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Development of a Green and Sustainable Manufacturing Process for Gefapixant Citrate (MK-7264). Part 5: Completion of the API Free Base via a Direct Chlorosulfonylation Process

Michael J. Di Maso,* Hong Ren,* Si-Wei Zhang, Wenjun Liu, Richard Desmond, Embarek Alwedi, Karthik Narsimhan, Alexei Kalinin, Patrick Larpent, Alfred Y. Lee, Sumei Ren, and Kevin M. Maloney

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ABSTRACT: A scalable two-pot sulfonamidation through the process has been developed for the synthesis of gefapixant citrate, a P2X3 receptor antagonist that is under investigation for the treatment of refractory and unexplained chronic cough. Direct conversion of the diaryl ether precursor to a sulfonyl chloride intermediate using chlorosulfonic acid, followed by treatment with aqueous ammonia hydroxide, provided the desired sulfonamide in high yield. A pH-swing crystallization allowed for the formation of a transient acetonitrile solvate that enables the rejection of two impurities. After drying, the desired anhydrous free base form was isolated in high yield and purity.

KEYWORDS: *electrophilic aromatic substitution, sulfonamide, transient solvate, pH-swing crystallization*

After successfully developing a streamlined synthesis of the diaminopyrimidine **1**,[1,2] we turned our attention to completing the synthesis of gefapixant through the installation of the sulfonamide functionality to give the API free base **3**. Unfortunately, the first-generation supply route protocol for this transformation suffered from several deficiencies that would preclude its use in a commercial route (Scheme 1A): (1) the synthetic sequence required three distinct chemical steps to install the sulfonamide; (2) the use of sulfolane, a Class 2 solvent with strict residual limits (<160 ppm),[3] was undesirable in the final steps of the synthesis; (3) the use of two highly toxic and hazardous chemicals, chlorosulfonic acid (HSO_3Cl) and $POCl_3$, was likewise unattractive; (4) issues with process robustness were observed on scale-up; and (5) multiple recrystallizations of the free base product were required to reach the purity specifications with respect to impurities **4**, **5**, and unidentified phosphate oligomers. Given the severity of these concerns, we set out to develop a one-step synthesis of the API that would address these issues and exceed our standards for a manufacturing route.[4]

Our studies began with a search for a one-step sulfonamidation reaction using various sulfur electrophiles (Scheme 2A). While the use of all of the reagents led to the formation of the desired C−S bond, the terminal functional group typically varied between the sulfonic acid and sulfonyl chloride with little of the desired sulfonamide formed. Interestingly, while using sulfamoyl chloride as the sulfonylating reagent, divergent reactivity, depending on whether a Brønsted or Lewis acid promoter was used, was observed. While employment of Brønsted acids predominantly afforded sulfonyl chloride **6**, upon switching instead to a Lewis acid, the same conditions provided the desired sulfonamide **3** exclusively. These conditions proved essential for the efficient synthesis of carbon-14 radiolabeled **3** to support drug metabolism and pharmacokinetic studies, environmental fate studies, and human ADME study (absorption, distribution, metabolism, and excretion). Crucially, this route reduced the number of steps with radiolabeled intermediates required to synthesize ^{14}C-**3** from four to two while increasing the overall yield. Unfortunately, while this one-step direct sulfonamidation reaction enabled radiolabeling studies, the reaction exhibited several limitations that rendered it unsuitable for use in a commercial manufacturing process. First, the reaction required the use of a chlorinated solvent, which is unattractive from a green chemistry standpoint. In addition, there are safety and handling concerns for sulfamoyl chloride itself as well as the superstoichiometic amounts of aluminum trichloride that are required, as both are highly reactive water-sensitive solids.

In view of the limitations of direct sulfonamidation, we set our sights on developing an efficient two-step protocol for this reaction. We therefore turned our attention to investigating the direct formation of the sulfonyl chloride **6** from arene **1** as this intermediate could easily be transformed into the desired sulfonamide **3** (Table 1). Although direct chlorosulfonylation can be accomplished with chlorosulfonic acid, this reagent typically forms sulfonic acids as the major products in many cases,[5−9] and the addition of a secondary chlorinating reagent (e.g., $POCl_3$) or the use of solvent quantities of the reagent are

