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Development of a Practical Synthesis of Functionalized Azaxanthene-Derived Nonsteroidal Glucocorticoid Receptor Modulators

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ABSTRACT: An efficient route to two functionalized 2-aryl-5*H*-chromeno[2,3-*b*]pyridines (azaxanthenes) is reported. The addition of lithiated 2,6-dichloropyridine to salicylaldehyde followed by cyclization was a key process improvement identified for the formation of the azaxanthene core. Further elaboration of 2-chloro-5*H*-chromeno[2,3-*b*]pyridin-5-ol at the 5 position was accomplished via Lewis acid-catalyzed coupling with commercially available ((1-methoxy-2-methylprop-1-en-1-yl)oxy)-trimethylsilane. A partial classical resolution coupled with a preparative chiral supercritical fluid chromatography (SFC) separation was used to isolate the desired enantiomer of the azaxanthene carboxylic acid that is a common intermediate for both compounds **1** and **2**. Suzuki−Miyaura cross-coupling with appropriately substituted boronic acids, followed by condensation with 2-amino-1,3,4-thiadiazole, provided the target compounds with an overall yield of approximately 10%. The use of stable, amorphous materials to support clinical comparison of functionalized azaxanthenes **1** and **2** is also discussed.

INTRODUCTION

Agonists of the glucocorticoid receptor (GR), such as prednisolone, have potent anti-inflammatory and immunosuppressive properties and have found broad utility in the treatment of autoimmune, allergic, and anti-inflammatory diseases.[1] However, the unparalleled efficacy of steroidal glucocorticoids (GC) is countered by serious side effects such as glucose intolerance, muscle wasting, skin thinning, and osteoporosis.[2] Our efforts to identify selective nonsteroidal glucocorticoid receptor modulators that possess anti-inflammatory activity similar to GCs with reduced side-effects culminated in the identification of two potent and selective compounds (compounds **1** and **2**, Scheme 1) with overall in vitro biological profiles that are clearly distinct from those of steroidal GCs and from each other. Although both in vitro and in vivo models have been used to identify anti-inflammatory activity, preclinical animal models are not good predictors of GC side effects in humans; therefore, we needed to rapidly prepare azaxanthene derivatives **1** and **2** for clinical evaluation.[3] The results of our development activities that led to the successful preparation of both functionalized azaxanthenes are described.

Original and Revised Routes to 1 and 2. The initial approach for the preparation of the 2-aryl-5*H*-chromeno[2,3-*b*]pyridines (azaxanthenes) is shown in Scheme 1.[4] The procedure developed by Villani,[5] which coupled 2-chloronicotinic acid with sodium phenoxide in an excess of the phenol at 180 °C followed by an intramolecular Friedel−Crafts reaction, was used to prepare 1-azaxanthone **5** in 47% yield over the two steps. Reduction of **5** with sodium borohydride generated secondary alcohol **6**. Installation of the isobutyrate fragment was readily achieved by treatment of the highly electrophilic, doubly benzylic alcohol **6** with ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (**25**) under Lewis acid-promoted Mukaiyama conditions to provide methyl ester **7** as a racemic mixture.[6] Treatment of **7** with *m*-CPBA followed by exposure to phosphorus oxychloride effected a regioselective chlorination to provide chloroazaxanthene **9**, which was saponified to provide a racemic mixture of carboxylic acids **10a** and **10b** in high yield. The mixture of carboxylic acids was separated by preparative chiral supercritical fluid chromatography (SFC) to afford the homochiral enantiomeric acid **10a**. An X-ray crystal structure of the (*R*)-(+)-α-methylbenzylamine salt of **10a** was used to determine that the desired acid had the (*R*) absolute configuration. Condensation of **10a** with 2-amino-1,3,4-thiadizaole gave chloride **11** in 99% yield, which was then subjected to a Suzuki−Miyaura cross coupling with boronic acid **13** to give penultimate **12** in 95% crude yield.[7] Subsequent condensation with dimethylamine or ethylmethylamine provided corresponding amides **1** and **2**, respectively. For removing impurities present in both dimethylamine and ethylmethylamine, a second SFC purification was required.

Although the process described in Scheme 1 was suitable for the preparation of multigram quantities of **1** and **2**, further scale-up to supply material for toxicological and clinical evaluation presented several challenges. The linear nature of this synthesis and our accelerated timeline prompted us to

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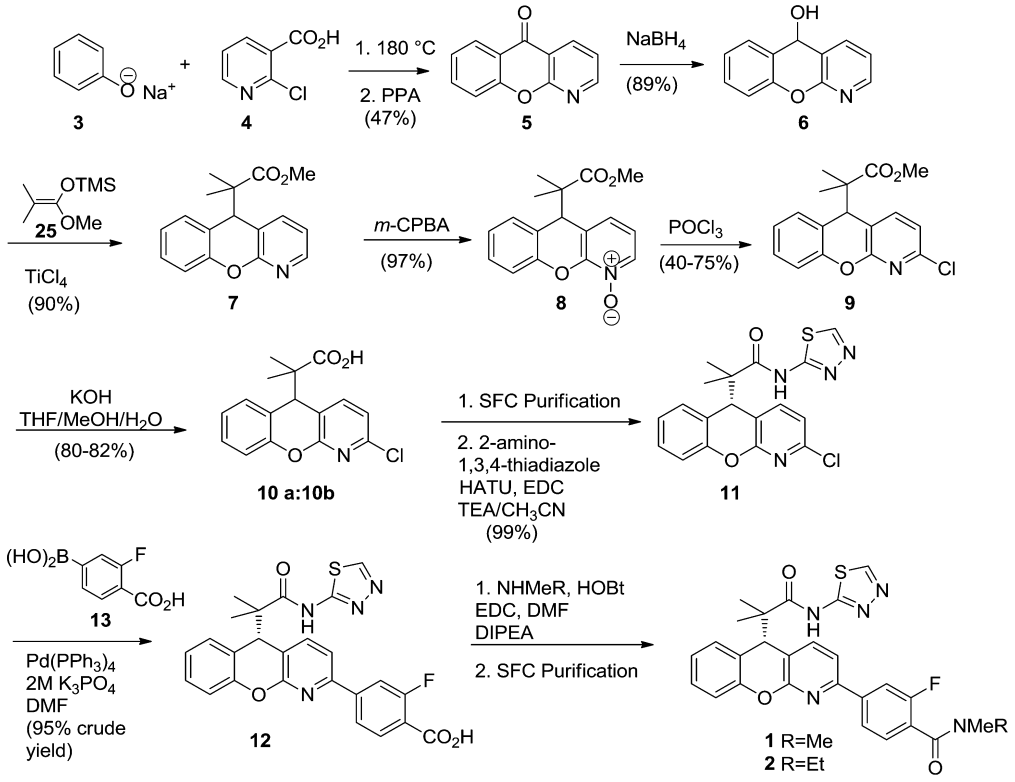
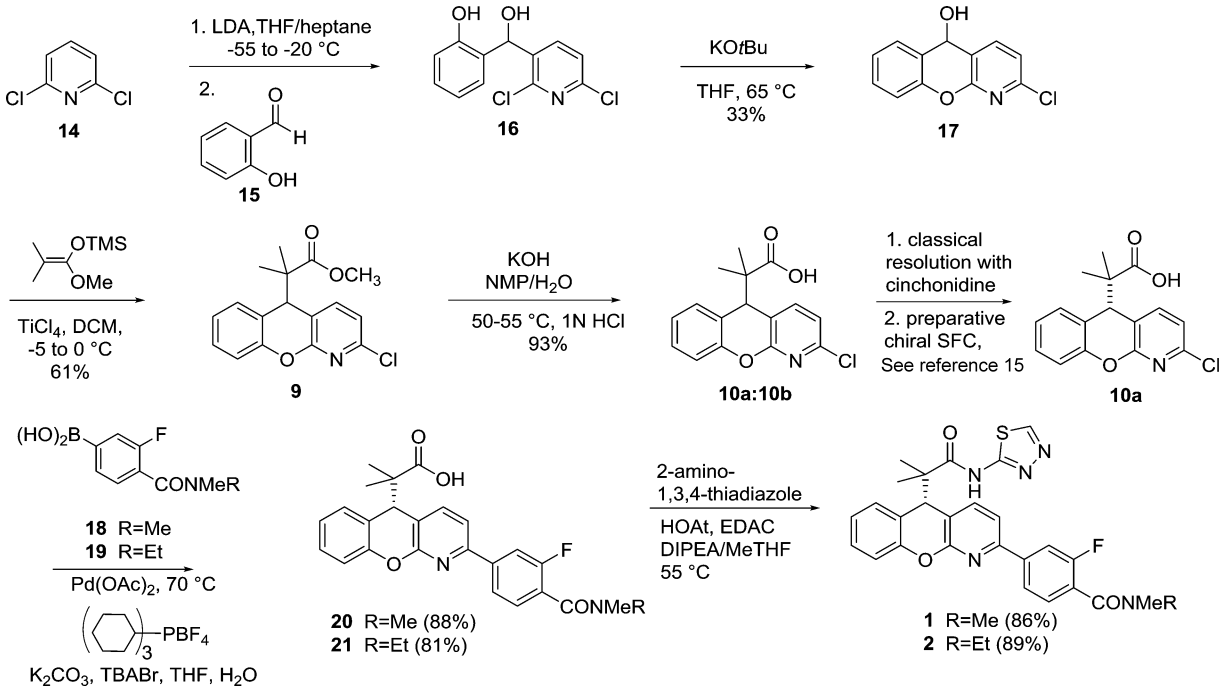
Scheme 1. Original Route to 1 and 2



Scheme 2. Revised Route to 1 and 2



pursue a more convergent approach for the scale-up. Strategically, we sought to effect a late stage coupling of an enantiopure azaxanthene core already suitably functionalized at the 2-position, utilizing the fully elaborated aromatic amides as their boronic acid derivatives **18** and **19** (Scheme 2). This approach would provide late stage intermediates **20** and **21.** These intermediates could be readily transformed to clinical candidates **1** and **2** by amide bond formation with 2-amino-1,3,4-thiadiazole.

