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Development of a Factory Process for Omecamtiv Mecarbil, a Novel Cardiac Myosin Activator

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Supporting Information

ABSTRACT: The development of a factory process to manufacture the novel cardiac myosin activator omecamtiv mecarbil (**1**) is described. Omecamtiv mecarbil is prepared via the convergent synthesis and coupling of two key fragments, aniline **2** and carbamate **4-HCl**, which serves as a masked isocyanate. To enable practical access to aniline **2**, reduction of the corresponding nitroaromatic was designed to control potential mutagenic impurities. Key to the efficient preparation of **2** was the benzylic bromination of **8** followed by selective debromination of a *gem*-dibromide byproduct and subsequent alkylation with **5-phosphate**. Overall, the longest linear sequence consists of six steps, including a final salt formation step to afford the drug substance in 55% overall yield. Because of poor performance of the original free-base form of the drug substance in modified-release formulations, an improved dihydrochloride hydrate form was developed to aid drug product performance and manufacturability.

KEYWORDS: *cardiac myosin activator, omecamtiv mecarbil, masked isocyanate, benzylic bromination, nitro reduction, urea formation*

INTRODUCTION

Heart failure is a degenerative and terminal disease that affects over 25 million people globally.[1] The high prevalence, high mortality rates, and significant health resource utilization associated with heart failure underscore the need for new medicines to treat this serious illness.[2] Omecamtiv mecarbil (**1**) is a first-in-class direct activator of cardiac myosin, the motor protein of the cardiac sarcomere that transfers chemical energy into the mechanical force required for heart contraction.[3] By promotion of the force-generating cycle of myosin, cardiac contractility is improved without altering cardiac myocyte intracellular calcium cycling.[4] Accordingly, **1** is being evaluated as a potential treatment for chronic heart failure with the goal of establishing a new continuum of care for patients in both the hospital and outpatient settings. To support the drug development program, including pivotal Phase 3 studies, practical access to multihundred-kilogram quantities of **1** were required. This article describes the design of a robust synthetic process to prepare omecamtiv mecarbil and highlights the challenges and opportunities at the drug substance–drug product interface. This includes a convergent synthesis of the unsymmetrical urea core of the target from stable precursors as well as engineering of the drug substance form and particle properties to aid drug product manufacturability and performance.

As shown in Scheme 1, **1** possesses an unsymmetrical urea core containing both aryl and heteroaryl components. Thus, a convergent route to **1** would comprise the synthesis and coupling of two key fragments, aniline **2** and isocyanate **3**. To enable large-scale manufacture of aniline **2**, an efficient synthesis starting from cheap and readily available precursors was needed. Key to this approach were (a) the development of a reliable benzylic bromination process for **8** that overcame the challenges associated with overbromination, (b) the development of a selective nitro reduction process ensuring control of potential mutagenic impurities in the drug substance, and (c)

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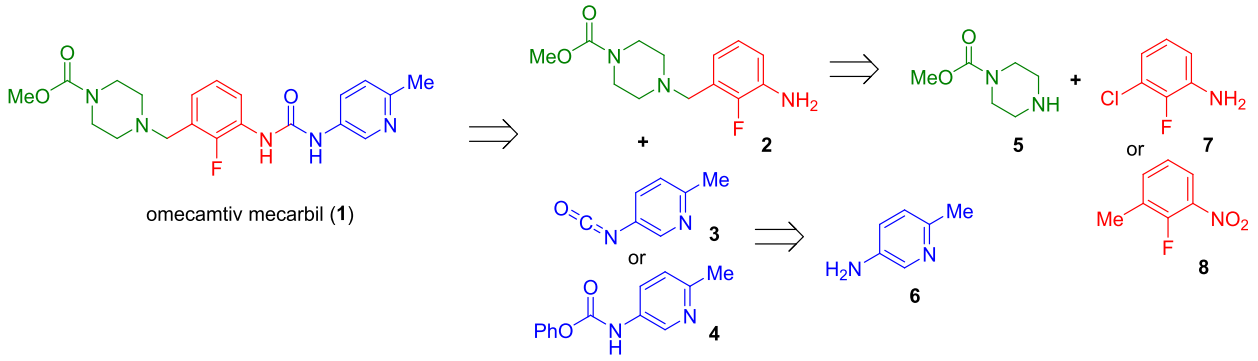
Scheme 1. Key Intermediates in the Retrosynthesis of Omecamtiv Mecarbil

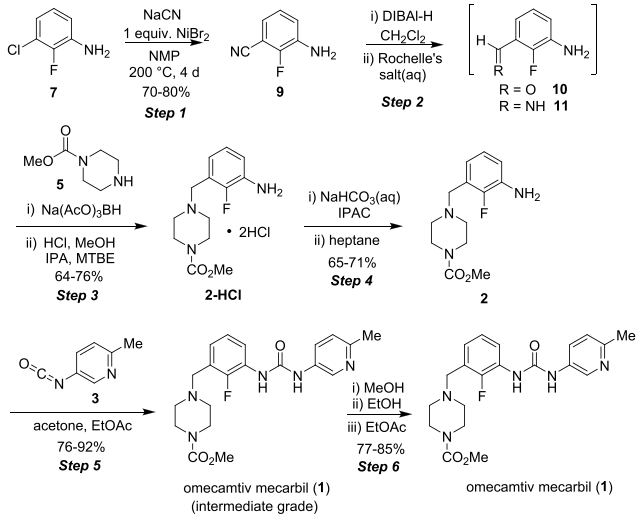


identification of a suitable salt form of **5** to improve its stability. Additionally, the poor stability and physiochemical properties of isocyanate **3** necessitated the development of a stable "masked isocyanate" **4** for use in a urea formation step. Lastly, the drug substance final form, crystallization, and milling process needed to be designed to ensure adequate drug product performance in controlled-release formulations. This paper describes how each of these challenges was addressed to develop a factory process to manufacture omecamtiv mecarbil.[5]

RESULTS AND DISCUSSION

Initial Clinical Manufacturing Route. The six-step synthesis of omecamtiv mecarbil used to supply early clinical studies is depicted in Scheme 2. In the first step of the process,

Scheme 2. Initial Clinical Manufacturing Route to Omecamtiv Mecarbil



nickel-mediated cyanation of **7** afforded benzonitrile **9**. Treatment of **9** with DIBAl-H followed by reductive amination with **5** in the presence of sodium triacetoxyborohydride (STAB)[6] afforded aniline **2**. Compound **2** was initially isolated as the corresponding dihydrochloride salt followed by a salt-break step to crystallize the desired free-base form. Finally, coupling of aniline **2** with isocyanate **3** generated the unsymmetrical urea core of omecamtiv mecarbil. Although this fit-for-purpose process was suitable to supply early clinical development, it was not optimal for the long-term manufacture of **1**, and a more robust and efficient process was desired. Step 1 of the sequence employed a relatively expensive aryl chloride raw material, and the cyanation process required stoichiometric nickel, long reaction times (days), and elevated temperatures (200 °C) to proceed. In the subsequent reductive amination step, small levels of over-reduction and polyalkylation side products were observed, necessitating a tedious sequence of salt formation and salt-break crystallization steps to purge these process impurities. The isocyanate starting material **3** was not practical for long-term use since it was found to be an unstable oil that degraded to a mixture of dimer and trimer impurities during storage (Figure 1).[7] The