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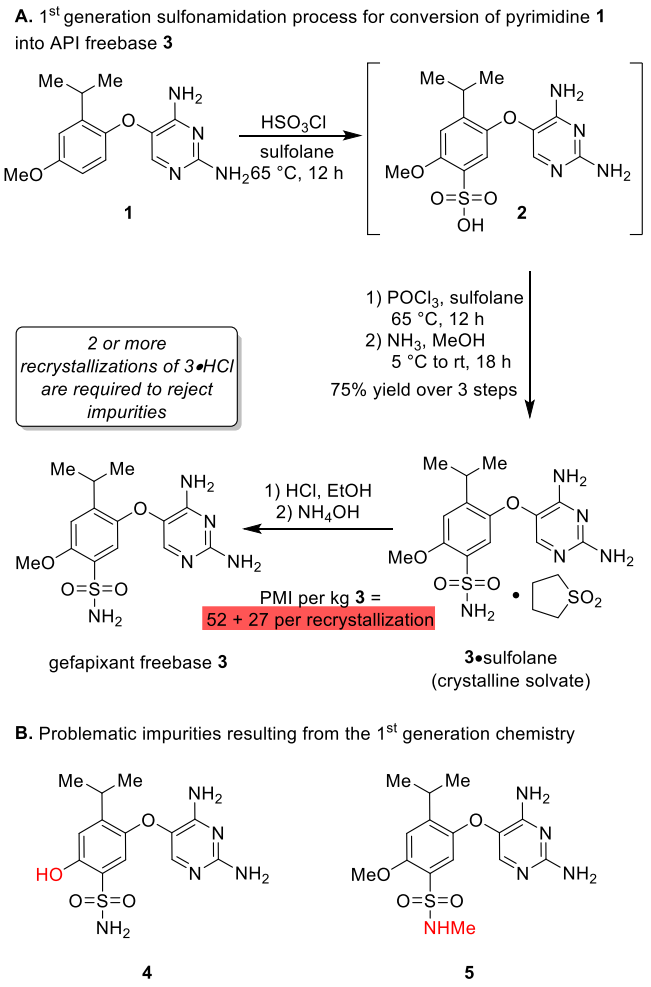
Scheme 1. (A) First-Generation Route to Provide Gefapixant Free Base. (B) Poorly Rejecting Impurities Arising from the First-Generation Sulfonamide Chemistry



needed to effect the selective transformation to the sulfonyl chloride.[10−16] Keen to minimize the amount of chlorosulfonic acid used and eliminate the use of a second hazardous reagent in this step, we screened the effect of solvent on the chlorosulfonation reaction to identify conditions for an efficient chlorosulfonylation using chlorosulfonic acid alone (Table 1). As expected, the use of three equivalents of chlorosulfonic acid, in a series of solvents, provided varying levels of conversion to the undesired sulfonic acid **2**. Although sulfolane, which was used in the supply route, gave almost exclusively the undesired acid **2**, we were pleased to find that, in acetonitrile, a 7:3 mixture of the sulfonic acid **2** and sulfonyl chloride **6** was formed.[17,18] Increasing the stoichiometry of chlorosulfonic acid from 3 to 5 equivalents provided almost complete selectivity for the sulfonyl chloride over the sulfonic acid. Time-course experiments later demonstrated that, under these conditions, pyrimidine **1** is initially converted to sulfonic acid **2**; upon aging at 45 °C for 16 h, acid **2** is then converted to the desired sulfonyl chloride **6**. Additionally, acetamide was observed by GC analysis of the mixture, along with 4−5% of acetylated product **8** (vide infra). This observation indicates that acid-promoted hydrolysis of acetonitrile occurs, which may be important to drive the reaction to the desired sulfonyl chloride by consuming water; further studies on the sulfonylation mechanism are ongoing in our laboratory to determine the reason for the effectiveness of this solvent. In line with the stated goals for our manufacturing process, this new method allows us to access sulfonyl chloride **6** directly from arene **1**, without the need to first form acid **2** in a separate step, and also eliminates the use of sulfolane and $POCl_3$.