We selected 2,6-dichloropyridine (**14**) as our starting material because it is an inexpensive commodity chemical. We were able to demonstrate that reaction of the 3-lithio species generated from 2,6-dichloropyridine with salicylaldehyde followed by cyclization under basic conditions provided a rapid entry to azaxanthene **17** and furnished the requisite

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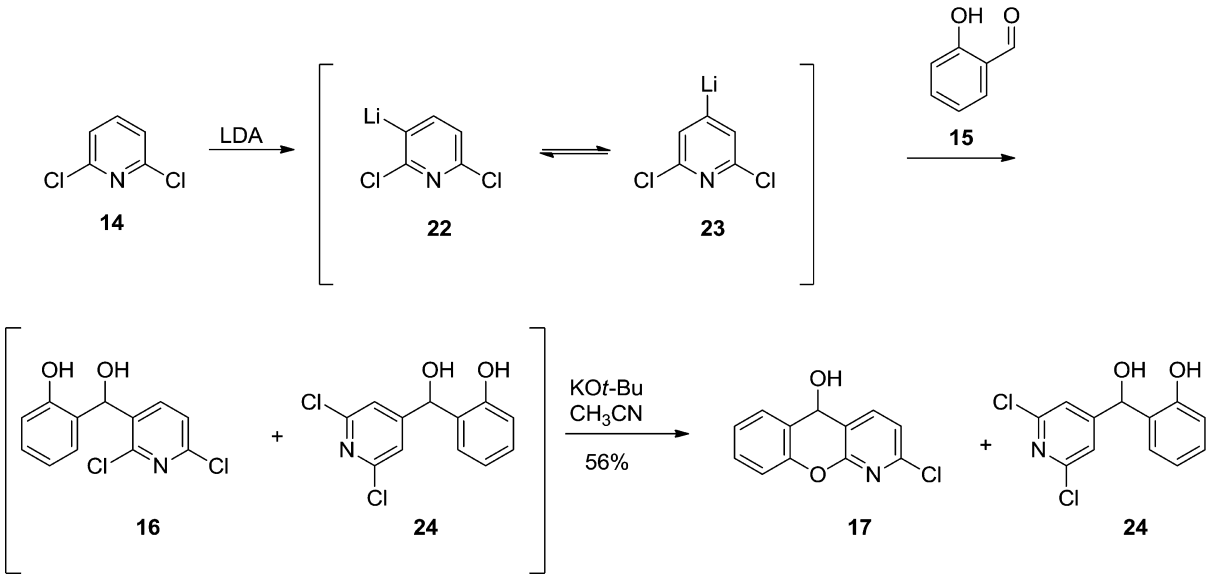
Scheme 3. Formation of the Azaxanthol Core (17)



functionality at C-2 of the azaxanthene ring system for further elaboration. This is the most expeditious route to the azaxanthene core that we have identified.[8] In addition, this approach circumvented the harsh conditions inherent in the reaction sequence reported by Villani that were utilized to generate the azaxanthene core in the original route and which were not amenable to scale-up. Performing the Suzuki–Miyaura cross-coupling on this C-2 functionalized azaxanthene **17** prior to incorporation of 2-amino-1,3,4-thiadiazole precluded the formation of impurities originating from degradation of the thiadiazole moiety during the high temperature (90 °C, 12 h) required for successful Suzuki–Miyaura cross-coupling. In the original route, the late-stage amidation with dimethylamine and ethylmethylamine necessitated a second SFC purification of the API to remove impurities arising from amine contaminants in these compounds. Suzuki–Miyaura cross-coupling using **18** and **19** with the dialkyl amide moieties already incorporated was envisaged to provide greater control of impurities associated with dimethylamine and ethylmethylamine at the arylboronic acid stage without chromatography.

Synthesis of the Azaxanthene Core (17). Radinov et al. reported that the lithiation of 2,6-dichloropyridine with LDA gave the 3-substituted pyridine as the major product (90:10) when chlorotrimethylsilane (TMSCl) was used as the electrophile; however, quenching with benzaldehyde was reported to provide only a 2:1 mixture, still favoring the 3-substituted product over the 4-substituted pyridine.[9a] Extending the time for the lithiation prior to the addition of benzaldehyde resulted in a significant increase in the selectivity for the 3-substituted product up to 98:2. This result was purported to be a result of an equilibration to the thermodynamically more stable 3-lithiopyridine.[9] Treatment of 2,6-dichloropyridine with an excess of lithium diisopropylamide (LDA) at −60 °C followed by the addition of salicylaldehyde provided a 4−5:1 mixture of regioisomers **16** and **24** (Scheme 3). Surprisingly, all efforts to equilibrate the lithiated species (**22** and **23**), including prolonged holds and substoichiometric base charges, failed to influence the product ratio. For determining if the modest selectivity was due to an elevated reactivity of the 4-lithiopyridine toward salicylaldehyde, TMSCl trapping experiments were conducted. Trapping aliquots of the lithiopyridine solution with TMSCl consistently gave the identical 5:1 ratio of products favoring the 3-silylpyridine over the 4-silylpyridine regardless of the equilibration time. This is in contrast to previously reported experiments that gave a 90:10 mixture of the 3-trimethylsilyl derivative.[9] Likewise, trapping the lithiopyridines with a substoichiometric amount of TMSCl gave a 5:1 ratio, indicating similar reactivity between TMSCl and salicylaldehyde with the lithiopyridines.

Despite the modest regioselectivity of the alkylation, the crude mixture of **16** and **24** could be treated with potassium *tert*-butoxide at elevated temperature (65 °C) to successfully effect the cyclization of **16** to azaxanthol **17** (Scheme 3). The undesired byproduct **24**, along with any remaining salicylaldehyde and 2,6-dichloropyridine, were removed during crystallization of **17** from a mixture of ethyl acetate/*n*-heptane to provide azaxanthol **17** in 56% yield over two telescope steps on a laboratory scale.

Upon initial scale-up to a 20 L vessel, a dramatic drop in reaction conversion to **16** was observed resulting in only a 19% isolated yield of **17**. Subsequent laboratory experiments identified the addition rate of the salicylaldehyde as a critical parameter for achieving high conversion. When salicylaldehyde was added in a single, rapid charge, >90% conversion was observed, whereas slower additions resulted in reaction stalling. The likely cause of the observed stalling is competitive attack on the aldehyde functionality in salicylaldehyde by LDA resulting in the formation of a hemiaminal that masks the salicylaldehyde under the reaction conditions. In fact, secondary amines have been previously utilized in this fashion as in situ aldehyde protecting groups during organolithium reactions.[10] For testing this possibility, an inverse addition experiment was conducted, where salicylaldehyde was incubated with two equivalents of LDA followed by the addition of 2,6-dichloropyridine. As anticipated, no reaction was observed, consistent with the formation of the hemiaminal mask. Upon treatment with TMSCl, no silylated pyridine species were detected, confirming that both equivalents of LDA were consumed by salicylaldehyde.

The preparative formation of **16** was carried out by charging the salicylaldehyde at the maximum possible rate while

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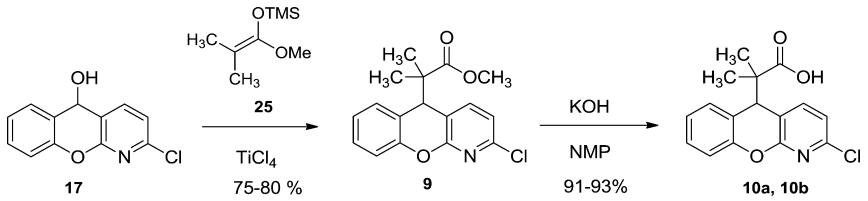
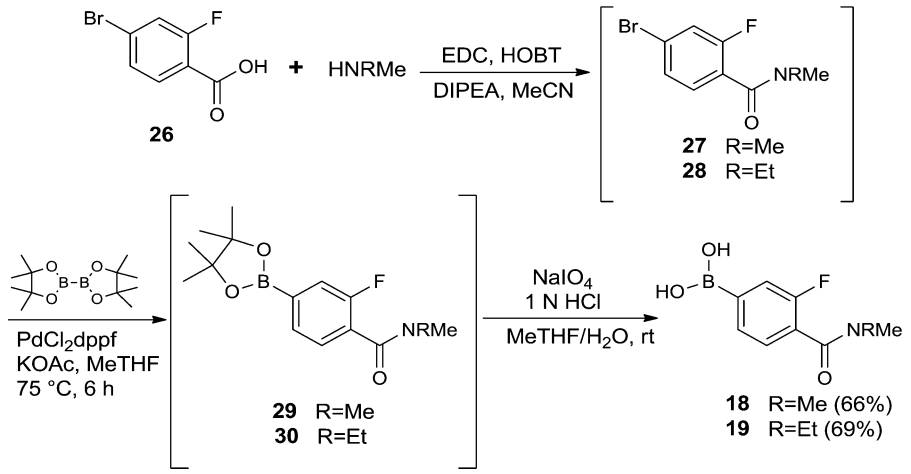
Scheme 4. Formation of Carboxylic Acids 10a and 10b



Scheme 5. Preparation of Suzuki Coupling Partners 18 and 19



maintaining a batch temperature below −40 °C to prevent degradation of the pyridyllithium species. Utilizing this procedure, typical reaction conversions of 80% were achieved (0.5 kg scale), resulting in a 37−42% isolated yield of **17**. Despite the modest yield, this is an expeditious route to the azaxanthene core. Indeed, we found that this approach provides a general process for the rapid preparation of a variety of substituted azaxanthene analogues.

Because of the exothermic nature of the reaction, any additional scale-up (>0.5 kg) of the reaction in a batch mode would require an extended salicylaldehyde charge to maintain the required low reaction temperature, resulting in further decreases in yield. To circumvent this issue, we considered investigating a flow process to allow for rapid mixing at the desired low temperature; however, an accelerated timeline precluded our investigation of this approach. Therefore, we limited the scale of the reaction and performed several batches to secure the required amount of **17**.