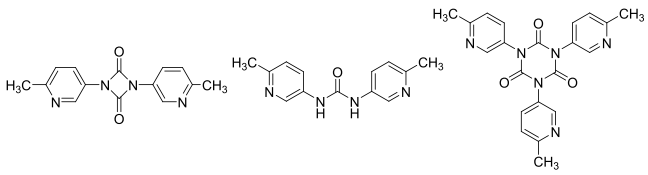


Figure 1. Degradation impurities that accumulate in isocyanate **3** during storage.

formation of these insoluble impurities also meant that reagent **3** needed to be filtered prior to use. Furthermore, because of the potential mutagenicity of the isocyanate and its late-stage introduction in the process, an additional recrystallization step from alcohol solvent was added as a control measure to destroy any residual isocyanate. In practice, this involved dissolution of **1** in methanol (50 volumes), polish filtration, a solvent switch to ethanol (10 volumes) via distillation, and cooling to complete the crystallization. Although this typically afforded **1** with excellent purity (>99.5 LC area %), the material was isolated as a mixture of small needle-shaped particles and agglomerated bundles, which resulted in long filtration and drying times.[8]

Development of an Improved Process for Aniline 2. A more robust and cost-effective synthesis of aniline **2** was devised that started from the relatively inexpensive and readily available nitrotoluene **8**. It was proposed that radical bromination of **8** followed by alkylation with methyl piperazine-1-carboxylate (**5**) and subsequent nitro reduction would represent an attractive route for large-scale production. The benzylic bromination was attempted using a variety of brominating reagents [*N*-bromosuccinimide (NBS), Br_2, dibromodimethylhydantoin], solvents (AcOH, MeCN, IPAC, CCl_4, cyclohexane) and initiators ($PhCO_2-O_2CPh$, AIBN), and the conditions shown in Scheme 3 were found to be optimal. Thus, semibatch addition of NBS to **8** in acetic acid (5 volumes) in the presence of 3% benzoyl peroxide at 83 °C

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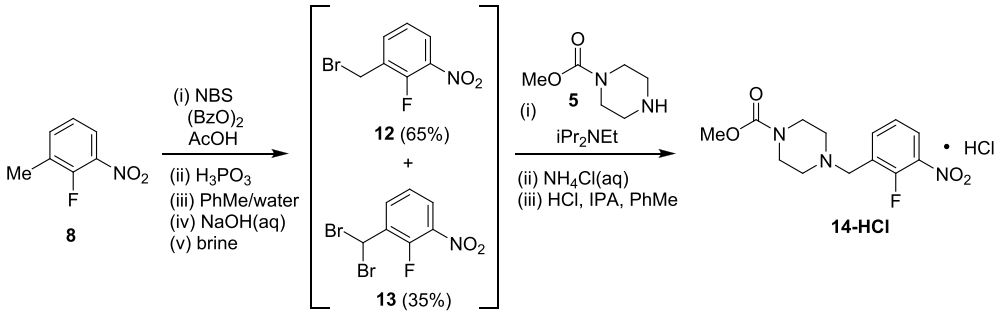
Scheme 3. Kilo-Lab Process for 14-HCl



for 12 h afforded a mixture of monobrominated product **12** and dibrominated product **13** in an ~2:1 ratio. Because of the highly corrosive nature of the bromination mixture, it was essential to ensure that there were no exposed metal parts in the reactor (see Figure 2).[9] At the end of the reaction,

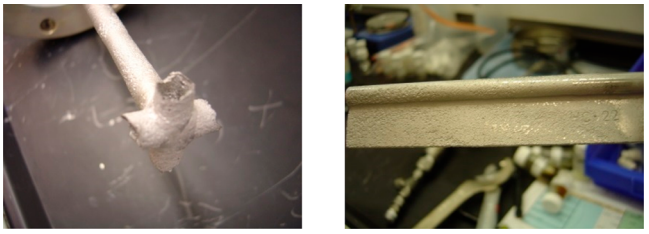


Figure 2. Corrosion of a Hastelloy impeller (left) and C22 coupon (right) by the bromination reaction mixture.

phosphorous acid (0.1 equiv) was charged to quench residual peroxide. Addition of water and toluene was followed by separation of the phases. The toluene phase was washed with aqueous sodium hydroxide to remove acetic acid and provide a solution of benzylic bromides **12** and **13** in toluene. The mixture of bromides could be employed directly in the alkylation step, as only monobromide **12** reacted with **5** to afford nitropiperazine **14**. The latter was isolated as a crystalline hydrochloride salt from a mixture of toluene and isopropanol. The crystallization process was effective in rejecting process impurities (including the dibromide), providing **14-HCl** in 63% overall yield with >99% purity.

Although further reaction optimization was unable to reduce the level of *gem*-dibromide **13**, selective debromination of this material was successfully achieved via treatment of the mixture of **12** and **13** with diethyl phosphite.[10] Thus, the crude polybrominated mixture in toluene was treated with diethyl phosphite (0.46 equiv) in methanol in the presence of diisopropylethylamine for 3 h at 40 °C to afford a >95% assay yield of the desired monobromide **12**.

During the course of development, it was found that commercial batches of starting material **5** contained varying amounts of residual piperazine and that the levels of this impurity increased during storage. To avoid the formation of impurity **15** (Figure 3), which could not be purged through crystallization of **14-HCl**, the amount of piperazine in **5** had to be controlled to a low level (<0.5%). To address this issue, **5-phosphate**, a stable crystalline sesquiphosphate salt of **5**, was developed (Scheme 4). This salt was prepared as a hydrate with high purity (containing <5000 ppm piperazine) and could be stored at room temperature and used directly in the alkylation process. This material was prepared from piperazine

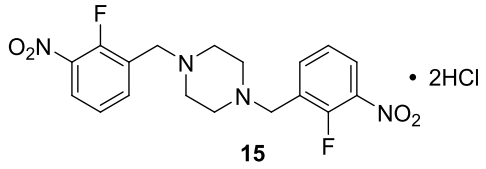
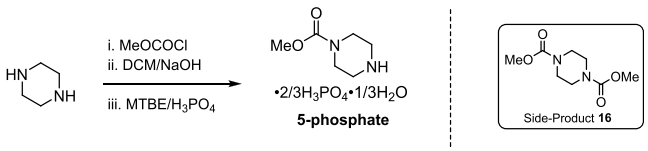


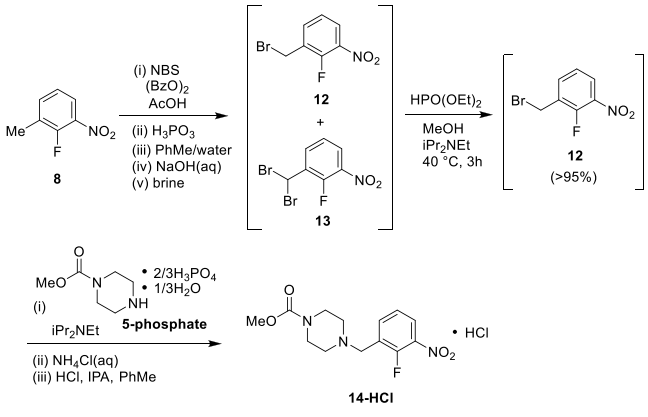
Figure 3. Structure of dialkylation impurity **15**.