In addition to the desired product **3**, varying levels of two impurities were observed from the sulfonylation step after the reaction was quenched with ammonium hydroxide (Table 2). These impurities were identified as chlorinated arene **9** and sulfinic acid **10**, suggesting the presence of sulfuryl chloride, a well-known chlorinating reagent,[19−23] in the batch of chlorosulfonic acid employed. Consistent with this hypothesis, the amounts of these impurities were found to depend on the batch of chlorosulfonic acid used (entries 1 and 2), and a significant increase in the quantity of both was observed upon the addition of one equivalent of sulfuryl chloride to the chlorosulfonic acid (entry 3). To control the formation of these impurities, 1,3-dimethoxybenzene (DMB) could be added to the reaction to scavenge the sulfuryl chloride (entry 4). For translation to the manufacturing process, an analytical method has been developed to quantify sulfuryl chloride levels in chlorosulfonic acid to ensure optimal reagent quality.[24]

With a process to form the sulfonyl chloride **6** in hand, we turned our attention to optimizing the sulfonamide formation (Table 3). In the supply process, this conversion was accomplished by quenching the stream of sulfonyl chloride into a methanolic solution of ammonia. However, this process led to methylated impurity **5** that was difficult to purge via crystallization (Scheme 1B). Alternatively, it was discovered that the desired sulfonamide **3** could be formed by quenching the solution of sulfonyl chloride **6** into an aqueous ammonium hydroxide solution, thereby eliminating the formation of methylated impurity **5**. Further investigation showed that higher temperatures during quenching led to an increased rate of hydrolysis of sulfonyl chloride **6** and the corresponding formation of increasing levels of the sulfonic acid **2**, which was attributed to the evaporation of ammonia from the solution. As mitigation, the addition was performed at an internal temperature of 0−15 °C, which enabled us to keep the sulfonic acid impurity levels below 2.0 LCAP.[25]

The sulfonamide precipitates from the solution during this quench procedure. Unfortunately, the direct isolation of this solid led to a low-weight-percent solid that contained up to 4−5% of the acetylated byproduct **8** (Table 4). While attempts to hydrolyze this impurity with the addition of exogenous amines were unsuccessful, the addition of aqueous sodium hydroxide served to hydrolyze the impurity to the API free base, resulting in a concomitant increase in the yield of the reaction. Of additional benefit, the existing solids underwent dissolution during the process and provided the opportunity to develop a controlled crystallization of the product and increase the purity of the isolated free base **3**.

To develop this crystallization, the solubility of sulfonamide **3** was studied as a function of pH (Figure 1). As expected, this compound is highly soluble under basic conditions owing to the deprotonation of the sulfonamide to form the corresponding sodium salt. As a result, we envisioned that the preferred procedure would entail the slow addition of acid to this basic solution to afford the neutral API in a reactive crystallization. Citric acid was chosen as the acid to minimize the risk of forming any other potential salts (as the final API form is the gefapixant citrate salt). From the solubility curve, seeding in

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Scheme 2. (A) High-Throughput Screen of a One-Pot Sulfonamidation Reaction. (B) Differential Selectivity with Brønsted or Lewis Acids and Sulfamoyl Chloride. (C) Application of Lewis Acid Conditions to the Synthesis of ^{14}C-3

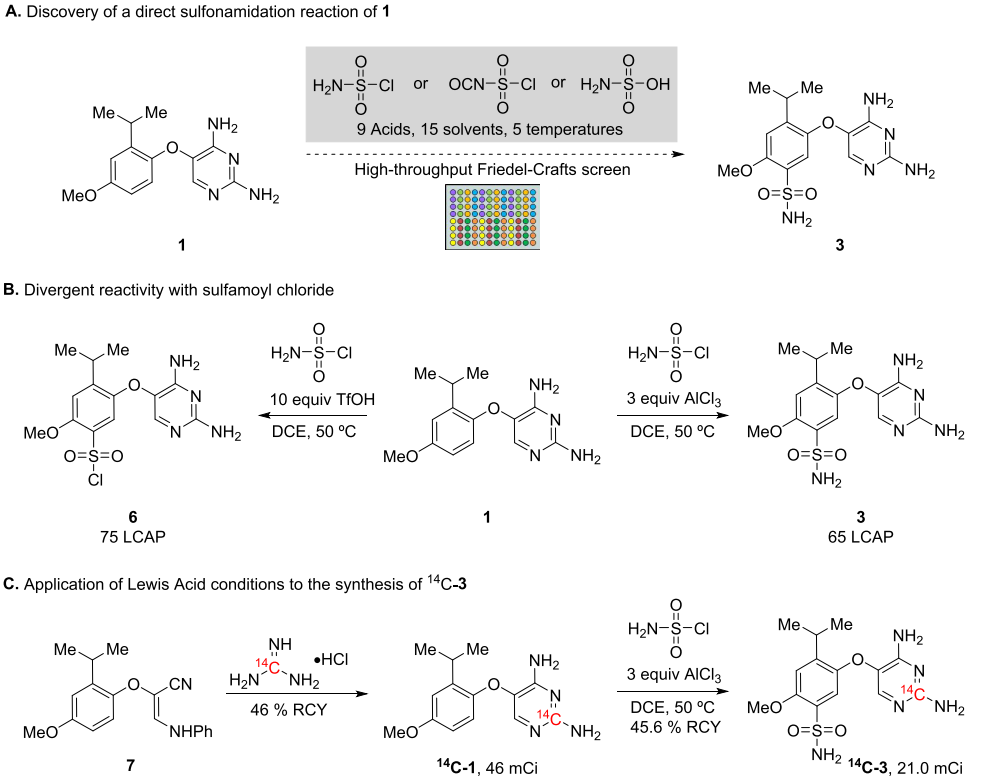
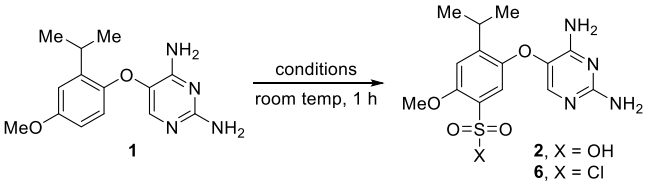