Having secured access to kilogram quantities of the azaxanthene core through multiple batches, the requisite 2-carbon homologation of **17** at the C-5 benzylic position was accomplished in an analogous manner to the original route by a Lewis acid-mediated alkylation with [(1-methoxy-2-methyl-prop-1-ene-1-yl)oxy]trimethylsilane **25** (Scheme 4).[11]

A solubility screen suggested that dichloromethane was a suitable solvent for the reaction of **17** with **25**, and a screen of Lewis acids determined that titanium tetrachloride delivered the highest yield. Not surprisingly, residual water and temperature were identified as critical parameters for this reaction. At Karl Fischer (KF) values greater than 1.5% and temperatures above 5 °C, we observed reaction stalling, and kicker charges of **23** and titanium tetrachloride were required to achieve the desired reaction end point. Dichloromethane streams of **17** were distilled to azeotropically remove water to a KF value below 500 ppm, which reproducibly provided quantitative conversion to **9** upon treatment with **25** and $TiCl_4$.[12] The removal of titanium byproducts proved to be problematic as the direct aqueous quench of $TiCl_4$ in the reaction mixture formed a difficult-to-filter titanium hydrogel.[13] After multiple attempts to prevent hydrogel formation, we found that the titanium salt could be easily removed by polish filtration after treatment of the reaction stream with wet ethyl acetate at controlled pH (see Experimental Section), which resulted in the precipitation of the titanium byproducts as filterable solids. Crystallization from ethyl acetate provided **9** in 75−80% isolated yield. Ester hydrolysis was readily accomplished with potassium hydroxide in NMP, and the mixture of **10a** and **10b** was isolated directly from the crude reaction stream upon addition of water and pH adjustment in 91−93% isolated yield. We subsequently determined that a stream of **9** in ethyl acetate could be taken directly into the hydrolysis step to provide **10a** and **10b** in 88% yield after solvent exchange into NMP; however, this two-step telescope was not developed in time to implement on scale.

Resolution of Carboxylic Acids 10a and 10b. In the original route, carboxylic acid **10a** was isolated from a mixture of **10a** and **10b** by chiral preparatory SFC. Because of our accelerated timeline and the amount of **10a** required to support multiple deliveries of both **1** and **2**, we explored the option of using a classical resolution for the purification of **10a**. Unfortunately, the only crystalline salt prepared from cinchonidine[14] was enriched with the undesired enantiomer **10b**. The filtrate that was enriched in **10a** was subjected to a salt break and used as the feed for the chiral preparatory SFC. Coupling of our optimized partial classical resolution with a chiral SFC process using the 85:15 mixture of **10a**:**10b** as feedstock allowed the production of enough material to support the initial development of both **1** and **2**, and this work is described in an accompanying paper.[15]

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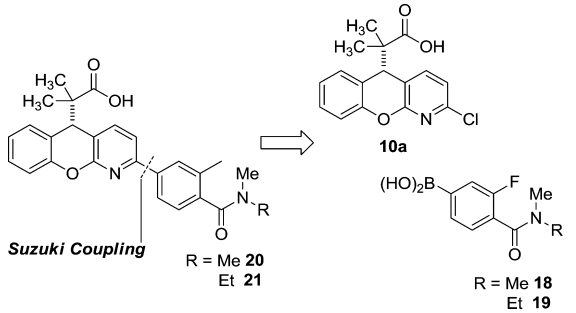
Suzuki–Miyaura Cross-Coupling. As previously mentioned, the original process utilized a Suzuki–Miyuara cross-coupling of **11** and boronic acid **13** to provide compound **12** (Scheme 1). In the final step of the synthesis, compound **12** was reacted with either dimethylamine or ethylmethylamine to provide **1** and **2**, respectively. This synthetic sequence provided flexibility in the preparation of different analogues and was sufficient for the initial deliveries; however, the use of this chemistry on a preparative scale was precluded by the following observations: incorporation of the 2-amino-1,3,4-thiadiazole prior to the Suzuki–Miyaura cross-coupling resulted in multiple impurities arising from decomposition of the thiadiazole moiety under the reaction conditions. In addition, multiple difficult to reject impurities were formed in the final step from contaminants in the corresponding amines used to form **1** and **2** that required a second SFC purification. As a result of these issues, we investigated an alternative route that changed the order of the reaction sequence. In an attempt to minimize the formation of the impurities resulting from contaminants in dimethylamine and ethylmethylamine, we turned our attention to developing processes to prepare the requisite nucleophilic Suzuki–Miyaura coupling partners **18** and **19** (Scheme 5). A three-step telescoped process starting from commercially available 4-bromo-2-fluorobenzoic acid **26** was developed.[16] Coupling of the active ester of **26** with either dimethylamine or ethylmethylamine gave the corresponding amides **27** and **28**. These were not isolated but rather converted directly to the boronate esters **29** and **30** using $B_2(Pin)_2$. We were unable to isolate the boronic esters due to the formation of an uncontrollable mixture that also contained the boronic acid. Therefore, acidic sodium periodate was used to convert free pinacol to acetone, eliminating the boronate ester and boronic acid equilibrium and providing exclusively arylboronic acids **18** and **19**.

The cross-coupling of highly functionalized 2-chloroazaxanthene **10a** and electron-deficient arylboronic acids **18** and **19**, two traditionally poor coupling partners, proved to be challenging (Scheme 6).[17] The initial Suzuki–Miyaura cross-coupling of **18** or **19** with **10a** led to low conversion of the 2-chloroazaxanthene fragment or homocoupling of the arylboronic acids under standard Suzuki–Miyaura coupling conditions.

Scheme 6. Suzuki–Miyaura Cross-Coupling to Prepare Amides 20 and 21



A high-throughput screening approach was employed to rapidly evaluate ligands, bases, solvents, and additives such as inorganic salts and phase transfer catalysts. After screening 288 different reaction conditions, the cross-coupling of **10a** and 3-fluoro-4-*N*,*N*-dimethylbenzoylphenylboronic acid **18** was shown to be very sensitive to the choice of ligand and base (Scheme 7). The most dramatic example included using dppe as the ligand in conjunction with monobasic potassium phosphate. No conversion of **10a** was observed, but rather, arylboronic acid **18** was fully consumed to deliver dimeric impurity **27** with no detectable cross-coupled product. In contrast, when tricyclohexylphosphonium tetrafluoroborate was employed with more basic potassium carbonate and tetrabutylammonium bromide (TBABr), 99 LCAP (HPLC area percent) of cross-coupled product **20** was observed with no detectable **31**.[18] This remarkable flip in product selectivity may be explained by the coordinative ligand saturation of the active catalyst.[19] The formation of the coordinatively unsaturated and highly reactive PdL species is more likely active when bulky ligands, such as PCy_3, are employed, thus promoting the oxidative addition of challenging substrates, such as the 2-chloroazaxanthene system. With bidentate dppe, however, oxidative addition into the carbon–Cl bond is slow when compared to the homocoupling of compound **18** due to the presence of a saturated PdL_2 catalyst system.[20] Interestingly, when TBABr was omitted as a reagent, up to 5 LCAP of **10a** remained after 24 h of reaction.

With Suzuki–Miyaura cross-coupling conditions in hand, we turned our attention to palladium remediation to less than 20 ppm at the penultimate stage so as to not burden the API crystallization with palladium removal. We were unable to achieve our target levels for palladium by treatment of MeTHF streams containing **20** with carbon- or sulfur-based adsorbents, such as thiourea or thiol-based scavengers, and the isolated solid contained 100–200 ppm of palladium. We then turned our attention to palladium removal via crystallization. We hypothesized that the carboxylic acid of **20** would allow for facile salt formation, and thus present an opportunity for a crystallative palladium removal strategy. We quickly found that the dicyclohexylamine (DCHA) salt of **20** was a highly crystalline solid that, when isolated, reduced palladium levels to 200 ppm. Liberation of **20** from the DCHA salt with 3 N HCl, followed by crystallization of the free carboxylic acid from *n*-BuOAc, provided a white, fluffy solid with >99.7 LCAP purity and <10 ppm of palladium.

On a 0.5 kg scale reaction, the Suzuki–Miyaura cross-coupling of 2-chloroazaxanthene **10a** and [3-fluoro-4-(dimethylaminocarbonyl)phenyl]boronic acid **18** delivered enantiomerically pure cross-coupled product **20** with >99.9 LCAP and <10 ppm of residual palladium in 83% yield. Similarly, the cross-coupling employing [3-fluoro-4-(ethylmethylaminocarbonyl)phenyl]boronic acid provided enantiomerically pure cross-coupled product **21** in 84% yield and >99.9 LCAP with <20 ppm of residual palladium (Scheme 2). Interestingly, both **20** and **21** were found to contain up to 0.3 wt % of residual dicyclohexylamine due to partitioning of the DCHA HCl salt byproduct into the organic stream during the palladium removal, which was then carried into the API step. For meeting purity specifications, DCHA was removed by washing MeTHF solutions of **1** or **2** (vide infra) with 10% aqueous citric acid, which effectively removed residual DCHA to undetectable levels by LC/MS/MS.[21]

Preparation of 1 and 2. With high-quality penultimate intermediates **20** and **21** in hand, we turned our attention to the coupling with 2-amino-1,3,4-thiadiazole to complete the synthesis of **1** and **2**. Initial optimization studies of the coupling of carboxylic acid **20** with 2-amino-1,3,4-thiadiazole to produce **1** centered on the conditions utilized in the original route to prepare **11**. Screening quickly identified 1-hydroxy-7-azabenzotriazole (HOAt) as a superior coupling reagent providing good

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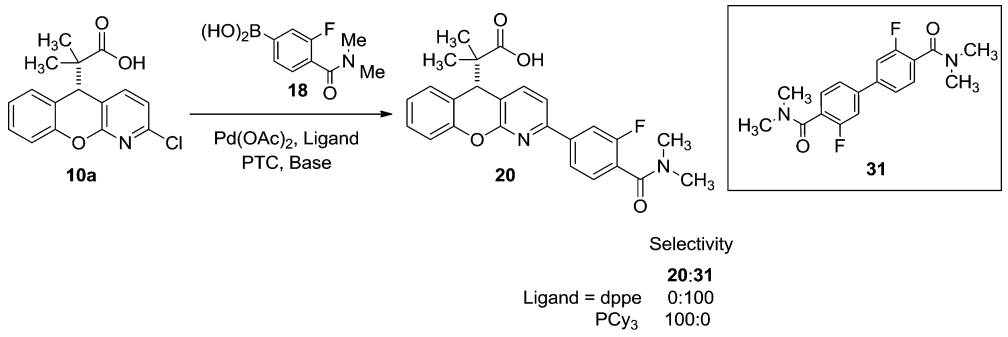
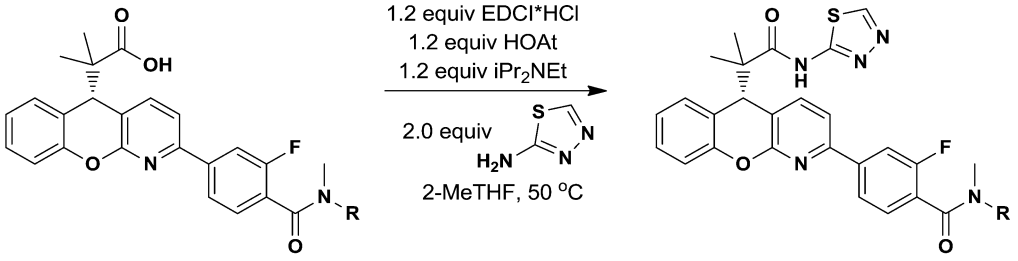
Scheme 7. High-Throughput Suzuki–Miyaura Screening