Scheme 4. Preparation of 5-Phosphate for Use in the Factory Process



via reaction with 1.1 equiv of methyl chloroformate followed by pH adjustment and washing to remove excess piperazine as well as bis(carbamate) side product **16** before final crystallization of **5-phosphate**. The process was readily scalable, and **5-phosphate** was prepared in 51% yield with >99 LC area % purity. By the use of this salt in the optimized alkylation process, **14-HCl** was successfully prepared in 81% overall yield with >99 LC area % purity (Scheme 5).

Scheme 5. Plant Process for 14-HCl



With nitroaryl **14-HCl** in hand, attention was focused on the development of a scalable catalytic hydrogenation process to prepare aniline **2**.[11] Nitro hydrogenations proceed via a stepwise process [nitro (**14**) → nitroso (**17**) → hydroxylamine (**18**) → aniline (**2**)], and in addition to the intermediates formed along the major pathway, several disproportionation side products [including azoxy (**19**), azo (**20**), and hydrazo

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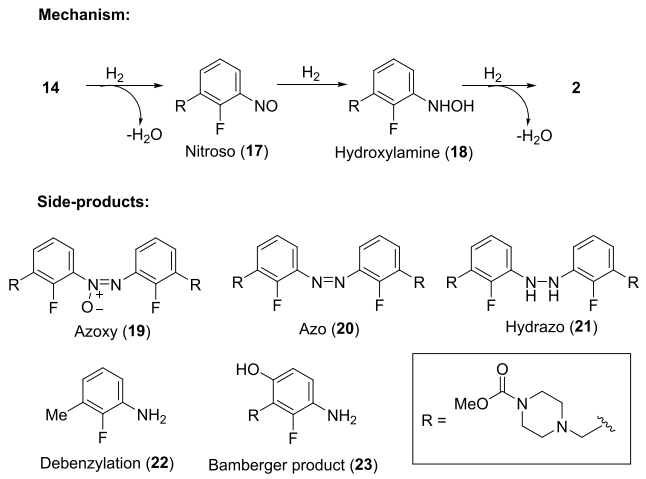
(**21**)] can be generated before final reduction to the aniline (Scheme 6). As these intermediates and side products are

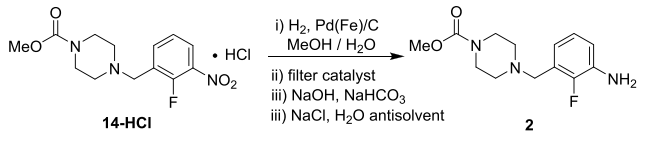
Scheme 6. Intermediates and Side Products Formed during Hydrogenation of Nitro 14



considered potential mutagenic impurities, the reaction design and isolation must ensure that they are controlled to low levels in the final drug substance.[12]

Screening of hydrogenation conditions revealed that the reaction proceeded in a variety of solvents using Pd, Pt, or Ni catalysts. The nitroso (**17**) and hydroxylamine (**18**) intermediates and the azoxy (**19**) and azo (**20**) side products were typically reduced smoothly under the hydrogenation conditions, and the residual hydrazo (**21**) and debenzylation (**22**) side products were the materials commonly carried into the isolation step. Fortunately, **22** was an oil that was well rejected in the downstream crystallization steps, and **21** was shown to be nonmutagenic in a bacterial reverse mutation test (in vitro Ames test). For the first kilo-lab campaign, a Pd(Fe)/C catalyst was selected because of its successful performance in reducing intermediate hydroxylamine levels in a previous development program.[13] Nitro salt **14-HCl** was used directly in the hydrogenation process in a 1:1 methanol/water mixture with 1% catalyst at 60 psi H_2. High conversion was achieved after several hours at 20−30 °C, but the batch was aged overnight (19 h) to ensure complete consumption of the reaction intermediates. Although the nitro−HCl starting material had poor solubility in this solvent system, the corresponding aniline salt was fully soluble, and after filtration to remove the catalyst, the pH of the filtrate was adjusted to crystallize **2**. By this process (Scheme 7), the aniline was isolated in 87% yield on a 9.1 kg scale and contained <1 ppm residual palladium. However, before moving to a larger scale, several issues needed to be addressed to improve the process performance and efficiency. Although the Pd levels in both the

Scheme 7. Catalytic Hydrogenation: Lab to Kilo-Lab Process for Aniline 2



product and mother liquor were found to be consistently low, leaching of iron from the Pd(Fe)/C catalyst occurred, and dark product solutions were obtained that necessitated extra cake washing to prevent contamination and discoloration of the product. Furthermore, in this case the iron-modified catalyst was not effective at preventing accumulation of hydroxylamine **18** (observed to be over 50% by LC when **14** was completely consumed), and an alternative system was desired. The crystallization from methanol/water was challenging, requiring the use of concentrated brine as an antisolvent for good product recovery and thorough washing of the filter cake to remove residual NaCl. Finally, although it was operationally convenient to use the salt **14-HCl** directly in the reduction process, the acid promoted the formation of aminophenol impurity **23**, presumably via Bamberger rearrangement of hydroxylamine intermediate **18**.[14]

Additional experimentation revealed that the free base **14** was a suitable substrate for the hydrogenation process and that in this case catalyst modifiers/additives were not needed to ensure clean conversion to **2** with low levels of process impurities. Accordingly, a Pd/C catalyst (Escat 1421) was selected to replace the specialty Pd(Fe)/C catalyst for the reduction step. As an improvement to the original crystallization of **2** from an aqueous mixture, a robust orthogonal crystallization process from toluene/heptane was developed, enabling better rejection of impurities. To further streamline operations, toluene solvent was also back-integrated into the hydrogenation step. Ethanol cosolvent was added to ensure miscibility of the water generated during the reaction and prevent clustering of the catalyst (with water) along the walls of the vessel. Thermal hazards evaluation confirmed that the reaction was highly exothermic (ΔH_{rxn} = −566 kJ/mol) with an adiabatic temperature rise of 78 °C. The catalyst loading and operating temperature were found to be the most important parameters influencing the hydrogenation reaction kinetics. Since the rate of the competing debenzylation (to give **22**) also increased at higher temperatures, maintaining the batch temperature below 25 °C was preferred. As shown in Figure 4, the reaction progress in a small-scale run was monitored in situ via ReactIR, which demonstrated that **14** was consumed after ∼5 h to afford ∼35% yield of hydroxylamine **18** and ∼65% of **2**, with the additional hold time serving to complete the conversation to **2**. For the optimized plant process (Scheme 8), a salt-break procedure was developed that