Table 1. Effect of Solvent on Ratio of Sulfonic Acid 2 to Desired Sulfonyl Chloride 6.



entry	solvent	equiv HSO_3Cl	conversion	ratio **2**:**6**
1	sulfolane	3	100	98:2
2	DMAc	3	<5	nd
3	DMSO	3	<5	nd
4	NMP	3	<5	nd
5[a]	MeCN	3	100	30:70
5[a]	MeCN	3	100	30:70
6[b]	MeCN	4	100	6:94
7[b]	MeCN	5	100	1.6:98.4

[a]Reaction aged for 3 h. [b]Reaction aged 16−18 h at 45 °C. nd = not determined.

the range of pH 12.7−13.0 was suitable to grow a seedbed before adjusting the pH to 10.8−11.3 for isolation. Adjusting the pH further failed to offer a significant improvement in the mother liquor losses.

While this crystallization procedure allowed for excellent rejection of several impurities, two problematic impurities were not consistently rejected under the same conditions or in the final citrate salt formation.[26] However, it was observed that the addition of two volumes of acetonitrile to the crystallization stream allowed for the isolation of the desired crystal form in increased purity with diminished amounts of these species. This observation raised the question of the form of the API throughout the entire crystallization process (Table 5). When the impurities are rejected, a seedbed of anhydrous form 1 grows before turning over to an acetonitrile solvate, and this solvate continues to crystallize from the solution throughout the pH swing. During the washing of the wet cake with water, the solids desolvate to provide the desired anhydrous form 1 of the API in the dry cake. At our original solvent composition (~14% MeCN/Water), form 1 and the acetonitrile solvate were both stable and turnover to the acetonitrile solvate was slow. The addition of two volumes of acetonitrile (20% MeCN/Water) biased the system toward the acetonitrile solvate and allowed for fast form turnover with concomitantly improved impurity rejection.[27]

To develop a successful thermodynamic crystallization, a study of the relative stabilities of the two forms in mixtures of acetonitrile and water was undertaken (Figure 2). Maintaining the acetonitrile level above 15% ensures that the acetonitrile solvate is thermodynamically preferred. While seeding with the acetonitrile solvate allows for the immediate growth of the acetonitrile solvate, desolvation of the seed on standing required additional processing to provide acetonitrile solvate. Therefore, seeding with form 1 was preferred due to the facile turnover to the transient solvate under the crystallization conditions, as well as the ease of storing the form 1 seed. This unexpected discovery of a transient acetonitrile solvate allowed for consistent impurity rejection while enabling isolation of the desired form of the product in high yield and purity was a key breakthrough in the development of this sulfonamidation process.