Scheme 8. Preparation of 1 and 2

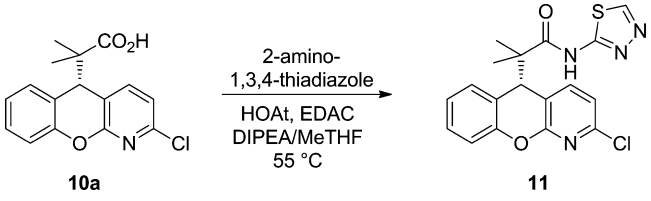


conversion in a variety of solvents, such as dimethyformamide and tetrahydrofuran. Other activators examined (HOBt and HOPO) provided slow or incomplete reactions. 2-Methyltetrahydrofuran was selected for further development to simplify the workup procedure. In addition, we found that two full equivalents of 2-amino-1,3,4-thiadiazole at 55 °C in MeTHF were required to effect complete conversion of the intermediate active esters to the desired target compounds **1** and **2** (Scheme 8). Treatment of **20** with HOAt, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride, and diisopropylethylamine in MeTHF followed by reaction of the intermediate active ester with 2-amino-1,3,4-thiadiazole furnished **1** as a solution in MeTHF after aqueous workup. After solvent exchange, **1** was crystallized from isopropyl acetate in 76% isolated yield.

In a similar manner, **2** was prepared by condensation of **21** with 2-amino-1,3,4-thiadiazole. After an aqueous workup, the rich organic stream was solvent exchanged into isopropyl acetate, and **2** was isolated as its crystalline isopropyl acetate solvate in 80% yield. It is worth mentioning that identifying crystallization conditions for **2** required additional studies and that, unlike **1**, compound **2** was isolated as an isopropyl acetate solvate.

Crystallization of **1** and **2** was found to effectively purge the majority of the known impurities except **11** (Scheme 9), which

Scheme 9. By-product Formation During the API Amidation



arises from the reaction of 2-amino-1,3,4-thiadiazole with residual **10a** in **20** or **21**. Subsequent fate and tolerance studies demonstrated that up to 0.2 LCAP of **11** could be purged by crystallization from isopropyl acetate. The improved Suzuki–Miyaura coupling conditions in the penultimate step, as well as optimization of the crystallization of **20** and **21**, provided material with <0.2 LCAP of **10a** on a preparative scale.

The solid-state form of the drug substance is an important specification that impacts the stability, dissolution, and bioavailability of the drug product. Crystallization afforded an avenue for purification; however, both **1** and **2** had previously been isolated as amorphous solids, and the amorphous solids were used in the exploratory toxicological studies. Focus then turned to the selection of the appropriate final form for both **1** and **2**.

Final API Form and Formulation Development. As previously mentioned during the original preparations of **1** and **2**, both compounds were isolated as amorphous solids. In addition, initially neither compound readily crystallized during preparation nor was form conversion evident under conditions expected during subsequent drug product processing and manufacturing. Interestingly, the amorphous forms of both **1** and **2** were found to be chemically and physically stable (under accelerated stability conditions of heat and humidity) as bulk powders under the conditions evaluated, suggesting that the amorphous materials possessed adequate stability for further development. Given that amorphous phases are generally less stable than crystalline forms, the potential risks associated with the use of amorphous materials to support the clinical comparison of **1** and **2** were assessed.

Our development efforts focused on assessment of the suitability of these amorphous forms for use in phase-appropriate formulations that could be prepared at a local compounding site. As shown in Figure 1, the amorphous forms

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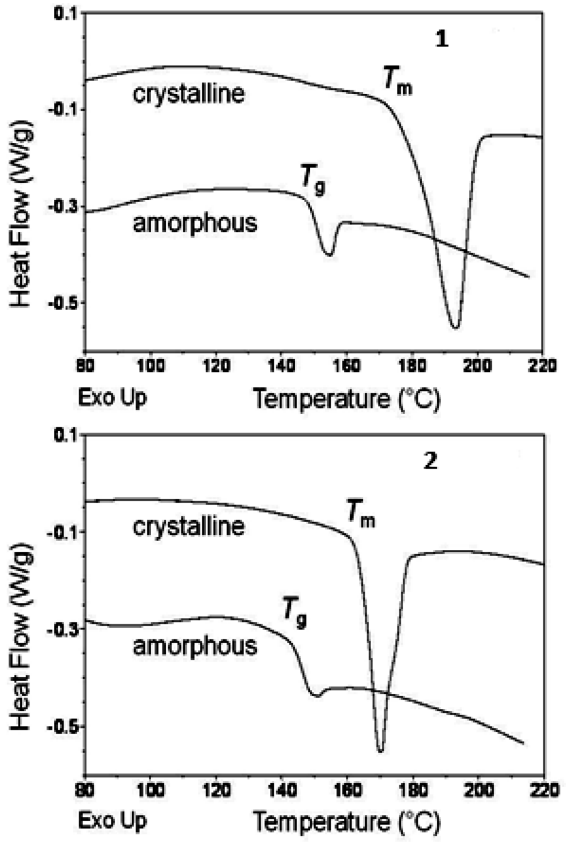

Figure 1. DSC overlay of crystalline and amorphous materials for **1** (T_m = 176.8 °C, T_g = 147.8 °C) and **2** (T_m = 162.9 °C, T_g = 141.8 °C).

of both **1** and **2** are characterized by atypically high glass transition temperatures (147.8 and 141.8 °C, respectively) that are well above the usual temperatures required for processing and manufacturing operations of the drug product. The same glass transition (T_g) temperatures were observed for multiple DSC scans when samples were run in pinhole pans. In addition, similar results were observed when different batches of **1** and **2** (spray-dried or rotovaped) were tested. A slight decrease in both the melting (T_m) and glass transition (T_g) temperatures was observed in sealed pans using samples that contained residual solvents (≤1.3 wt %).

Thermal studies were conducted on the corresponding desolvated crystalline materials (confirmed by TGA analysis), and these results are shown in Figure 1. For both compounds, a relatively small difference ($\Delta T = T_m - T_g$) was observed between melting (T_m) and glass transition (T_g) temperatures. For **1**, ΔT = 29 °C and T_g (K)/T_m = 0.94, whereas for **2**, ΔT = 21 °C and T_g/T_m = 0.95. This small ΔT suggests unusually high stability for both compounds as amorphous materials.[22]

Powder X-ray Diffraction (PXRD). PXRD was used to detect crystallinity in amorphous samples of **1** and **2**. Following exposure to a variety of temperature and relative humidity (R. H.) conditions (i.e., 5 °C, 25 °C/60% R. H., 40 °C/75% R. H., and 50 °C), all of the PXRD patterns were consistent with initial samples in that no crystalline reflections were observed. In addition, the PXRD patterns collected from amorphous samples stored at 5 and 40 °C/75% R. H. for six months showed no signs of crystallinity. Hence, amorphous **1** and **2** were expected to remain physically stable under conditions required for manufacturing, handling, and storage. However, the propensity of both molecules toward crystallization under the expected clinical dosing conditions remained unknown.

Development of Solution and Suspension Formulations for Clinical Dosing. For enabling rapid progression into clinical trials, a drug-in-bottle (DIB) approach was selected to support clinical administration as either a solution or suspension across a dose range of 5−1200 mg. The equilibrium aqueous solubility of amorphous **1** and **2** at 24 ± 3 °C was measured at 0.012 mg/mL (pH 5.6) and 0.005 mg/mL (pH 4.9), respectively, by quantitative reverse-phase HPLC analysis. The addition of a surfactant increased the apparent aqueous solubility of amorphous **1** from 0.012 to 0.092 mg/mL and that of **2** from 0.005 to 0.075 mg/mL. For assessing the suitability of the amorphous materials for use in suspension formulations, the physical stability of aqueous suspensions with and without 0.1% w/v polysorbate 80 (added to aid wetting) were monitored for 24 h using capillary PXRD. Although the apparent aqueous solubility of both compounds increased by an order of magnitude in the presence of surfactants, crystallization did not occur over the duration of the studies (24 h). Regardless of the exact mechanism of physical stability, it was determined that both compounds exhibited suitable physical stability as amorphous solids under the anticipated storage and handling conditions that would be used in the clinical setting.

Suspension vehicles evaluated for clinical dosing included citric acid anhydrous USP (25 mM) and Simple Syrup, NF (25% v/v, to improve palatability), and additional screening studies were then conducted to determine whether the method used to prepare the amorphous materials (i.e., spray-drying vs rotary evaporation) impacted suspension characteristics. Visual observations indicated that spray-dried samples of **1** and **2** dispersed more readily than material prepared by rotary evaporation. However, it was possible to prepare smooth suspensions using material prepared by either process, particularly after the addition of 1% (w/v) microcrystalline cellulose PH101 to aid dispersion and hydroxypropyl cellulose EXF to increase viscosity and improve the suspension homogeneity. The addition of microcrystalline cellulose was also advantageous in that the visual appearance of the constitution vehicle closely resembled that of the active suspensions, thereby ameliorating the need for development of a separate placebo. Crystallization of **1** or **2** in aqueous suspensions prepared at 10 or 30 mg/mL in 1% (w/v) hydroxypropyl cellulose EXF, 1% (w/v) MCC PH101, 25 mM citric acid, 25% (v/v) Simple Syrup, NF, and 0.1% (w/v) Tween 80 at 5 or 25 °C for up to 24 h could not be detected by slurry PXRD, indicating that both amorphous compounds had suitable physical stabilities as amorphous materials to support Phase I clinical dosing as oral suspensions.