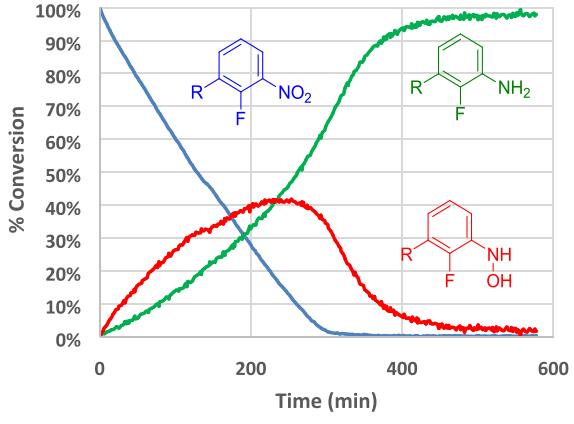


Figure 4. Reaction profile for the reduction of **14** with 0.7% Pd/C at 15 °C and 60 psi H_2.

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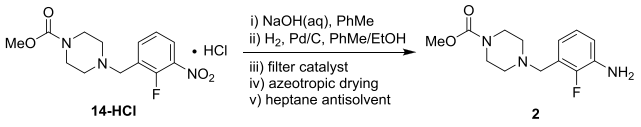
Scheme 8. Catalytic Hydrogenation: Plant Process for Aniline 2



consisted of treatment of **14-HCl** with aqueous NaOH in toluene, separation of the phases, and telescoping of the organic phase into the hydrogenation step. The reduction was performed in toluene/ethanol (6 volumes) at 15−20 °C for 12 h using 0.7% Pd/C at 60 psi H_2. Upon reaction completion, the catalyst was removed via filtration, and the filtrate was concentrated by distillation to remove ethanol and water. The batch was seeded at 35 °C and cooled to 20 °C and heptane was added to complete the crystallization of **2**, which was isolated in 90% yield with 99 LC area % purity.

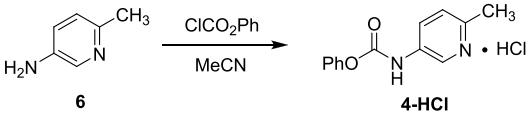
Development of a Masked Isocyanate and Urea Formation. After evaluating a variety of carbamates as potential isocyanate equivalents, we selected phenyl carbamate salt **4-HCl** as affording the best balance of stability, ease of preparation, and reactivity in the subsequent coupling step.[15] This material was prepared by a one-pot direct drop isolation process from aminopyridine **6** and phenyl chloroformate (Scheme 9).[16] Aminopyridine **6** was dissolved in acetonitrile (15 volumes) at 20 °C, and phenyl chloroformate was added (over ∼3 h) at a rate low enough to maintain the batch temperature below 30 °C. Reactive crystallization of **4-HCl** was well-controlled by the feed rate, and the product was isolated in excellent yield after filtration. By means of this process, **4-HCl** was prepared in 95% yield with >98 LC area % purity. Importantly, in contrast to the unstable isocyanate reagent employed previously, the crystalline carbamate **4-HCl** was stable for over 2 years at room temperature and for over 6 months under the accelerated conditions of 40 °C and 75% relative humidity.

The urea coupling between aniline **2** and carbamate **4-HCl** to generate omecamtiv mecarbil was studied extensively by varying the solvent, base, temperature, operating mode (batch vs semibatch, workup vs direct isolation), and crystallization performance. The coupling process proceeded as a slurry-to-slurry transformation under many of the conditions examined, with poorly controlled reactive crystallizations of the product. The heavy precipitation of salts and product in many solvents also resulted in thick mixtures that were difficult to stir. However, it was found that heating a mixture of **2** (1.0 equiv), **4-HCl** (1.1 equiv), and iPr_2NEt (1.2 equiv) as the base in 1:1 THF/acetonitrile (5 volumes) at 55 °C for 20 h afforded a clean solution of **1** in >95% assay yield. Importantly, excess iPr_2NEt was necessary for high conversion and purity, serving to both neutralize the HCl introduced with the carbamate and promote isocyanate release via E1cb elimination of phenol.[17] The crystallization of **1** was completed by charging water (5 volumes), seeding, and adding additional water (10 volumes) over 3 h (Scheme 10), thus completing a practical isolation of the free-base form of omecamtiv mecarbil.[18] In contrast to the fine particles obtained in the initial synthetic process, in this case agglomeration of the product needles produced large oval particles during the addition of water antisolvent (Figure 5). Formation of these large agglomerates (∼200−2000 μm in length) led to fast filtration and drying times, affording crystalline free base **1** with >99.9 LC area % purity in 82% yield.

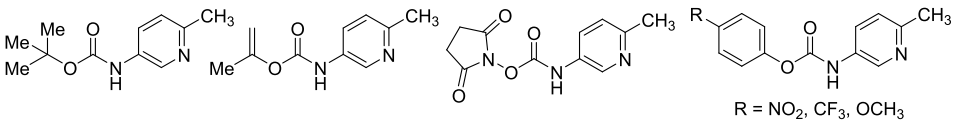
Design of Drug Substance Final Form and Bulk Properties. During the drug development program, five different modified release (MR) oral formulations, an immediate release oral formulation, and an intravenous (IV) formulation were contemporaneously evaluated. Because of the potential risk of excessive pharmacological effects (e.g., myocardial ischemia or infarction) at high plasma concentrations of omecamtiv mecarbil, the MR formulations were developed with the goal of preserving bioavailability while lowering C_{max} and the peak to trough ratio as well as attenuating the influence of gastrointestinal pH on drug release and absorption. These formulations spanned a range of delivery technologies, including swellable core tablets (osmotic pumps), matrix tablets, and multiparticulate capsules.[19] Given the challenges in developing the various drug products, our objective was to reduce any complexity introduced by the drug substance across the formulations. Therefore, the drug substance needed to be delivered with a consistent morphology, controlled particle size distribution (PSD), low aspect ratio, and suitable bulk flow properties and had to be stable during manufacture of the various tablets/capsules.[20]

However, MR matrix tablet prototypes revealed that the free-base form of omecamtiv mecarbil reacted with acidic excipients in the formulations (including citric or fumaric acid), generating high levels of amorphous citrate/fumarate salts.[21] To avoid undesired chemistry and mixtures of forms in the tablets, salt screening was conducted to identify an alternative drug substance form that would be stable during drug product manufacture and storage. As a result, the omecamtiv mecarbil dihydrochloride salt hydrate form was identified and subsequently selected for long-term development. The salt readily crystallized in high yield from isopropanol/water mixtures as long rodlike particles. Polymorph screening on the dihydrochloride salt revealed only one