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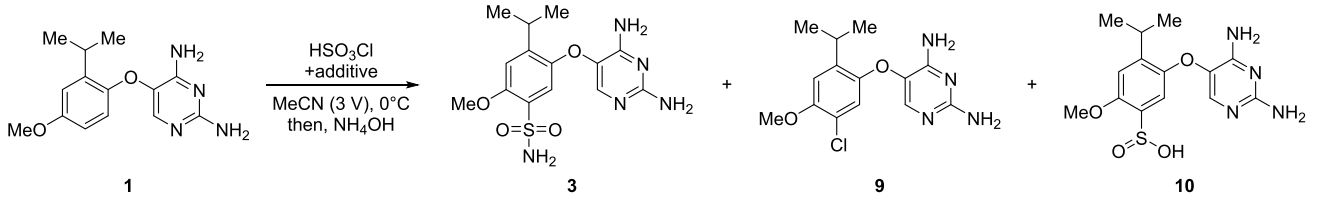
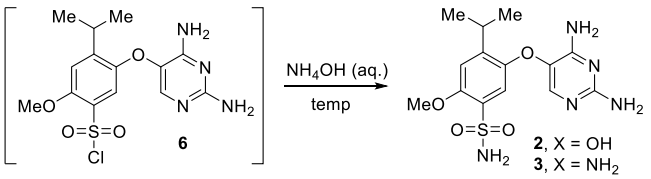
Table 2. Formation of Impurities Chloroarene 9 and Sulfinic Acid 10 During Sulfonylation with Sulfuryl Chloride



1 3 9 10

entry	conditions	3 (LCAP)	9 (LCAP)	10 (LCAP)
1	99% HSO_3Cl (supplier A)	93.0	0.2	0.2
2	97% HSO_3Cl (supplier B)	80.6	4.1	3.7
3	99% HSO_3Cl + 1 equiv SO_2Cl_2	32	22	21
4	97% HSO_3Cl + 20 mol % DMB	93.0	0.92	2.3

Table 3. Temperature Screening for the Reverse Quench of Sulfonyl Chloride 6.



entry	temperature (°C)	3 (LCAP)	2 (LCAP)
1	0	89.9	1.0
2	15	87.0	5.4
3	30	82.5	11.3

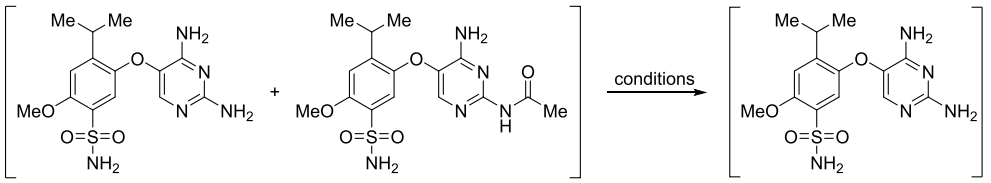
CONCLUSIONS

The new sulfonamidation process significantly improves on all aspects of the supply route (Scheme 3). Careful solvent selection in the chlorosulfonylation reaction allowed for the elimination of sulfolane and $POCl_3$. These changes provide a greener and operationally simpler process, while also preventing the formation of a dimeric impurity resulting from the reaction of sulfonamide **3** with phosphorus oxychloride. While the highly corrosive chlorosulfonic acid remains an important reagent in the new process, engineering controls have been put in place to handle the reagent safely on scale.[28] By setting purity specifications for the chlorosulfonic acid, it is now possible to prevent the formation of several impurities generated from the dissolved sulfuryl chloride that can be present in this reagent. Additional impurity control resulting from the new quench procedure, along with the controlled pH-swing crystallization and the discovery of a transient acetonitrile solvate, allows for single, direct isolation of the API in excellent purity and greatly increased yield. These combined improvements result in a vastly improved isolation procedure that eliminates the tedious multiple recrystallizations required in the first-generation process, resulting in a 42% reduction in the amount of waste generated in the sulfonamide installation. Indeed, the overall PMI for the new process from arene **1** to sulfonamide **3** is now lower than the PMI of a single one of the multiple recrystallizations of product **3** that were originally required. The new process has been transferred to our scale-up facilities and successfully demonstrated on up to 440 kg scale with a 90−94% yield and >98.5% purity of gefapixant free base.