Given the promising stability profile obtained from the aqueous suspension of amorphous materials, significant effort was spent on identifying suitable conditions for the preparation of amorphous **1** and **2**. Although spray-drying reproducibly yielded amorphous materials, concerns over the potential for compromised yield led to additional solvent screening studies for the rotary evaporation process. Our initial attempt to prepare amorphous **1** by dissolution in methanol followed by rotary evaporation to a solid residue was not completely successful. Recovered **1** was found to contain residual methanol that could not be removed even after extended drying at elevated temperature. Subsequent PXRD analysis indicated that we had prepared amorphous **1** contaminated with a significant amount of a crystalline methanol solvate. Although bulk

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

preparation of completely amorphous **1** by rotary evaporation from MeOH proved difficult, it was possible using EtOH as the solvent. Conversely, ethanolic solutions of **2** were prone to crystallization, but rotary evaporation of a MeOH solution reproducibly yielded amorphous material even on a larger scale. For preparing the clinical batches, solutions of either **1** or **2** in MeTHF (unstabilized) were washed with a 10 wt % citric acid solution to remove residual DCHA. After additional aqueous washes, the solvent was removed, and the appropriate alcohol was added. This solution was passed through a 1 μm line filter, and the volatiles were removed by rotary evaporation (100 mmHg, 60 °C bath). The pressure was then reduced to 5 mmHg, and the batch was stripped to dryness. The solids were collected, passed through a 16-mesh screen, and further dried in a vacuum oven to give amorphous solids of both **1** and **2**. The isolated solids were jet milled to provide a particle size distribution that readily formed a uniform suspension in the aqueous vehicle used at the clinical compounding site for the DIB products.

CONCLUSIONS

In conclusion, we have demonstrated an improved synthesis of a new class of potential GR agonists. Notable features of this work include the development of a novel and efficient route to azaxanthols and the combination of a partial classical resolution with a preparative chiral SFC that allowed us to meet our accelerated delivery timelines. A telescoped procedure for the preparation of the amide boronic acids (**18** and **19**) that generated material with excellent purity was also developed and implemented. In addition, the amorphous forms of **1** and **2** were shown to exhibit acceptable physical stabilities for oral suspension development, storage, and use-time period required to support the limited Phase I clinical studies for the program. Development of amorphous APIs and their use in phase-appropriate suspensions provided a means to accelerate the development of the program and allowed rapid evaluation of the clinical/biologic hypothesis for this chemotype. This approach aided the rapid investigation of the proof of mechanism for these dissociated GR agonists and may be applicable to other clinical candidates.

EXPERIMENTAL SECTION

Preparation of 2-Chloro-5*H*-chromeno[2,3-*b*]pyridin-5-ol (17). To a 20 L Hastelloy reactor were added THF (2.0 L), *n*-heptane (2.0 L), and diisopropylamine (1.15 L), and the resulting solution was cooled to −40 °C. Then, *n*-butyl lithium (3.15 L, 2.56 M) was added over 45 min. A 21 °C exotherm to −19 °C was observed with active cooling during the course of the addition. The batch temperature was adjusted to −55 °C, and a solution of 2,6-dichloropyridine (500 g) in THF (1.5 L) was added over 40 min, maintaining the temperature below −50 °C. The resulting suspension was cooled to −60 °C and held at this temperature for 2 h. Then, salicylaldehyde (367 mL) was added rapidly via an addition funnel in three equal portions, maintaining the batch temperature below −40 °C. After each addition, the batch temperature was readjusted to −53 to −55 °C before the next fraction was added. After the final portion was added, the reaction mixture was stirred at −50 °C for 1 h and then warmed to −20 °C. The reaction was quenched with 10 wt % aqueous ammonium chloride (4.25 L). The organic phase was separated and washed with 7.5 wt % of acetic acid (2 × 2.5 L then 1.25 L) to an apparent pH endpoint of 7. The organic phase was washed with 15 wt % of brine (1.25 L) and then concentrated under reduced pressure (300 mmHg, 75 °C jacket temperature) to give a mixture of **16** and **24** as a light orange oil. This was dissolved in THF (4.0 L), and then potassium *tert*-butoxide (395 g) was added all at once. An exotherm from 20 to 33 °C was observed. The resulting solution was heated to 65 °C for 5 h after which time HPLC analysis indicated that <1 LCAP of intermediate **16** remained. The reaction mixture was then cooled to 20 °C and partitioned between water (3.0 L) and ethyl acetate (4.0 L). The organic phase was washed with 15% brine (1.5 L) and then concentrated via distillation (310 mmHg, 80 °C jacket temperature) to a volume of 1 L. The KF was adjusted to 700 ppm via azeotropic distillation with ethyl acetate to a final volume of 1.4 L. *n*-Heptane (2.0 L) was added, and the suspension was heated to 75 °C for 2 h. The suspension was cooled to 20 °C over 1 h, and the solids were collected via filtration. The cake was slurry washed with 1 L of 4:1 *n*-heptane:ethyl acetate, deliquored, and then dried at 40 °C in a vacuum oven to provide 266 g (32.7%) of **17** as a tan solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (d, J = 8.2 Hz, 1H), 7.60 (dd, J = 7.7, 1.4 Hz, 1H), 7.50−7.37 (m, 2H), 7.32−7.22 (m, 2H), 5.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.66, 149.35, 147.18, 143.04, 129.65, 129.39, 124.30, 123.58, 120.33, 118.27, 116.32, 61.22. HRMS (ESI): calcd for $C_{12}H_8O_2NCl$ (M^+ + H) 234.0316. Found: 234.0314.

Preparation of 2-(2-Chloro-5*H*-chromeno[2,3-*b*]-pyridin-5-yl)-methyl-2-methylpropanoate 9. To a jacketed 20 L Chemglass reactor were charged **17** (500 g, 2.14 mol) and dichloromethane (6.62 kg, 5 L). The mixture was cooled to −5 °C, and titanium tetrachloride (1 M in dichloromethane, 2.35 L, 2.35 mol) was charged over a 30 min period. The resulting solution was stirred for an additional 30 min at −5 °C, and then 1-methoxy-1-trimethylsilyloxy-2-methyl-1-propene (**23**, 1.02 L, 4.81 mol) was added over a 30 min period, maintaining the batch temperature between 0 and −5 °C. The reaction mixture was stirred at this temperature for an additional 1 h, after which time HPLC analysis indicated reaction completion. Ethyl acetate (2.5 L, 2.25 kg) was added followed by a slow addition of ammonium hydroxide (7.19 M in water, 0.5 L, 3.60 mol) to an apparent pH of 9−10. The mixture was warmed to 20 °C and held at this temperature for 1 h, and then the titanium salts were removed via polish filtration. Water (3 L) was added to the filtrate, and the biphasic reaction mixture was stirred for 30 min. Agitation was stopped, and the lower spent aqueous stream was drawn off for disposal. The dichloromethane was removed via codistillation with ethyl acetate, and the final volume was adjusted to 1 L. The solution was cooled to 25 °C over 3 h and held at this temperature for 1 h to give a slurry. The crystals were collected via filtration, and the cake was washed with 0.2 L of ethyl acetate. The cake was dried under vacuum (30 Torr, 50 °C) to an LOD end point of <0.5 wt % to give **9** as a white solid (370 g, 99.2 LCAP, 99.1 wt %, 61% corrected yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (1H, d, J = 7.83 Hz), 7.39−7.36 (2H, m), 7.22−7.17 (3H, m), 4.39 (1H, s), 3.60 (3H, s), 0.92 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.33, 158.47, 152.05, 146.68, 142.72, 129.63, 128.91, 127.27, 121.03, 120.07, 116.49, 115.48, 51.83, 49.02, 45.63, 21.33, 21.17. HRMS (ESI): calcd for $C_{17}H_{17}O_3NCl$ (M^+ + 1) 318.08981. Found: 318.08915.

Preparation of 2-(2-Chloro-5*H*-chromeno[2,3-*b*]-pyridin-5-yl)-2-methylpropanoic Acid (10a, 10b). To a 20 L jacketed Chemglass reactor were charged **9** (380 g, 1.00

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

equiv, 1.20 mol) and *N*-methylpyrrolidone (2.81 L; 2.89 kg). The mixture was warmed to 50−55 °C, and then an aqueous solution of potassium hydroxide (4.78 mol; 409.6 mL; 596.4 g) was charged over 15 min. The reaction mixture was stirred at this temperature range for 1 h after which time HPLC analysis indicated reaction completion. The mixture was adjusted to an apparent pH of 5 with 3.8 L of 1 N HCl to give a cloudy solution. The batch was warmed to 65 °C, an additional 2.18 L of 1 N HCl was added, and then the reaction mixture was warmed to 85−90 °C. Then, 3.80 L of water was added, maintaining the reaction temperature between 85 and 90 °C. The resulting slurry was cooled to 20 °C over 2 h and held at this temperature for an additional 1 h. The crystals were collected via filtration, washed with 3.8 L of water, deliquored for 1 h, and dried on the filter overnight to give 339 g (93.4% yield) of a mixture of **10a** and **10b** as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (1H, s), 7.82 (1H, d, J = 8.08 Hz), 7.39−7.35 (3H, m), 7.33−7.18 (2H, m), 4.42 (1H, s), 0.87 (s, 3H), 0.87 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.87, 158.55, 152.11, 146.57, 142.83, 129.89, 128.80, 124.20, 121.35, 120.00, 116.45, 115.82, 48.79, 45.16, 21.31, 21.27. HRMS (ESI): calcd for $C_{16}H_{15}O_3NCl$ (M^+ + 1) 304.07350. Found: 304.07413.