Scheme 9. Preparation of Carbamate 4-HCl



Other Carbamates Examined:



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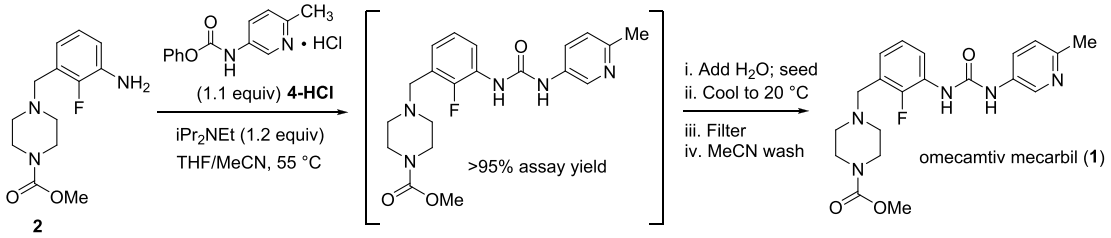
Scheme 10. Urea Formation and Crystallization of Omecamtiv Mecarbil (1)



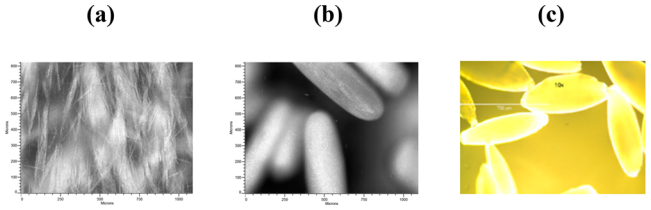
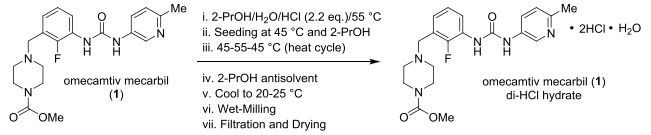


Figure 5. Agglomeration of free base **1** needles during crystallization: (a) PVM image after 1 h of water addition; (b) PVM image after 3 h of water addition; (c) microscope image of the isolated product at 10× magnification, showing ∼750 μm long particles.

hydrated form that was nonhygroscopic and existed as a channel hydrate as per single-crystal X-ray analysis. Importantly, no omecamtiv mecarbil dihydrochloride hydrate form conversion or erosion of crystallinity was observed during MR matrix tablet manufacturing.

A scalable salt formation process was developed that involved treatment of a solution of omecamtiv mecarbil in isopropanol with aqueous HCl (2.2 equiv), followed by polish filtration, cooling, and addition of more isopropanol to complete the dihydrochloride hydrate crystallization (Scheme 11). Wet milling with an in-line high-shear rotor−stator mixer

Scheme 11. Omecamtiv Mecarbil (1) Dihydrochloride Hydrate Salt Formation and Isolation



was implemented to reduce the aspect ratio of the crystals, improve the bulk properties, and aid downstream drug product processing (Figure 6).[22] During development runs, in-line focused beam reflectance measurement (FBRM) was used to monitor the progress of the milling and the number of cycles required to pass in-process-test acceptance criteria. Slurry samples were collected periodically to profile the milling by off-

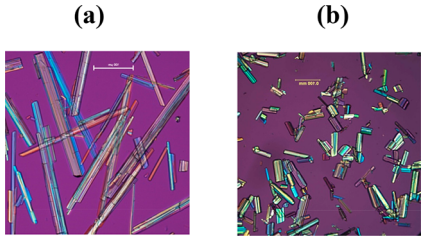


Figure 6. Crystallization of omecamtiv mecarbil dihydrochloride hydrate (a) before and (b) after wet milling.

line PSD analysis via laser light diffraction (Figure 7). The rotor tip speed was kept constant during scale-up to achieve a consistent terminal particle size. After wet milling, the slurry was filtered, washed, and dried. Water levels in the filter cake consistent with the monohydrate form could be maintained by using a final wash with 5% v/v water in isopropanol and vacuum drying. By means of this process, omecamtiv mecarbil dihydrochloride hydrate was prepared in 93% yield with >99.9% purity (Scheme 11).

CONCLUSIONS

A safe, efficient and robust process to manufacture the novel cardiac myosin activator omecamtiv mecarbil has been developed.[23] The longest linear sequence consists of six steps, including a final salt formation step to afford the drug substance in ∼55% overall yield. Relative to the initial route used to supply preclinical and early clinical studies, the E-factor for the optimized process was reduced from 308 to 72 (>75% reduction).[24] Additionally, as a result of the amorphous conversion of the free-base form in the presence of excipients, a more stable dihydrochloride hydrate form of omecamtiv mecarbil was developed. Overall, the process has been successfully implemented on a large scale to afford >1 metric ton of drug substance to support registrational studies. Scheme 12 summarizes the plant process to prepare omecamtiv mecarbil dihydrochloride hydrate.

EXPERIMENTAL SECTION

Manufacture of 5-Phosphate. A 6000 L glass-lined jacketed reactor set at 20 °C under a nitrogen atmosphere and vented through a scrubber (containing 5 N NaOH) was charged with piperazine (450 kg, 5224 mol, 1.0 equiv) followed by water (1800 L, 4 volumes). The suspension was heated to 35−40 °C and agitated until dissolved. The resulting solution was cooled to 20 ± 5 °C, and methyl chloroformate (543 kg, 5746 mol, 1.1 equiv) was added over 5 h so as to maintain the internal temperature below 30 °C. The reaction mixture was washed twice with dichloromethane (2 × 450 L, 2 volumes) to remove **16**. The pH of the aqueous layer was adjusted with 30 wt % aqueous sodium hydroxide (557 kg, 4179 mol, 0.8 equiv) to a pH of 9.8. Sodium chloride (450 kg, 1 kg/kg of piperazine) was charged, and the mixture was agitated until the solids were dissolved. **5** was extracted from this aqueous solution (containing unreacted piperazine) three times with dichloromethane (3 × 1800 L, 12 volumes). The combined organic extracts were then solvent-switched to methyl *tert*-butyl ether (MTBE) by concentration under reduced pressure (300−400 mbar) to 2.5 volumes while the internal batch temperature was maintained at ≤25 °C followed by charging of MTBE (2028 L, 4.5 volumes). This concentration and MTBE addition process was repeated. A final batch concentration to 2.5 volumes was followed by

