g, 0.75 mmol) and then hydrogen peroxide (51.0 g, 450 mmol, 30% in water), followed by *n*-butylacetate (180 mL) at room temperature. The clear biphasic mixture was stirred rapidly for 10 min. The mixture was then heated to 50 °C, and the crude solution of **13** in toluene (60 g, 50% w/w, ca. 150 mmol) was added slowly over 30 min at a rate such that the temperature remained below 50 °C. The biphasic mixture was stirred vigorously for 12 h at 50 °C. At completion, the mixture was cooled to room temperature, and a half-saturated sodium chloride solution (255 mL) was added. The phases were separated, and the aqueous phase extracted with *n*-butylacetate (60 mL). The combined organic phases were washed with sodium hydrogen sulfite solution (15 mL; ca. 20% w/w). A saturated sodium chloride solution (255 mL) was added at room temperature with vigorous stirring, and then sodium hydrogen carbonate was added until pH = ca. 6.5 (4.6 g was required). The phases were separated, and the organic phase was partially concentrated under vacuum (≤50 mbar, ca. 60 °C) to afford 25% w/w of solution (ca. 138 g). The concentrate was warmed to 60 °C and subjected to a rapid hot-filtration to remove precipitated inorganic salts. The cake was washed portion-wise with warm *n*-butylacetate (60 mL). The clear filtrate was partially concentrated under vacuum to afford a 50% w/w solution (ca. 69 g). This concentrate was stirred at 60 °C for 10 min and then allowed to cool to −20 °C over 2 h with seeding at ca. 50 °C. The mixture was held at −20 °C for 1 h, and the solid was collected by filtration. The cake was washed with cold *n*-butylacetate/TBME mixture (24 mL, 1:1 v/v), and the solid was dried in a vacuum oven overnight (20 mbar, 40 °C) to afford **3** as a pale yellow solid (25.2 g, 72.9% (5 steps), 109.4 mmol; purity, 99.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, J = 7.83 Hz, 1H), 7.16 (dd, J = 11.3, 1.3 Hz, 1H), 7.12 (dd, J = 11.3, 1.3 Hz,, 1H), 3.84 (s, 2H), 3.22 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 159.6, 157.1, 144.8, 128.8, 126.7, 126.6, 118.4, 48.6, 43.6, 29.9; HRMS (M + H) calcd 231.04129, obsd 231.04850.

1-Chloro-1-(3-fluoro-4-methanesulfonyl-phenyl)propan-2-one (3). The intermediate **3** (23.0 g, 100 mmol) was dissolved in dry acetonitrile (50 mL) at room temperature, and the clear solution obtained was cooled to 0–5 °C. Sulfuryl chloride (13.9 g, 102 mmol) was added over 1 h (exothermic; HCl and SO_2 gas evolved), and the reaction mixture was stirred for 30 min at 0–5 °C. The mixture was warmed slowly to 45 °C (gas evolution) and subjected to distillation (100 mbar, ca. 45 °C, ca. 8 mL acetonitrile removed) to afford a pale yellow solution of **13** in acetonitrile (57.1 g; concentration, ca. 46% w/w; purity, 96.7%; theoretical yield, 26.5 g, 100 mmol) used as such in the next step.

***N*-[5-(3-Fluoro-4-methanelsulfonyl-phenyl)-4-methyl-thiazol-2-yl]acetamide (2).** *N*-Acetyl-thiourea (8.45 g, 110 mmol) and 5-ethyl-2-methylpyridine (27.2 mL, 200 mmol) were added to dry acetonitrile (100 mL) at room temperature to provide a free-flowing suspension. The mixture was warmed to 50 °C,

and a solution of **13** in acetonitrile (57.1 g, ca. 100 mmol) was added over 15 min. The reaction mixture was stirred for 1 h at 50 °C. Water (200 mL) was added over ca. 20 min at this temperature, and the resulting suspension was cooled to room temperature over ca. 1 h. The precipitate was collected by filtration after a 1 h hold, and the cake was washed with a mixture of water/acetonitrile (100 mL, 2:1 v/v). The solid was dried in a vacuum oven (20 mbar, 50 °C) to obtain **2** as an off-white powder (29.3 g, 89.2% (over 3 steps), 89.2 mmol; purity, 99.8%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.62 (dd, J = 11.5, 1.5 Hz, 1H), 7.54 (dd, J = 8.2, 1.5 Hz, 1H), 3.36 (s, 3H), 2.43 (s, 3H), 2,16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.1, 157.5, 156.6, 145.2, 140.6, 129.7, 126.1, 124.6, 121.2, 116.1, 43.7, 22.4, 16.5; HRMS (M + H) calcd 329.03516, obsd 329.04235.

***N*-[5-(3-Imidazol-1-yl-4-methanesulfonyl-phenyl)-4-methyl-thiazol-2-yl]acetamide (1).** *N*-Methylpyrrolidine (160 mL) was charged to a vessel containing intermediate **2** (26.3 g, 80 mmol), imidazole (10.9 g, 160 mmol), and potassium carbonate (22.1 g, 160 mmol). The suspension was heated to 145 °C and stirred overnight. The suspension was cooled to an internal temperature of 90 °C, and acetic anhydride (4.9 g, 48 mmol) was added over ca. 5 min. The mixture was stirred for an additional 30 min at 90 °C, and water (320 mL) was added over ca. 20 min at a rate such that the temperature remained between 70 and 90 °C. The mixture was cooled to room temperature over 1 h and stirred for 1 h. The precipitate was collected by filtration and washed, portion-wise, with water (180 mL) and ethanol (100 mL). The solid was dried in a vacuum oven (20 mbar, 50 °C) to obtain the crude free base **1** as a brown powder (26.5 g, ca. 88.0%, ca. 70.4 mmol; purity, 98.9%). Mp 293 °C. Anal. Calcd for $C_{16}H_{16}N_4O_3S_2$: C, 51.05; H, 4.28; O, 12.75. Found: C, 50.92; H, 4.27; O, 12.93. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (m, 1H), 9.50 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.05–8.02 (m, 1H), 7.98 (dd, J = 11.5, 1.5 Hz, 1H), 7.88 (s, 1H), 3.26 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 157.0, 145.9, 139.1, 138.1, 134.1, 133.1, 131.1, 130.6, 129.3, 124.8, 120.7, 119.8, 43.7, 22.4, 16.5; HRMS (M + H) calcd 377.06638, obsd 377.07359.

A suspension of crude free base **1** (26.4 g, 70 mmol) in dimethylsulfoxide (105 mL) was heated to 60 °C and stirred for 30 min. To the suspension was added water (26 mL) over 15 min at a rate such that the temperature remained constant. The mixture was cooled to room temperature over 1 h and stirred for an additional 1 h. The suspension was filtered, and the cake was washed successively with a water/DMSO mixture (93 mL, 1:1 v/v) and with water (10 mL). The solid was dried in a vacuum oven (20 mbar, 50 °C) to provide the pure free base **1** as an off-white powder (25.4 g, 96.4%, 67.5 mmol; purity, 99.5%).

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