Isolation of 10a. As described in the accompanying paper, a combination of a partial classical resolution with cinchonidine combined with preparative chiral SFC was used to isolate **10a**.[15]

Preparation of 4-Bromo-2-fluoro-*N,N*-dimethylbenzamide (27). To a 20 L reactor were charged 4-bromo-2-fluorobenzoic acid **26** (695 g, 3.17 mol), dimethylamine hydrochloride (650 g, 7.97 mol), 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (1.22 kg, 6.36 mol), 1-hydroxybenzotriazole hydrate (980 g, 6.4 mol), acetonitrile (4.48 kg), and diisopropylethylamine (1050 g, 8.12 mol). The reaction mixture was heated to 69 °C and held at this temperature until HPLC analysis indicated that <2% LCAP of unreacted **26** remained. The reaction mixture was concentrated at 70 °C and 60 mmHg to a volume of 5 L. Then, 2-methyltetrahydrofuran (7 L) and 1 N sodium hydroxide (7 L) were added to the reaction, and the mixture was stirred for 15 min. Agitation was stopped, and the bottom spent aqueous stream was drawn off for disposal. The rich organic stream was washed with half-saturated brine (4 L), and the KF was adjusted to <0.2 wt % via azeotropic distillation at 70 °C and 60 mmHg.

Preparation of 2-Fluoro-*N,N*-dimethyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (29). To the rich MeTHF stream of **27** were charged bis(pinacolato)diboron (970 g, 3.82 mol), potassium acetate (930 g, 9.48 mol), and (1,1′-bis(diphenylphosphino)ferrocene) palladium(II) chloride (26.0 g, 32.8 mmol). The reaction was heated to 80 °C and held at this temperature for 16 h after which time <3% LCAP of **30** remained as determined by HPLC. The reaction was cooled to 20 °C and washed with water (7.2 L) and then with 4% brine (7 L). Palladium was removed via filtration of the rich organic stream through a 0.9 sq ft R53SP carbon Cuno cartridge. This was charged to a 20 L reactor followed by 1 N sodium hydroxide (7 L) and water (0.8 L). The biphasic mixture was agitated for 5 min and then allowed to settle. The lower rich aqueous stream was drawn off, and the spent organic stream was extracted again with 1 N NaOH (3 L). The combined rich aqueous streams were charged back into a clean reactor and cooled to 0 °C. To this were added 2-methyltetrahydrofuran (7 L) and 2 N HCl (3.5 L), and the mixture was agitated for 5 min. The lower spent aqueous stream was back extracted with 2-methyltetrahydrofuran (1.5 L). The combined rich organic streams were used immediately in the preparation of **18** without further purification.

Preparation of [4-(Dimethylcarbamoyl)-3-fluorophenyl]boronic Acid (18). The rich MeTHF stream of **29** was charged to a 20 L reactor and cooled to 10 °C. To this were charged sodium periodate (1.02 kg, 4.77 mol) and water (7 L), and the mixture was agitated for 1 h. An exotherm from 10 to 18 °C was observed. Then, 1 N HCl (5 L) was charged to the reactor, and the resulting biphasic mixture was stirred at room temperature overnight after which time HPLC analysis indicated that <2 LCAP of **29** remained. Agitation was stopped, and the layers were allowed to separate. The bottom spent aqueous stream was back extracted with 2-methyltetrahydrofuran (2 L). The combined organic streams were washed with a 15 wt % sodium thiosulfate solution (2 L) and then with half-saturated brine (3 L). The organic stream was filtered through a 0.9 sq ft R53SP carbon Cuno cartridge and concentrated under vacuum to a volume of approximately 3 L. In a separate crystallizer were charged **18** seed crystals (7 g) and 2 L of *n*-heptane. To this were added 3 L of the rich MeTHF stream of **18** simultaneously with *n*-heptane (4.8 L) over 2 h at 23 °C. The resulting thick slurry was agitated for 1.5 h at room temperature. The crystals were collected via filtration, and the cake was washed with a 1:1.5 mixture of 2-methyltetrahydrofuran and *n*-heptane (1.25 L) and then with *n*-heptane (1 L). The wet cake was deliquored for 1 h and dried under vacuum at room temperature overnight to give 443 g (66% yield from **26**, 99.9 LCAP) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (br s, 2H), 7.79−7.54 (m, 2H), 7.41−7.29 (m, 1H), 3.03−2.96 (m, 3H), 2.85−2.78 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.20−165.00 (m, 1C), 158.5, 156.0, 130.3 (d, J = 2.9 Hz, 1C), 127.9 (d, J = 3.7 Hz, 1C), 126.1 (d, J = 18.3 Hz, 1C), 120.4 (d, J = 19.0 Hz, 1C), 37.8 34.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −118.13 to −118.25 (m, 1F); HRMS (+CI) m/z 211.0939 [$(M)^+$; calcd for $C_9H_{11}BFNO_3$, 211.0931].

Preparation of 4-Bromo-*N*-ethyl-2-fluoro-*N*-methylbenzamide (28). To a jacketed 20 L Chemglass reactor fitted with an overhead stirrer were charged **26** (700 g, 3.20 mol), 1-hydroxybenzotriazole hydrate (987 g, 6.45 mol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (1225 g, 6.39 mol), acetonitrile (5.62 L), diisopropylamine (1.4 L, 8.01 mol), and ethylmethylamine (715 mL, 8.26 mol). The reaction mixture was heated at 62 °C (bath temperature of 70 °C) for 1.5 h after which time HPLC analysis indicated the complete consumption of **26**. The volume was adjusted to approximately 4 L via distillation under reduced pressure and then cooled to 20 °C. Then, MeTHF (11.7 kg, 23.6 L) and 1 N sodium hydroxide (3.64 kg, 3.5 L, 3.5 mol) were added, and the biphasic mixture was stirred for 5 min. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was washed with 1 N sodium hydroxide (3.63 kg, 3.49 L, 3.49 mol) followed by half-saturated brine (3.82 kg, 3.2 L) and then transferred through a 0.9 sq ft R53SP carbon cartridge followed by a 0.5 μm in-line filter to a 20 L Schott filter flask. The rich organic stream was concentrated under reduced pressure (100−60 mmHg) to a volume of 4 L. The volume was adjusted to 7 L with MeTHF. The water content was 0.09 wt % as determined by Karl Fischer titration.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Preparation of *N*-Ethyl-2-fluoro-*N*-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (30). To the MeTHF solution of **28** were charged bis(pinacolato) diboron (970 g, 3.82 mol), potassium acetate (920 g, 9.37 mol), and (1,1′-bis(diphenylphosphino)ferrocene) palladium(II) chloride (26 g, 31.8 mmol). The reactor was evacuated to 200 mmHg, and the vacuum was broken slowly with nitrogen. The reaction mixture was heated to 78 °C (jacket temperature of 80 °C) and stirred at this temperature for 15 h after which time HPLC analysis indicated complete consumption of **28**. The reaction was cooled to 20 °C. Water (7 L) was added, and the biphasic mixture was stirred at room temperature for 10 min. Agitation was stopped, and the lower spent aqueous stream was drawn off for disposal. The rich organic stream was washed with water followed by half-saturated brine (8 L) and then transferred through a 0.9 sq ft R53SP carbon cartridge followed by a 0.5 μm in-line filter into a clean reactor. The lines were rinsed with an additional 3.4 L of MeTHF. Then, 1 N sodium hydroxide (7 kg) was added, and the biphasic mixture was stirred for 30 min. The upper spent organic stream was drawn off for disposal. This was found to contain 2.6% of **30** as determined by HPLC analysis. To the lower rich aqueous stream was added MeTHF (7 L), and the mixture was cooled to 2 °C. Then, 2 N hydrochloric acid (4.2 L) was added to an apparent pH end point of 2. The biphasic mixture was stirred and allowed to warm to room temperature over 0.5 h. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was back extracted with MeTHF (3.8 L), and the combined rich organic stream of **30** was used immediately in the next reaction without further purification.

Preparation of [4-Ethyl(methyl)carbamoyl]-3-fluorophenyl Boronic Acid (19). The rich MeTHF solution of **30** was cooled to 6.5 °C. Then, sodium periodate (960 g; 4.49 mol) and water (5.1 L) were added. The mixture was stirred for 1 h as the temperature was warmed to 20 °C. Then, 1 N hydrochloric acid (4.46 L) was added, and the biphasic mixture was stirred at room temperature overnight after which time HPLC analysis showed complete consumption of **30**. Agitation was stopped, and the layers were allowed to separate. The bottom spent aqueous stream was back extracted with MeTHF (2.1 L). To the combined organic layers was added 20% sodium thiosulfate (3 L), and the biphasic mixture was stirred for 15 min. A 6 °C exotherm from 20 to 26 °C was observed as the dark reaction mixture turned light yellow. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was washed with half-saturated brine (3 L) and then transferred through a 0.9 sq ft R53SP carbon cartridge followed by a 0.5 μm in-line filter to a clean reactor. The volume was adjusted to 3.8 L via distillation under reduced pressure (90 mmHg, jacket temperature of 70 °C, batch temperature of 25 °C). To a clean crystallizer were charged *n*-heptane (5.7 kg) and 26 g of **19** seed crystals. To this were simultaneously added 3.8 L of the rich MeTHF stream of **19** and *n*-heptane (4.3 kg) over a 2 h period. The thick white slurry was stirred overnight at 20 °C. The crystals were collected via filtration and washed with a 1:1 mixture of MeTHF:*n*-heptane (3 L) and heptane (1 L). The cake was deliquored for 1 h and then dried at 45 °C for 72 h to obtain 486 g (69% yield from **26**) of a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6, rotamers) δ 8.32 (br s, 2H), 7.80−7.50 (m, 4H), 7.43−7.26 (m, 2H), 3.53−3.37 (m, 2H), 3.21−3.06 (m, 2H), 3.02−2.88 (m, 3H), 2.84−2.71 (m, 3H), 1.16−1.09 (m, 3H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.46−164.98 (m, 1C), 158.4, 155.9, 130.3 (dd, J = 5.1, 2.9 Hz, 1C), 128.02−127.19 (m, 1C), 126.64−126.08 (m, 1C), 120.4 (d, J = 19.0 Hz, 1C), 44.9, 41.2, 35.2, 31.3, 13.2, 11.9; ^{19}F NMR (376 MHz, DMSO-d_6) δ −118.52, −118.72. HRMS (+CI) m/z 225.1097 [$(M)^+$; calcd for $C_{10}H_{13}BFNO_3$, 225.1087].