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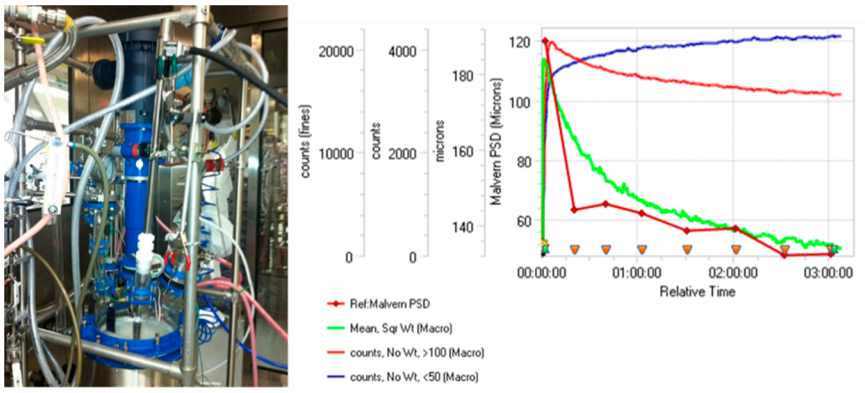
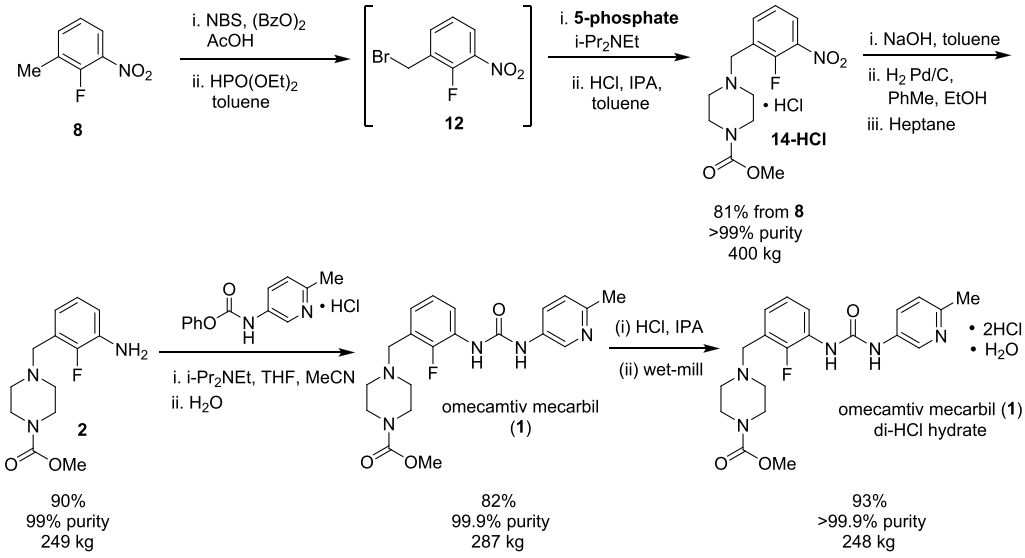


Figure 7. Crystallization of omecamtiv mecarbil dihydrochloride hydrate. A good correlation between in-line FBRM chord length measurements (mean chord length in green) and off-line PSD (dark-red dots) was observed.

Scheme 12. Factory Process To Prepare Omecamtiv Mecarbil Dihydrochloride Hydrate



charging of MTBE (1350 L, 3.0 volumes). The mixture was then transferred to an 8000 L glass-lined jacketed reactor through a lenticular filter to remove any salts that precipitated during the solvent switch. To a separate vessel, MTBE (1575 L, 3.5 volumes) and 85 wt % aqueous phosphoric acid (211 kg, 1828 mol, 0.35 equiv) were charged. The batch in the 8000 L reactor was heated to 40 ± 5 °C, and the phosphoric acid solution in MTBE was added over 3 h, maintaining an internal temperature of 40 ± 5 °C. The resulting suspension was cooled to 20 ± 5 °C over 2 h and agitated for an additional 1 h. The product was isolated in a centrifuge, washing the cake with MTBE (900 L, 2 volumes) and deliquoring. The wet cake was dried in an agitated contact dryer under vacuum (10−50 mbar) with a 30 °C jacket for 16 h to afford 573.7 kg (51% yield) of the product **5-phosphate** as white solid with >99 LC area % purity. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (br s, 3H) 3.60 (s, 3H) 3.40−3.48 (m, 4H) 2.79−2.85 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 155.0, 52.4, 43.5, 42.3; melting point = 95−97 °C.

Manufacture of 14-HCl. In a 6000 L glass-lined reactor (*containing no exposed metal parts*) equipped with a reflux/return condenser and a scrubber charged with a 5 N NaOH solution, a mechanically stirred mixture of **8** (225.0 kg, 1450 mol, 1.0 equiv), *N*-bromosuccinimide (25.8 kg, 145 mol, 0.1 equiv), benzoyl peroxide (14.1 kg, 44.0 mol, 0.03 equiv, containing 25 wt % water), and acetic acid (450 L, 2.0 volumes) was heated at 83 °C under an atmosphere of nitrogen for 1.5 h. A suspension of *N*-bromosuccinimide (408 kg, 2292 mol, 1.58 equiv) and acetic acid (792 L, 3.52 volumes), prepared in a separate vessel, was added in three portions (approximately 1/4, 1/4, and 1/2 of the total mass) over 5 h at 83 °C. Acetic acid (225 L, 1.0 volume) was added, rinsing any residual *N*-bromosuccinimide into the reactor. The reaction mixture was agitated at 83 °C for 12 h. A solution of H_3PO_3 (17.0 kg, 145 mol, 0.1 equiv, containing 30 wt % water) and acetic acid (22.5 L, 0.1 volume), prepared in separate vessel, was added, and the mixture was agitated for 2.5 h. The reaction mixture was cooled to 25 °C, and deionized (DI) water (1240 L, 5.5 volumes) and toluene (1800 L, 8 volumes) were charged. The biphasic mixture was agitated (30 min), and the layers were separated. Aqueous 1.6 N NaOH (1600 L, 7.1 volumes) was added to the organic layer at a rate allowing the batch temperature to stay under 25 °C, and the pH of the resultant aqueous phase was measured to be 12.5. The biphasic mixture was filtered through a sparkler filter, and the layers were separated. To the organic layer at 20 °C was added diisopropylethylamine (99.35 kg, 769 mol, 0.53 equiv) followed by methanol (20 L, 494 mol, 0.34 equiv), and the mixture was heated to 40 °C. A solution of diethyl phosphite

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(91.5 kg, 667 mol, 0.46 equiv) in methanol (82 L, 2024 mol, 1.4 equiv) was prepared and added to the reaction mixture at 40 °C over 2.5 h at such a rate that the batch temperature stayed at 40 ± 5 °C. The contents were stirred for a period of 5 h at 40 °C until complete conversion to **12** was achieved. Characterization data for **12**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98−8.05 (m, 1H), 7.69−7.76 (m, 1H), 7.28−7.34 (m, 1H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, chloroform-*d*) δ 153.3, 137.7, 136.5, 128.5, 126.1, 124.5, 23.6; melting point = 53−55 °C; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_6BrFNO_2$ $[M + H]^+$ 233.9566, found 233.9561.