EXPERIMENTAL SECTION

Preparation of Gefapixant Free Base Form 1 (3). To a suspension of 5-(2-isopropyl-4-methoxyphenoxy)pyrimidine-2,4-diamine (47.0 kg, 171 mol) in 141 L of acetonitrile at −10 °C was added chlorosulfonic acid (63.1 L, 942 mol) while maintaining the internal temperature below 25 °C. The solution was aged for 1 h at 25 °C and then heated to 45 °C for 12 h. The solution was allowed to cool to 20 °C and added to a solution of 235 L ammonium hydroxide and 71 L of acetonitrile at −10 °C while maintaining the internal temperature below 15 °C. The slurry was aged at 10 °C for 1 h, heated to 25 °C, and aged for 1 h. The slurry was diluted with 560 L of water and 190 L of 50 wt % sodium hydroxide to provide a homogeneous solution that was heated to 35 °C for 2 h. The solution was allowed to cool to 22 °C and the pH of the solution was adjusted to 12.9 with a 2 M aqueous solution of citric acid. The solution was seeded with gefapixant free base

Table 4. Hydrolysis of an Acetylated Byproduct and Slurry Dissolution



3 8 4–5 LCAP 3

Slurry *Homogeneous*

entry	conditions	outcome
1	1,2-ethylenediamine, 50 °C	no change
2	1,2-ethanolamine	no change
3	NaOH, H_2O, 40 °C	slurry dissolves, complete hydrolysis in 2 h

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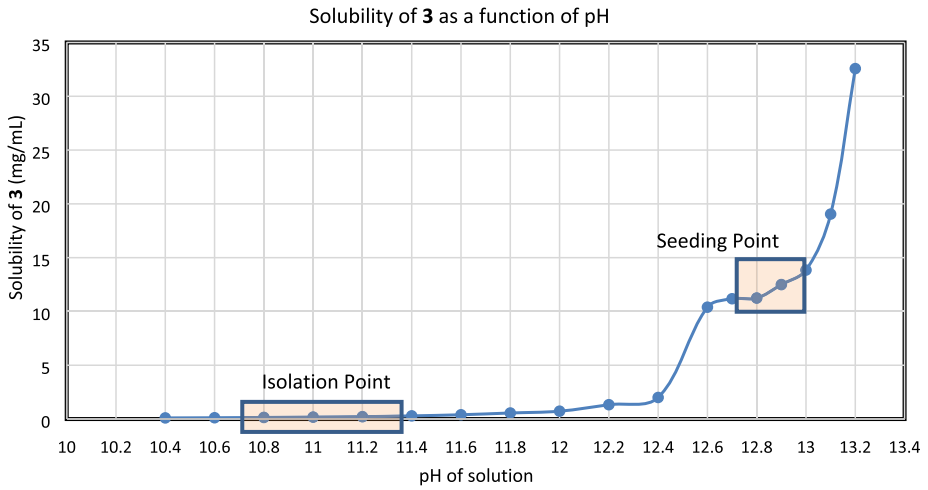


Figure 1. Solubility of sulfonamide **3** in the reaction solvent based on solution pH. pH was adjusted using a 2 M aqueous citric acid solution.

Table 5. Crystal Form Studies for the Isolation of API Free Base 3

MeCN/Water solution → (Seed with Form 1 or MeCN solvate) → Slurry → (Wash/Dry; *End of Crystallization*) → Dry Cake

solvent composition	<15% MeCN	>15% MeCN	<15% MeCN	>15% MeCN
seed form	form 1	form 1	MeCN solvate	MeCN solvate
slurry form	form 1	MeCN solvate	form 1	MeCN solvate
dry cake form	form 1	form 1	form 1	form 1
impurities (LCAP)	0.20, 0.21	0.04, 0.02	0.20, 0.21	0.04, 0.02

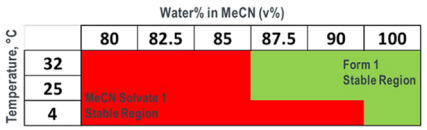
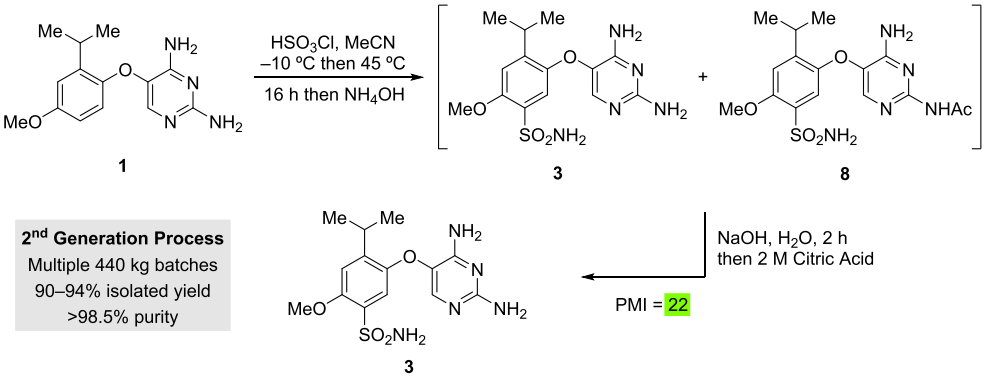