Preparation of 2-[(5*S*)-2-[4-(Dimethylcarbamoyl)-3-fluorophenyl]-5*H*-chromeno[2,3-*b*]pyridin-5-yl]-2-methylpropanoic Acid (20). Compounds **10a** (0.243 kg, 0.801 mol) and **18** (0.254 kg, 1.20 mol) were charged to a 10 L Chemglass reactor under nitrogen. Then, solid potassium carbonate (0.225 kg, 1.61 mol) and tetrabutylammonium bromide (TBABr, 0.026 kg, 0.080 mol) were charged, followed by tricyclohexylphosphonium tetrafluoroborate (0.012 kg, 0.032 mol), tetrahydrofuran (THF, 1.3 L, 5 mL/g), and water (1.3 L, 5 mL/g). While the solution was agitated, a nitrogen line was introduced directly into the biphasic solution with vigorous bubbling. After 20 min, $Pd(OAc)_2$ (3.64 g, 0.016 mol) was added directly to the solution, and nitrogen sparging was continued for an additional 5 min. The nitrogen line was removed from the solution, and the reaction mixture was warmed to 70 °C. After 3 h, in-process HPLC analysis showed 1.19 relative area percent (RAP) (**10a**/**20**), and the reaction was determined to be complete. The reaction mixture was cooled to 20 °C. THF (1.3 L, 5 mL/g) and water (1.3 L, 5 mL/g) were added, followed by 3 N hydrochloric acid (850 mL, 3.5 mL/g) to an apparent pH of 2.5. Agitation was stopped, and the phases were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The upper rich organic stream was washed with 14% aq sodium chloride (1.3 L, 5 mL/g) and dried over sodium sulfate (0.3 kg). The dark rich THF solution was passed through a Cuno zeta pad (R53SP). It was observed during filtration through the zeta pad that a white solid was precipitating from solution, later identified as product **20**. The carbon-filtered solution was introduced back into the clean reactor, followed by *n*-butylacetate (2.6 L, 10 mL/g). The reactor jacket was set to 80 °C with vacuum (120 psig max), and THF was removed via distillation. During the course of the distillation, **20** began to precipitate from solution. After the distillation was complete, the slurry was cooled to 20 °C. Then, *n*-heptane (1.3 L, 5 mL/g) was added over 15 min, and the thick white slurry was allowed to stir at room temperature for 12 h. The crystals were collected via filtration, washed with *n*-heptane (1 L), deliquored for 5 h, and dried under vacuum at 50 °C for 24 h to give **20** (0.307 kg, 88.2%) as a white powder.

Preparation of 2-[(5*S*)-2-{4-[Ethyl(methyl)carbamoyl]-3-fluorophenyl}-5*H*-chromeno[2,3-*b*]pyridin-5-yl]-2-methylpropanoic Acid (21). Compounds **10a** (0.100 kg, 0.033 mol) and **19** (0.096 kg, 0.427 mol) were charged to a 3-neck, 2 L round-bottom flask equipped with an overhead stirrer. Then, solid potassium carbonate (0.091 kg, 0.658 mol) and tetrabutylammonium bromide (TBABr, 0.011 kg, 0.033 mol) were charged, followed by tricyclohexylphosphonium tetrafluoroborate (4.85 g, 0.001 mol), MeTHF (0.5 L, 5 mL/g), and water (0.5 L, 5 mL/g). The solution was agitated, and a nitrogen line was introduced directly into the biphasic mixture with vigorous bubbling. After 20 min, $Pd(OAc)_2$ (1.48 g, 0.006 mol) was added directly to the solution, and nitrogen sparging was continued for an additional 5 min. The nitrogen line was removed from the solution; the flask was heated to 90 °C and held at this temperature for 10 h after which time in-process HPLC analysis showed <0.1 RAP (**10a**/**21**). The reaction mixture was cooled to room temperature. Then, 3 N

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

hydrochloric acid (360 mL, 3.5 mL/g) was added to the reaction mixture to an apparent pH end point of 2.5. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The upper rich organic stream was washed with 14 wt % aq sodium chloride (0.5 L, 5 mL/g). The rich MeTHF layer was drained from the reactor into an Erlenmeyer flask (3 L). With stirring, dicyclohexylamine (98 mL, 0.492 mol) was added, followed by *n*-BuOAc (1 L, 10 mL/g). After 10 min, a light gray solid precipitated out of solution, and stirring was continued for an additional 1 h. The slurry was filtered, washed with *n*-BuOAc (0.2 L, 2 mL/g), and dried via passing air through the cake over 2 h. After 2 h of drying, the cake was transferred into a 4 L Erlenmeyer flask, and THF (1 L, 10 mL/g) and water (0.75 L, 7.5 mL/g) were added. This mixture was agitated for 30 min, and some solids were still not dissolved; however, 3 N HCl (180 mL, 1.8 mL/g) was added until a thick precipitate (dicyclohexylamine HCl salt) crashed out of solution. The gray biphasic slurry was polish filtered (Celite), resulting in a clean phase split. The filtrate was transferred to a 4 L separatory funnel, and *n*-BuOAc (0.50 L, 5 mL/g) was added to assist in the phase split. The bottom aqueous layer was removed, and the upper organic layer that was a mixture of THF and *n*-BuOAc layer was distilled to remove THF. After removal of THF (0.80 L, 8 mL/g), a thick white precipitate formed. The white slurry was added to a 4 L Erlenmeyer flask with overhead stirring. Additional *n*-BuOAc (0.50 L, 5 mL/g) was added, and the thick white slurry was stirred for 2 h. The slurry was filtered, washed with *n*-heptane (0.50 L, 5 mL/g), and dried by passing air through the cake for 1 h. The cake was loaded into a tray and vacuum-dried at 50 °C for 15 h. Product **21** (0.120 kg, 81.3%) containing 20 ppm of residual palladium was isolated with an LCAP purity of 99.9%.

Preparation of 2-Fluoro-*N*,*N*-dimethyl-4-[(5*S*)-5-{1-methyl-1-[(1,3,4-thiadiazol-2-yl)carbamoyl]ethyl}-5*H*-chromeno[2,3-*b*]pyridin-2-yl]benzamide (1). Compound **1** was prepared by coupling **20** with 2-amino-1,3,4-thiadiazole, and the crude product crystallized from isopropyl acetate. The crystalline isopropyl acetate solvate was then converted to the amorphous material.

*Preparation of Crystalline **1**.* To a 3 L 3-neck round-bottom flask equipped with an overhead stirrer, temperature probe, and nitrogen inlet were sequentially added **20** (274.0 g, 0.631 mol), 1-hydroxy-7-azabenzotriazole (HOAt, 103.0 g, 0.757 mol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (146.0 g, 0.762 mol), MeTHF (2.77 L), and diisopropylethylamine (134.9 mL, 0.773 mol). The resulting yellow suspension was stirred under nitrogen at ambient temperature for 30 min. 2-Amino-1,3,4-thiadiazole (128.0 g, 1.266 mol) was added, and the resulting mixture was heated to 55 °C for 16 h after which time HPLC analysis indicated that <0.5 RAP of **20** as the HOAT adduct remained. The solution was cooled to room temperature. Then, 1 N hydrochloric acid (1.38) kg was added, and the resulting biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was washed with 5% aqueous sodium bicarbonate (1.0 L) and half-saturated brine (0.5 L) and then concentrated under reduced pressure to a volume of approximately 2 L. Solvent exchange was accomplished by intermittent addition of 4 kg of isopropyl acetate and distillation between 100 and 300 mg of Hg to a final volume of approximately 800 mL. The isopropyl acetate solution of **1** was warmed to 75−80 °C and stirred at this temperature overnight. The resulting slurry was cooled to 20 °C and held at this temperature for an additional 24 h. The crystals were collected via filtration and washed with 500 mL of isopropyl acetate, and the cake was deliquored for 3 h. The cake was dried at 20 °C for 18 h to give 281 g (86.7% yield) of crystalline **1** as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.67 (1 H, br s), 9.24 (1 H, s), 8.03 (1 H, dd, J = 8.11, 1.51 Hz), 7.99 (1 H, dd, J = 11.13, 1.24 Hz), 7.90 (1 H, d, J = 7.70 Hz), 7.67 (1 H, d, J = 7.97 Hz), 7.51 (1 H, t, J = 7.56 Hz), 7.37 (1 H, ddd, J = 8.25, 6.60, 2.20 Hz), 7.31 (1 H, d, J = 7.97 Hz), 7.15−7.19 (1 H, m), 7.11−7.16 (1 H, m), 4.85 (1 H, s), 3.03 (3 H, s), 2.89 (3 H, s), 1.06 (3 H, s), 1.04 (3 H, s), ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.17, 164.94, 158.92 (2 C, s), 157.99 (1 C, d, J = 259.40 Hz), 152.53, 151.48, 148.97, 140.34−140.44 (1 C, m), 140.27, 129.20 (2 C, br s), 128.79, 125.18 (1 C, d, J = 17.80 Hz), 123.88, 122.66, 120.92, 116.74, 116.58, 116.03, 113.37 (1 C, d, J = 22.89 Hz), 49.66, 44.61, 37.69, 34.19, 20.93, 20.69.

Preparation of Amorphous 1 from Crystalline Material. Crystalline **1** (358 g) was charged to a 10 L reactor. To this was added 3.1 kg of nonstabilized 2-methyltetrahydrofuran, and the resulting mixture was agitated until complete dissolution was obtained. Then, 3.0 kg of a 10 wt % citric acid solution was charged to the reactor, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. To the rich organic stream was charged 3 kg of water, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. Then, 3.1 kg of a saturated aqueous sodium bicarbonate solution was charged to the batch, and the biphasic solution was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. To the rich organic stream was charged 3.2 kg of half-saturated brine, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layer were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was transferred to a rotary evaporator through a 1 μm in-line filter, and the transfer line was rinsed with 1 L of 2-methyltetrahydrofuran. The solvent was removed via rotoevaporation at 60 mmHg with a bath temperature of 60 °C. The batch temperature was 22−25 °C. Then, 3 kg of absolute ethanol was charged to the rotary evaporator. The solvent was removed under the same conditions. The solids were dried at 55 °C and 1 mmHg on the rotovap. The solids were removed from the flask, passed through a 16 mesh screen, and dried at 55 °C overnight to give 342 g (92.6% recovery corrected for 3% residual ethanol) of **1** as a white solid. This was determined to be amorphous by PXRD. A portion of the solids were passed through a jet mill to provide 319 g of **1**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.67 (1 H, br s), 9.24 (1 H, s), 8.03 (1 H, dd, J = 8.11, 1.51 Hz), 7.99 (1 H, dd, J = 11.13, 1.24 Hz), 7.90 (1 H, d, J = 7.70 Hz), 7.67 (1 H, d, J = 7.97 Hz), 7.51 (1 H, t, J = 7.56 Hz), 7.37 (1 H, ddd, J = 8.25, 6.60, 2.20 Hz), 7.31 (1 H, d, J = 7.97 Hz), 7.15−7.19 (1 H, m), 7.11−7.16 (1 H, m), 4.85 (1 H, s), 3.03 (3 H, s), 2.89 (3 H, s), 1.06 (3 H, s), 1.04 (3 H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.17, 164.94, 158.92 (2 C, s), 157.99 (1 C, d, J = 259.40 Hz), 152.53, 151.48, 148.97, 140.34−140.44 (1 C, m), 140.27, 129.20 (2 C, br s), 128.79, 125.18 (1 C, d, J = 17.80 Hz), 123.88, 122.66, 120.92, 116.74, 116.58, 116.03, 113.37 (1 C, d, J = 22.89 Hz),

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

49.66, 44.61, 37.69, 34.19, 20.93, 20.69. ^{19}F NMR (471 MHz, DMSO-d_6) δ −115.75 (1 F, t, J = 7.27 Hz). HRMS (ESI): calcd for $C_{27}H_{24}FN_5O_3S$ (M^+ + 1) 518.16567. Found: 518.16642.