In a 6700 L glass-lined reactor equipped with a reflux/return condenser and scrubber charged with a 5 N NaOH solution, a mechanically stirred mixture of **5-phosphate** (336 kg, 1538 mol, 1.06 equiv) and methanol (360 L, 1.6 volumes) was heated to 40 °C. To a separate 3000 L reactor containing a toluene solution (9 volumes) of **12** (prepared in the previous step) at 25 °C under an atmosphere of nitrogen were added diisopropylethylamine (433 kg, 3350 mol, 2.31 equiv) and methanol (45 L, 0.2 volumes). This mixture was added to the reactor containing the methanol solution of **5-phosphate** over 1 h, followed by a vessel rinse with methanol (180 L, 0.8 volume) and toluene (225 L, 1.0 volume). The combined mixture was agitated at 25 °C for 6.5 h, and analysis of a sample confirmed completion of the alkylation reaction. The reaction mixture was treated with water (1125 L, 5.0 volumes), and the biphasic mixture was agitated for 30 min, after which the layers were separated and the aqueous phase was discarded. The organic layer was washed twice with aqueous NH_4Cl (20 wt %, 1240 L, 5.5 volumes; prepared from 225 kg of NH_4Cl and 1125 L of DI water), and the biphasic mixture was agitated for 30 min. The layers were separated, and the organic layer was washed with aqueous $NaHCO_3$ (9 wt %, 1175 L, 5.2 volumes; prepared from 101 kg of $NaHCO_3$ and 1125 L of DI water). The organic layer was then filtered through a 5 μm Teflon in-line cartridge filter into a 6700 L glass-lined reactor, followed by a vessel and filter rinse with toluene (225 L, 1.0 volume).

To a mechanically stirred toluene solution of free base **14** (prepared as described above) at 22 °C in a 6700 L reactor under an atmosphere of nitrogen, isopropanol (2183 L, 9.7 volumes) and DI water (93 L, 0.41 volume) were charged. The mixture was heated to 55 °C, and 20% of the 32 wt % aqueous HCl (41.76 kg, 367 mol, 0.25 equiv) was charged. The contents were agitated for 15 min, and **14-HCl** seed (15 kg, 45 mol, 0.03 equiv) was charged as a suspension in isopropanol (45 L, 0.2 volumes). The mixture was agitated for 30 min, and the remaining 32 wt % aqueous HC1 (162.4 kg, 1425 mol, 0.983 equiv) was added over a period of 4 h. The mixture was stirred at 55 °C for 1 h, cooled to 20 °C in a linear manner over 3 h, and agitated at this temperature for 10 h. The suspension of the product was filtered in an agitated filter dryer. The filter cake was washed twice with isopropanol (1260 L, 5.6 volumes) and dried to constant weight under vacuum at a jacket temperature of 30−50 °C (42 h), and **14-HCl** (400.5 kg, 81.3% corrected yield) was isolated with 100 wt % and 99.7 LC area % purity. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17−8.34 (m, 1H), 7.98−8.15 (m, 1H), 7.44−7.63 (t, *J* = 8 Hz, 1H), 4.47 (s, 2H), 3.52−3.66 (m, 8H), 3.25 (br s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 155.7, 154.7, 152.2, 139.8, 137.4, 127.9, 125.1, 119.6, 52.8, 51.4, 50.3; melting point = 248−250 °C; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{17}FN_3O_4$ $[M + H]^+$ 298.1203, found 298.1198.

Manufacture of 2. To a 3600 L jacketed reactor were added **14-HCl** (340 kg, 1.00 equiv) and toluene (1360 L, 4.0 volumes). To the suspension was added 4 wt % aqueous sodium hydroxide solution (1161 kg, 1.1 equiv). The mixture was stirred for >15 min, resulting in a clear biphasic mixture. Agitation was stopped, and the layers were allowed to settle. The organic layer was washed twice with 6.5 wt % aqueous sodium chloride (1091 kg, 1.2 equiv). The resulting organic layer was concentrated to 3.8 volumes under reduced pressure and transferred through an in-line filter into a 4000 L Hastelloy hydrogenator, removing precipitated salts. The 3600 L reactor and lines were rinsed with an additional portion of toluene (340 L, 1.0 volume). To the reaction mixture were added 5.0 wt % palladium on carbon (2.38 kg, Escat 1421, approximately 50% water) and ethanol (340 L, 1.0 volume). The hydrogenator was purged three times with nitrogen, cooled to 10 °C, and then pressurized to 60 ± 5 psig with hydrogen. The reaction mixture was stirred at 15 ± 5 °C while a hydrogen pressure of 60 ± 5 psig was maintained until reaction was deemed complete, waiting for 2 h after hydrogen uptake ceased (typically 10−15 h). At the end of the reaction, the hydrogenator was purged with nitrogen twice (pressurized to 60 ± 10 psig and then vented to atmospheric pressure). The crude reaction mixture was filtered through a sparkler filter followed by a 0.45 μm cartridge filter in series into a 3600 L reactor. The hydrogenator, filter, and lines were washed with an additional aliquot of toluene (340 L, 1.0 volume). The reaction mixture was concentrated under reduced pressure (typically 50−300 mbar) at a batch temperature of 50 ± 5 °C until the total reaction volume was approximately 820 L (2.4 volumes). The batch was cooled to 38 ± 3 °C and seeded with 2.7 kg of **2**. The resulting slurry was stirred at 35 ± 5 °C for 1 h and then cooled to 20 ± 5 °C over 1 h. Heptane (1900 L, 5.6 volumes) was added over 3 h, and the batch was allowed to stir at 20 ± 5 °C for >1 h. The reaction slurry was filtered in an agitated filter dryer, and the cake was displacement-washed with a mixture of toluene (204 L, 0.6 volumes) and heptane (476 L, 1.4 volumes) followed by heptane (680 L, 2.0 volumes). The cake was dried under vacuum at 50 °C for >12 h until sample dryness was confirmed by LOD analysis. Product **2** (249 kg, 90% yield) was isolated with 99.0 wt % purity by HPLC and 98.9 LC area % purity (containing <1 ppm Pd). ^{1}H NMR (400 MHz, MeOH-d_4) δ 6.86 (t, *J* = 7.7 Hz, 1H), 6.76 (td, *J* = 8.2, 1.6 Hz, 1H), 6.65 (m, 1H), 3.67 (s, 3H), 3.57 (d, *J* = 1.4 Hz, 2H), 3.44−3.48 (m, 4H), 2.44−2.48 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 157.7, 153.2, 150.9, 137.0, 124.9, 121.3, 117.7, 56.5, 53.7, 53.4, 44.8; melting point = 89−91 °C; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{19}FN_3O_2$ $[M + H]^+$ 268.1456, found 268.1448.

Manufacture of 4-HCl. An 8000 L glass-lined, jacketed reactor set at 20 °C under a nitrogen atmosphere and vented through a scrubber (containing 5 N NaOH) was charged with **6** (125 kg, 1156 mol, 1.0 equiv) followed by acetonitrile (1875 L, 15 volumes). Phenyl chloroformate (190 kg, 1214 mol, 1.05 equiv) was added via a pump over 3 h so as to maintain the internal temperature at or below 30 °C. The reaction mixture was agitated for 3 h at 20 ± 5 °C and then filtered using an agitated filter dryer. The mother liquor was forwarded to a glass-lined jacketed reactor for quenching of excess phenyl chloroformate with NaOH. The product cake was washed twice with acetonitrile (2 × 250 L, 4 volumes) and dried under vacuum at 35 °C for 24 h to afford 290 kg (95% yield) of **4-HCl** as a solid with 100 wt % and 99.6 LC area % purity. ^{1}H

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NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 8.81 (s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.48−7.44 (m, 2H), 7.32−7.26 (m, 3H), 2.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 151.7, 150.0, 147.5, 136.1, 133.8, 130.0, 129.5, 127.8, 125.9, 121.7, 18.6; melting point = 224−226 °C; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{13}N_2O_2$ $[M + H]^+$ 229.0972, found 229.0961.

Manufacture of Omecamtiv Mecarbil (1). To a 12 000 L glass-lined reactor were charged **2** (222 kg, 829 mol, 1.0 equiv), **4-HCl** (242 kg, 912 mol, 1.1 equiv), tetrahydrofuran (554 L, 2.5 volumes), acetonitrile (554 L, 2.5 volumes), and diisopropylethylamine (129 kg, 998 mol, 1.2 equiv). The batch was heated at 57 °C for 21 h. Water (1109 L, 5.0 volumes) was added, maintaining the batch temperature at 55 ± 5 °C, followed by seeding with **1** (16.8 kg, 42 mol, 0.05 equiv). Water (2218 L, 10.0 volumes) was added to the reactor over 3 h. The resulting suspension was cooled to 22 °C and filtered in an agitated filter dryer. The filter cake was washed with a mixture of acetonitrile (166 L, 0.75 volumes) and water (499 L, 2.25 volumes) followed by three cake washes of acetonitrile (3 × 665 L, 9 volumes). The cake was dried under vacuum (10−50 mbar) with a jacket temperature of 35−40 °C for 17 h. Omecamtiv mecarbil (**1**) (287 kg, 82% yield) was isolated as a white solid with 99.6 wt % purity by HPLC and 99.9 LC area % purity. ^1H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.46 (d, J = 2.5 Hz, 1H), 8.03 (t, J = 7.3 Hz, 1H), 7.82 (dd, J = 8.4, 2.6 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 6.8 Hz, 1H), 3.54−3.60 (m, 6H), 3.31−3.30 (m, 4H), 2.34−2.42 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 155.0, 152.3, 151.9, 151.1. 139.2, 133.6, 127.3, 127.2, 125.8, 124.1, 124.0, 123.8, 122.8, 119.5, 54.5, 52.1, 43.4, 23.2; melting point = 197−202 °C; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{25}FN_5O_3$ $[M + H]^+$ 402.1941, found 402.1936.

Manufacture of Omecamtiv Mecarbil (1) Dihydrochloride Hydrate. **1** (218 kg, 542 mol, 1.0 equiv) was charged to a 12 000 L glass-lined reactor, followed by water (333 L, 1.35 volumes) and 2-propanol (566 L, 2.60 volumes). The slurry was agitated and heated to approximately 40 °C, whereupon aqueous 6 N HCl (199 L, 1192 mol, 2.2 equiv) was charged to the slurry, resulting in a colorless homogeneous solution. The solution was heated to between 55 and 60 °C and transferred through an in-line filter to a 6000 L glass-lined reactor preheated to 55 °C. A rinse of the reactor and filter consisting of 2-propanol (72 L, 0.33 volume) and water (72 L, 0.33 volume) was also transferred to the 6000 L reactor. The batch was cooled to 45 °C, and omecamtiv mecarbil (**1**) dihydrochloride hydrate seed (8 kg, 3.7 wt %) was charged. The mixture was aged at 45 °C for 0.5 h, and then 2-propanol (846 L, 3.9 volumes) was added over 3 h. A heat cycle (heating to 55 °C for 0.5 h followed by cooling to 45 °C over 1 h) was conducted, and the mixture was agitated at 45 °C for an additional 2 h. 2-Propanol (1603 L, 7.37 volumes) was added over 4 h, and the mixture agitated at 45 °C for 1 h and cooled to 20 °C over 2 h. The batch was recirculated through a wet mill for three to four batch turnovers to reduce the particle aspect ratio. The slurry was filtered in an agitated filter dryer, and the cake was washed twice with 95:5 v/v 2-propanol/water solution (2 × 435 L, 4 volumes). The cake was dried under vacuum with a jacket temperature of 35−40 °C. Omecamtiv mecarbil (**1**) dihydrochloride hydrate (248 kg, 93% yield) was isolated as a colorless crystalline solid with 100 wt % purity by HPLC and >99.9 LC area % purity. ^1H NMR (500 MHz, D_2O) δ 8.87 (s, 1H), 8.22 (d, J = 8.9 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.35−7.29 (m, 2H), 4.48 (s, 2H), 4.24 (br s, 2H), 3.73 (s, 3H), 3.31 (br s, 6H), 2.68 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, D_2O) δ 156.8, 154.2, 153.9, 147.8, 136.3, 136.1, 130.1, 129.4, 128.0, 127.2, 125.5, 125.1, 116.1, 53.5, 50.9, 40.5, 18.2; melting point = 252−254 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00200.

Copies of ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(8) (a) A 42 kg batch of drug substance produced via this process required a filtration time of 3 days and a drying time of over 1 week. (b) For a detailed summary of the solid-state characteristics of the anhydrous free-base form of omecamtiv mecarbil and comparison to a hemihydrate form, see: Morrison, H.; Quan, B. P.; Walker, S. D.; Hansen, K. B.; Nagapudi, K.; Cui, S. Appearance of a New Hydrated Form during Development: A Case Study in Process and Solid-State Optimization. *Org. Process Res. Dev.* **2015**, *19*, 1842−1848. (c) Prolonged refluxing of omecamtiv mecarbil in EtOH during the recrystallization can lead to degradation, which lowers the yield. For example, characterization studies demonstrated that heating omecamtiv mecarbil in ethanol at reflux for 6 h resulted in an erosion of the solution chemical purity from >99% to 86% by LC analysis..

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(13) Iron, vanadium, and other additives have been reported to reduce the accumulation of hydroxylamine intermediates in nitro group reductions. In the screening for this project, an Fe-doped catalyst was used instead of adding Fe powders or salts to existing catalyst systems. For a lead reference on metal modifiers used in catalytic supported hydrogenations, see: Baumeister, P.; Blaser, H.-U.; Studer, M. Strong reduction of hydroxylamine accumulation in the catalytic hydrogenation of nitroarenes by vanadium promoters. *Catal. Lett.* **1997**, *49*, 219−222.

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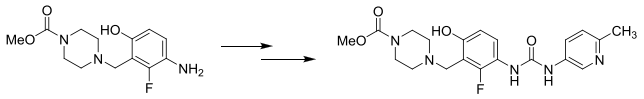

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