Figure 2. Thermodynamic stability of the acetonitrile solvate **1** and form 1 crystal forms of API free base **3** with respect to temperature and solvent concentration (V/V% water/acetonitrile).

(470 g, 1.19 mol) aged for 2 h, acidified to pH 10.5−11.3 with a 2 M aqueous solution of citric acid over 5−10 h, and then aged for 2 h. The slurry was filtered, the resulting cake was washed with 9:1 water:acetonitrile (2 × 118 L) and water (2 × 235 L) and dried at 55 °C under vacuum to provide gefapixant free base **3** (50.9 kg, 91%) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 (s, 1H), 7.07 (s, 1H), 7.05−6.89 (m, 3H), 6.37 (s, 2H), 5.85 (s, 2H), 3.89 (s, 3H), 3.41 (hept, J = 6.6 Hz, 1H), 1.27 (d, J = 6.8 Hz, 6H).

^{14}C-labeled-**1**. To a solution of 2-(2-isopropyl-4-methoxy-phenoxy)-3-phenylamino-acrylonitrile (**7**)[29] (805 mg, 2.61 mmol, 1.5 equiv) in anhydrous DMSO (5.6 mL, 7 V) was added [^{14}C]-guanidine hydrochloride (170 mg, 1.74 mmol, 1.0 equiv, 100 mCi), followed by potassium *t*-butoxide (215 mg, 1.91 mmol, 1.1 equiv) at 22 °C. The mixture was stirred at 120 °C for 28 h and then allowed to cool to 22 °C. The mixture was partitioned between EtOAc and water. The organic layer was separated, dried over sodium sulfate, and evaporated. The crude product was applied to a silica gel column, eluting with DCM/MeOH/Et_3N = 100:1:1 to afford the desired product ^{14}C-**1** (46 mCi; RCP > 98%, 46.0% radiochemical yield (RCY)).

Scheme 3. Safe, Scalable, and Green Manufacturing Route to Gefapixant Free Base 3



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^{14}C-labeled-**3**. To a solution of ^{14}C-**1** (46 mCi, ∼0.8 mmol) and sulfamoyl chloride (414 mg, 3.6 mmol) in anhydrous DCE (6 ml) was added $AlCl_3$ (426 mg, 3.2 mmol) at 20 °C. The mixture was stirred at 50 °C overnight (17 h) under nitrogen. The reaction mixture was quenched with 5% aq. citric acid solution and then purified by high-performance liquid chromatography (HPLC). The fractions containing the desired product (radiochemical purity (RCP) > 99%, chemical purity (CP) > 99%) were pooled and evaporated under reduced pressure to yield 21.0 mCi of the product as off-white solid (RCP > 99%, CP > 99%, 45.6% RCY) as a TFA salt. The specific activity was determined to be 58.4 mCi/mmol by MS analysis.

AUTHOR INFORMATION

Corresponding Authors

Michael J. Di Maso − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0003-1262-6126; Email: mike.dimaso@merck.com

Hong Ren − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0002-0754-7282; Email: hong.ren@merck.com

Authors

Si-Wei Zhang − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0001-8677-3722

Wenjun Liu − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Richard Desmond − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Embarek Alwedi − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0002-7031-2427

Karthik Narsimhan − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Alexei Kalinin − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Patrick Larpent − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Alfred Y. Lee − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0003-3684-4101

Sumei Ren − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States*

Kevin M. Maloney − *Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0003-1422-5422

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.0c00247

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

LCAP=liquid chromatography area percent
RCY=radiochemical yield

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(26) Please insert citation for the following manuscript in this series of papers.
(27) We posited that the addition of other solvents to our crystallization may allow for the isolation of an alternative solvate of the API that we could isolate while rejecting these impurities. The addition of 1−2 volumes of several solvents did lead to an increase in the rejection of these impurities; however, we were unwilling to risk taking new solvates into our final crystallization step.
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