Preparation of *N*-Ethyl-2-fluoro-*N*-methyl-4-[(5*S*)-5-{1-methyl-1-[(1,3,4-thiadiazol-2-yl)carbamoyl]ethyl}-5*H*-chromeno[2,3-*b*]pyridin-2-yl]benzamide (2). Compound **2** was prepared by coupling **21** with 2-amino-1,3,4-thiadiazole, and the crude product was crystallized from isopropyl acetate. The two batches of crystalline material were combined and processed into a single lot of amorphous material. The procedure below details the preparation of the first batch and the turnover of the combined material.

*Preparation of Crystalline **2**.* To a 20 L reactor equipped with an overhead stirrer, temperature probe, and nitrogen inlet were charged **21** (265 g, 0.591 mol), 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (135.9 g, 0.709 mol), 1-hydroxy-7-azabenzotriazole (HOAt, 96.51 g, 0.709 mol), 2-methyltetrahydrofuran (3.09 kg, 3.5 L), and diisopropylethylamine (91.6 g, 123.7 mL, 0.709 mol). The resulting yellow suspension was stirred under nitrogen at 23 °C for 3 h after which time HPLC analysis indicated complete conversion to the HOAT adduct. Then, 2-amino-1,3,4-thiadiazole (126.0 g, 1.25 mol) was added, and the resulting mixture was heated to 60 °C for 16 h after which time HPLC analysis indicated that <0.5 RAP of **21** as the HOAT adduct remained. The solution was cooled to room temperature. Then, 1 N hydrochloric acid (1.38) kg was added, and the resulting biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was washed with 5% aqueous sodium bicarbonate (1.0 L) followed by half-saturated brine (0.5 L) and concentrated under reduced pressure (275 mg Hg with jacket temperature set to 100 °C to a volume of approximately 2 L. Solvent exchange was accomplished by intermittent addition of 5.3 kg of isopropyl acetate and distillation at 275 mg Hg to a final volume of approximately 1 L. The resulting slurry was warmed to 60−65 °C and held at this temperature overnight. The slurry was then cooled to 20 °C over a 2 h period and held at this temperature for an additional 1 h. The crystals were collected via filtration using a 5−10 μm polypropylene filter cloth with a Whatman #1 filter paper. The crystals were washed with 0.53 kg of isopropyl acetate, and the cake was deliquored for 4 h after which time the LOD end point had been reached and no further drying was necessary. Compound **2** was obtained in 88.9% yield (306 g) as a crystalline IPAc solvate.

Preparation of Amorphous 2 from Crystalline Material. Crystalline isopropyl acetate solvate **2** (388 g) was charged to a 10 L reactor. To this was added 4.4 kg of nonstabilized 2-methyltetrahydrofuran, and the resulting mixture was agitated until complete dissolution was obtained. Then, 3 kg of a 10 wt % citric acid solution was charged to the reactor, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. To the rich organic stream was charged 3 kg of water, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. Then, 3.0 kg of a saturated aqueous sodium bicarbonate solution was charged to the batch, and the biphasic solution was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. To the rich organic stream was charged 3.1 kg of half-saturated brine, and the biphasic mixture was agitated for 5 min. Agitation was stopped, and the layers were allowed to separate. The lower spent aqueous stream was drawn off for disposal. The rich organic stream was transferred to a rotary evaporator through a 1 μm in-line filter, and the transfer line was rinsed with 1 L of MeTHF. The solvent was removed via rotoevaporation at 60 mmHg with a bath temperature of 70 °C. The batch temperature was 25 °C. Then, 3.2 kg of methanol was charged to the rotary evaporator to completely dissolve the batch. The solvent was removed under the same conditions. The solids were dried at 55 °C and 1 mmHg on the rotary evaporator. The solids were removed from the flask, passed through a 16 mesh screen, and dried at 55 °C overnight to give 362 g (94.0% recovery corrected for 0.3% residual methanol) of **2** as a white solid. This was determined to be amorphous by PXRD. The solids were passed through a jet mill to provide 352 g of **2**.

At 27 °C in DMSO-d_6, a 52:48 mixture of rotational isomers around the tertiary amide bond could be seen in both the ^{1}H and ^{13}C NMR spectra. Upon heating to 120 °C in DMSO-d_6, the aromatic protons in the ^{1}H NMR sharpened significantly. In addition, the doubled methyl and methylene signals of the tertiary amide each broadened and collapsed to a single broad resonance. ^{1}H NMR of **2** at 27 °C: mixture of rotational isomers (500 MHz, DMSO-d_6) δ 12.67 (2 H, br s), 9.24 (2 H, s), 8.03 (2 H, ddd, J = 7.97, 3.16, 1.51 Hz), 7.99 (2 H, dt, J = 11.07, 1.75 Hz), 7.90 (2 H, dd, J = 7.70, 1.92 Hz), 7.67 (2 H, d, J = 7.70 Hz), 7.50 (2 H, t, J = 7.56 Hz), 7.37 (2 H, ddd, J = 8.25, 6.60, 2.20 Hz), 7.31 (2 H, d, J = 7.97 Hz), 7.16−7.18 (2 H, m), 7.11−7.16 (2 H, m), 4.85 (2 H, s), 3.51 (2 H, q, J = 7.06 Hz), 3.19 (2 H, q, J = 7.06 Hz), 3.00 (3 H, s), 2.85 (3 H, s), 1.16 (3 H, t, J = 7.01 Hz), 1.06 (6 H, s), 1.04 (6 H, s), 1.02−1.05 (3 H, m)

^{1}H NMR of **2** at 120 °C (500 MHz, DMSO-d_6) δ 12.09 (1 H, br s), 9.11 (1 H, s), 7.95 (1 H, d, J = 7.97 Hz), 7.89 (1 H, d, J = 11.00 Hz), 7.73−7.78 (1 H, m), 7.69 (1 H, d, J = 7.42 Hz), 7.43 (1 H, t, J = 7.56 Hz), 7.34 (1 H, t, J = 7.70 Hz), 7.25 (1 H, d, J = 8.25 Hz), 7.17−7.22 (1 H, m), 7.10 (1 H, t, J = 7.42 Hz), 4.81 (1 H, s), 3.22−3.51 (2 H, m), 2.83−2.95 (3 H, m), 1.10 (3 H, br s), 1.08 (3 H, br s), 1.03−1.15 (3 H, m). ^{13}C NMR of **2** at 27 °C (126 MHz, DMSO-d_6) δ 174.25 (2 C, br s), 164.80 (1 C, s), 164.56 (1 C, s), 159.10 (2 C, br s), 158.94 (2 C, s), 157.88 (2 C, d, J = 241.60 Hz), 152.57 (2 C, s), 151.52 (2 C, s), 148.93 (2 C, br s), 140.29 (2 C, s), 140.16 (2 C, d, J = 7.63 Hz), 129.25 (2 C, s), 129.07 (2 C, br s), 128.79 (2 C, br s), 125.47 (2 C, d, J = 20.34 Hz), 123.88 (2 C, br s), 122.70 (2 C, br s), 120.96 (2 C, s), 116.72 (2 C, s), 116.60 (2 C, s), 116.03 (2 C, br s), 113.43 (1 C, d, J = 22.89 Hz), 113.39 (1 C, d, J = 22.89 Hz), 49.68 (2 C, s), 44.81 (1 C, br s), 44.65 (2 C, s), 41.17 (1 C, s), 35.12 (1 C, s), 31.32 (1 C, s), 20.97 (2 C, br s), 20.71 (2 C, s), 13.12 (1C,s), 11.85 (1 C, s). For the ^{19}F spectrum of **2** at 27 °C, the resonances are distinguishable between the two rotational isomers. ^{19}F NMR (471 MHz, DMSO-d_6) δ −116.12 (1 F, t, J = 7.27 Hz), −116.21 (1 F, t, J = 7.26 Hz). HRMS (ESI): calcd for $C_{28}H_{26}FN_5O_3S$ (M^+ + 1) 532.18132. Found: 532.18144.

Differential Scanning Calorimetry (DSC). DSC measurements were performed using a TA Instruments DSCQ1000 under a 50 mL/min N_2 purge. Samples in the weight range of 2−5 mg were scanned at 10 °C/min in hermetically sealed aluminum pans that were pierced with a pin to allow escape of residual solvent and other volatiles. The temperature and heat flow were calibrated using indium. Both the melting (T_m) and

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

glass transition temperatures (T_g) were reported as the onsets of the thermal transitions.

Powder X-ray Diffraction (PXRD). PXRD data was obtained using a Bruker C2 GADDS. The radiation was Cu Kα (40 kV, 40 mA). The sample−detector distance was ∼15 cm. Powder samples were packed in sealed glass capillaries of 1 mm or less in diameter; suspension samples were centrifuged into capillaries of this size. The capillary was rotated during data collection. Data was collected in the range $2 \leq 2\theta \leq 35°$ with a sample exposure time of at least 1000 s. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional PXRD pattern with a step size of 0.05 degrees 2θ in the approximate range of 2−35 degrees 2θ.

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The authors declare no competing financial interest.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX