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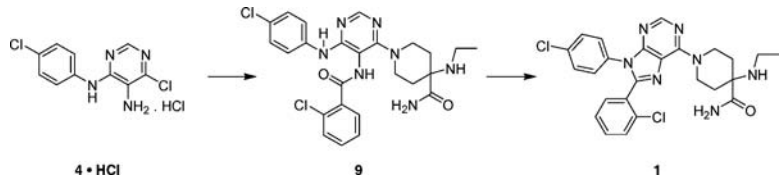

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Development of a Practical and Efficient Synthesis of CP-945,598-01, a CB_1 Antagonist for the Treatment of Obesity

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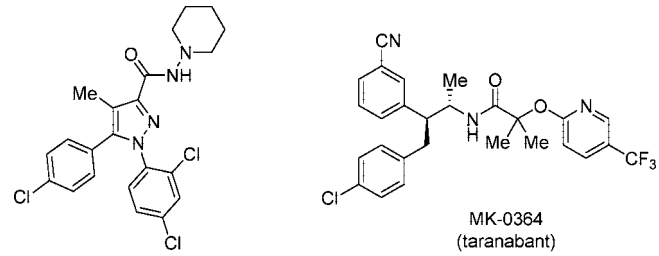
Abstract:

Development of an efficient bond-forming sequence and optimization of reaction conditions are described for the synthesis of CP-945,598-01 (1·HCl), a CB_1 antagonist in clinical studies for the treatment of obesity. Reordering of the bond-forming sequence provided a more efficient synthesis and avoided the use of phosphorous oxychloride. A telescoped reaction sequence (4 → 9) was developed to avoid a problematic isolation. Product isolations were developed so as to provide efficient throughput by minimizing solvent volumes and avoiding slow filtrations.

1. Introduction

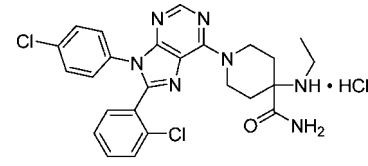
The endocannabinoid system (ECS), and specifically the CB_1 receptor, plays a pivotal role in energy homeostasis.[1] As such, stimulation of the ECS promotes food intake and energy storage and may be chronically overactive in obese subjects.[2,3] In contrast, blockade of the CB_1 receptor decreases food intake and increases energy expenditure, leading to a reduction in body weight.[4−7]

CB_1 receptor antagonists (Figure 1) may provide effective therapy options for the management of metabolic disorders, such as obesity. Several CB_1 receptor inverse agonists/antagonists are in clinical development including the diarylpyrazole SR141716A[8] (rimonabant, **2**) and the acyclic amide MK-0364[9] (taranabant, **3**).



2 **3**

Figure 1. **Structures of CB_1 antagonists.**



1 • HCl

Figure 2. **Structure of CP-945,598-01 (1·HCl).**

1-(8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl)-4-(ethylamino)-piperidine-4-carboxamide hydrochloride (CP-945,598-01, **1**·HCl) (Figure 2) was identified by Pfizer Discovery chemists as a promising CB_1 antagonist for the treatment of obesity[10,11] and nominated for development in 2002. This paper describes the original synthesis used to prepare CP-945,598-01, the identification of a more efficient bond-forming sequence, and optimization of the reaction conditions for this synthesis to support scale-up from laboratory (<50 g) to pilot plant (20−50 kg) to commercial pilot scale (>100 kg) campaigns.

† Submitted in memory of Dr. Chris Schmid, a valued friend and colleague whose many contributions to the field of process chemistry continue to benefit this growing community of scientists.

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□ Pfizer Global Manufacturing, Ringaskiddy API Plant.

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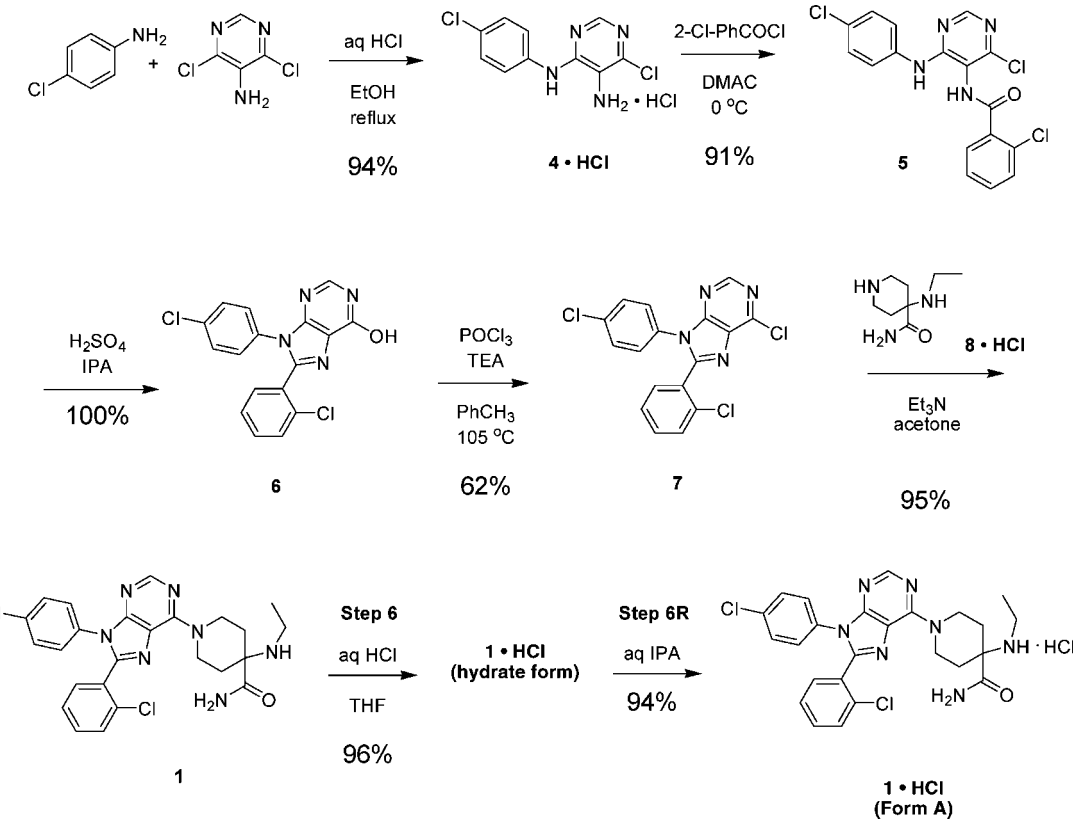
Scheme 1. **Synthesis used in first cGMP campaign**



2. Discussion

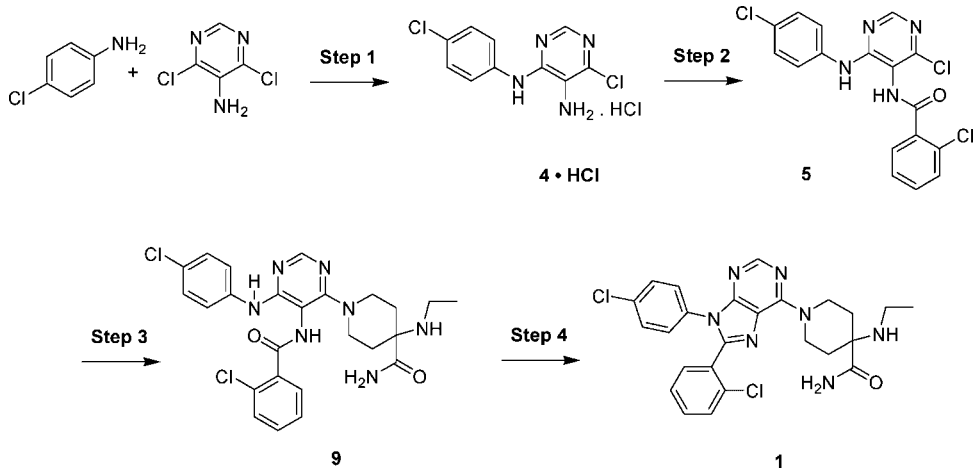
The synthesis utilized for the later Discovery lots and first cGMP (current Good Manufacturing Practice) campaign is shown in Scheme 1. The cGMP campaign proceeded remarkably well for a compound at this early stage of development, providing 13.8 kg of active pharmaceutical ingredient (API). All but one of the steps proceeded in >90% yield; the sole exception was the chlorination to generate chloropyrimidine **7**. In addition to the modest yield (62%), the use of phosphorous oxychloride presented handling and potential safety challenges that we felt might be avoided by a reordering of the bond-forming steps.

In the third step in Scheme 1, the sulfuric acid-mediated dehydration of chloropyrimidine **5** generated 8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-ol (**6**), in which the chloropyrimidine had undergone hydrolysis to the pyrimidinone. Other, milder conditions for this cyclization led to mixtures of the chloropyrimidine and pyrimidinone, so for the first bulk campaign it was deemed expedient to use conditions that completely hydrolyzed the chloropyrimidine, thus simplifying product isolation and analysis. This required a subsequent chlorination, which was effected with phosphorous oxychloride. The piperidine side chain was then installed by coupling of piperidine **8** with the regenerated chloropyrimidine (**7**) to deliver **1**. We reasoned that if the piperidine was installed *prior* to the acid-mediated cyclization, this could obviate the need for the rechlorination step.

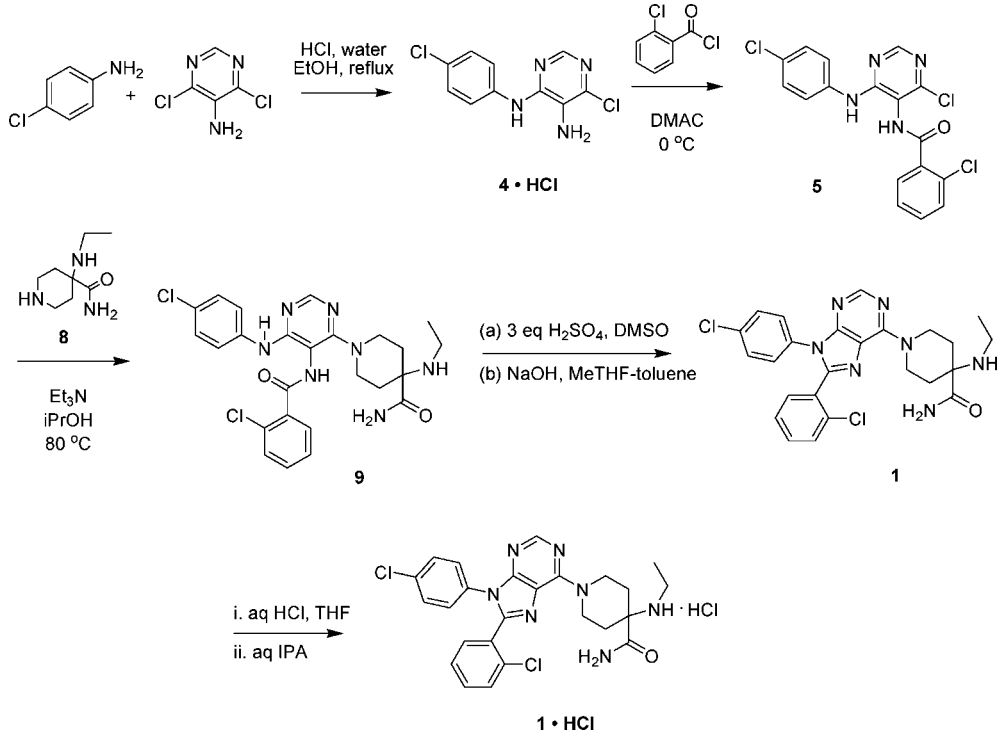
The first variant of this bond-forming sequence was successful on laboratory scale, as shown in Scheme 2. The two-step synthesis of chloropyrimidine **5** was unchanged from the previous route. Coupling of **5** with the piperidine side chain (**8**) was effected with triethylamine in refluxing isopropanol; this coupling required higher temperatures than the analogous coupling in the earlier synthesis (**7** to **1** in Scheme 1) but occurred cleanly to generate a new intermediate (**9**). The cyclization of **9** to **1** was mediated by H_2SO_4 in methanol, and the product was isolated by direct filtration of the sulfuric acid salt. This material was then converted to free base (Na_2CO_3 in aq acetone) and then to the HCl salt (HCl in isopropanol) for comparison to reference standards. Several attempts were made to perform the cyclization with HCl in place of H_2SO_4, in the hope that the HCl salt could be isolated directly. These efforts were unsuccessful. We initially attributed this failure to the higher water content of concd HCl relative to concd H_2SO_4. However, subsequent experiments showed that dilute aq H_2SO_4 solutions led to successful cyclizations; therefore, it appears to be related to acid strength, or other, unidentified, factors.

The first scale-up of the new bond-forming sequence was performed in the pilot plant in Groton, Connecticut, and delivered 19 kg of API. The chemistry utilized is shown in Scheme 3 and included several modifications from the first laboratory-scale experiments. The cyclization of **9** to **1** was effected by concd H_2SO_4 in DMSO at 90−100 °C. The product was isolated as the free base by an extractive workup involving neutralization with aq NaOH and product extraction into 2-methyltetrahydrofuran. Solvent displacement with toluene by vacuum distillation led to precipitation of **1** as the crystalline free base. The salt formation was performed in two stages: addition of concd HCl to the free base in THF generated the HCl salt as a mixture of three less stable polymorphs. A reslurry in aq isopropanol then converted this mixture to Form A, the desired, thermodynamically stable polymorph.

Scheme 2. **Alternative bond-forming sequence**

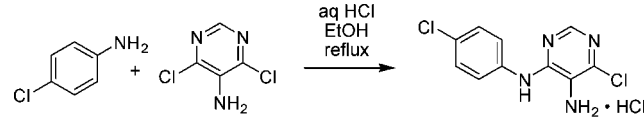


Scheme 3. **First scale-up of the new bond-forming sequence**



The next series of bulk campaigns were performed in the pilot plant in Sandwich, Kent, UK. Over the course of several campaigns in 2006, over 150 kg of API were delivered in this facility. During the course of these campaigns and associated laboratory development work, optimizations were made to each step in the synthesis. The process improvements that arose from the scale-up knowledge gained in Sandwich were critical in improving our process from the first scale-up experience (Scheme 3) to the ultimately successful transfer of the process to our commercial manufacturing group in Ireland (Scheme 4). These improvements are summarized below for each step.

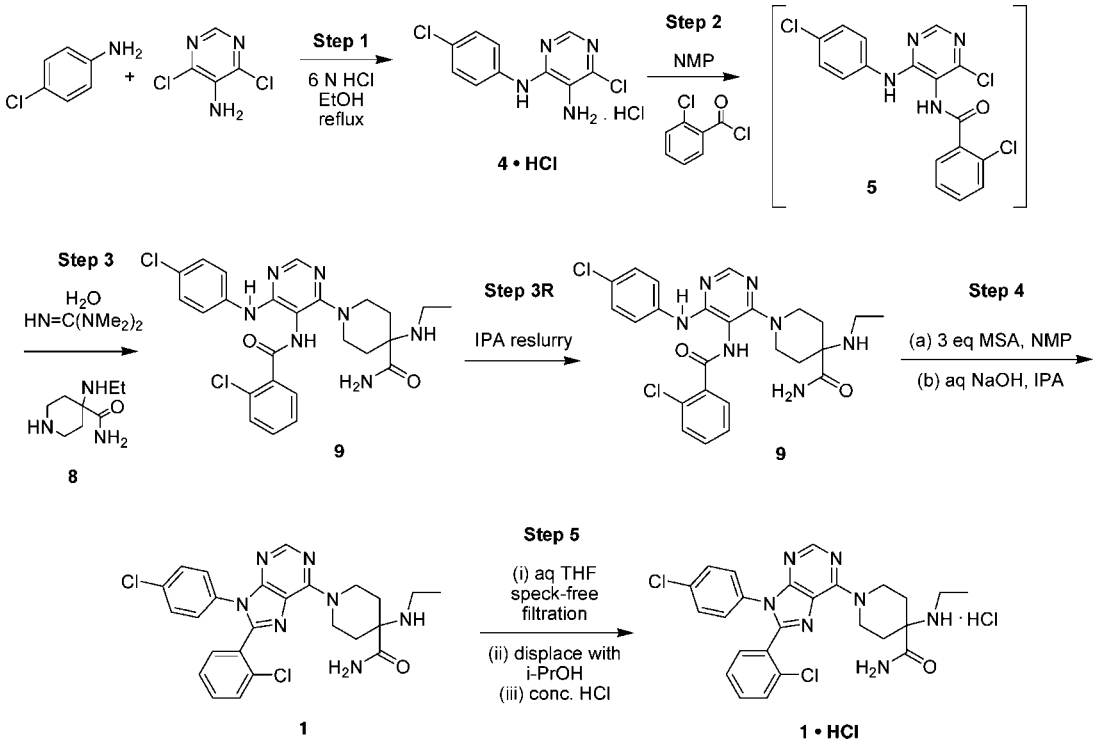
2.1. Preparation of 5-Amino-6-chloropyrimidine Hydrochloride·HCl. This step was modeled closely after the original literature report.[12] We observed formation of only one significant impurity in this step, the bis-adduct **10**, which arises from addition of a second molecule of 4-chloroaniline to the dichloropyrimidine core. Although this impurity was well-controlled by downstream crystallizations, minimizing its formation would increase reaction efficiency. Experiments in which the HCl stoichiometry was varied showed a negative linear correlation between the levels of this impurity and the equivalents of HCl, ranging approximately 10-fold from 2 to 3% levels with 0.4 equiv down to 0.2−0.3% levels with 2 equiv. Based on these studies, the HCl stoichiometry was increased from 0.4 to 2.0 equiv.



Optimization of the product isolation led to a switch in the final rinse solvent from hexanes (or heptanes) to ethyl acetate.

(12) Greenberg, S. M.; Ross, L. O.; Robins, R. K. *J. Org. Chem.* **1959**, *24*, 1314–1317.

Scheme 4. **Optimized API synthesis utilized in commercial pilot-plant campaign**



This provided shorter drying times, as the increased water miscibility lead to more efficient displacement of residual water from the filter cake. We confirmed that the potential N-acylated impurity **11** (Figure 3) was not present in batches prepared using the ethyl acetate rinse.

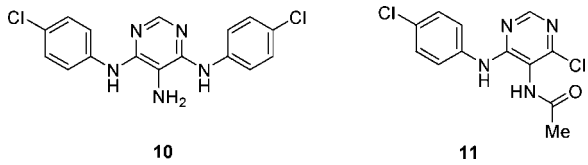
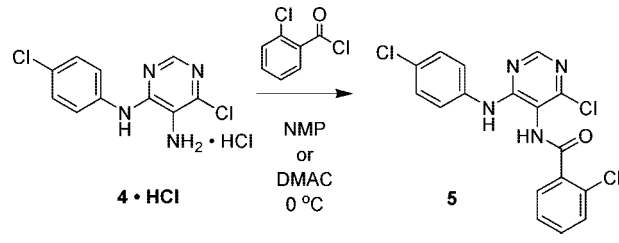


Figure 3. **Structures of known or potential impurities in formation of 4.**

We and earlier chemists on the project had initially assigned the step 1 product (**4**) as the free base. This was based on the literature precedent,[12] in which the free base is isolated following a recrystallization from methanol. However, subsequent analysis during the optimization studies described above showed that we were in fact isolating the mono-HCl salt. The discrepancy with the literature arises from our isolation method, which is to directly filter the product from the aq HCl-ethanol reaction medium. If this material is recrystallized from 50% aq methanol (per the literature report, 70 mL/g), the free base is obtained. The same conversion to free base was also realized by reslurrying the HCl salt in 20 mL/g of 50% aq methanol. These data show that the initially isolated product is in fact the mono-HCl salt of **4**, and that recrystallizing from aq methanol converts the salt to the free base; this likely reflects the relatively weak basicity of the aminopyrimidine, as no external base is added during this conversion. This caused some concern as to the solid state stability of **4**·HCl. However, a sample challenged in a vacuum oven (25−30 mmHg) at 90 °C for one week showed no loss of HCl, indicating that in the solid state, the salt is stable and robust, in contrast to its behavior in methanol solution. We found no advantage to using free base (**4**) in the acylation step. In fact, the hydrochloride salt was considerably more soluble in DMAC or NMP, and was thus preferred as a substrate for the next reaction.

Although all bulk campaigns run to date have utilized the free base 4-chloroaniline, we have also demonstrated that the aniline HCl salt can be substituted with no adverse impact on product yield or purity. It should be noted that the HCl salt of 4-chloroaniline is a higher melting and much more easily handled solid.



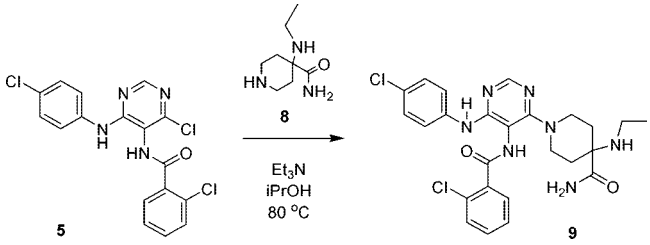
Preparation of acylated amino-chloropyrimidine 5. The acylation of the 5-aminopyrimidine (**4**·HCl) with 2-chlorobenzoyl chloride was performed in a polar, aprotic solvent, initially dimethylacetamide (DMAC), and eventually *N*-methylpyrrolidinone (NMP). The reaction performed equally well in either solvent, and the only significant driver for the switch to NMP was to minimize the total number of solvents used in the synthesis, since NMP was utilized in a later step (cyclization of **9** to **1**), thus simplifying the testing for residual solvents. Kinetic analysis of this reaction showed it to be a standard, second-order nucleophilic acylation (first-order in both aminopyrimidine **4** and acid chloride). Because of the kinetics, it was difficult to drive the acylation to completion without using an excess of one of the reagents. Given the low cost of the acid chloride and its simple purge following aqueous quench

Table 1. **Predicted yield (%) of acylation product 5 as a function of temperature and water**

	% H_2O in starting material (**4**·HCl)			
T (°C)	0.5	1	2	4
5	99	92	83	65
15	99	95	85	70
25	99	97	87	74
35	99	98	89	77

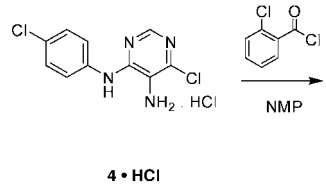
and product crystallization, we chose to use this reagent in slight excess (1.2−1.3 equiv). The kinetic experiments also examined hydrolysis of the acid chloride, a potential competing side reaction if water is present. This is also a second-order reaction, first order in both acid chloride and water. At relatively modest water content relative to **4**·HCl (e.g., 0.5−4.0 wt %, or 8−65 mol % relative to **4**), the observed rate is comparable to the rate of the desired acylation. Table 1 shows the predicted reaction yield as a function of water content and temperature (0.5 to 4.0 wt % H_2O). On the basis of these data, the hydrolysis was controlled by specifying the water content of **4**·HCl at not more than (NMT) 1.0%. These results also suggest that there is no advantage to running the acylation below room temperature.

Another aspect of this reaction observed on scale-up to >20 kg was the slow filtration of the acylated product (**5**) following the aqueous quench. One particularly onerous campaign (76 kg scale) required 14 days for filtration, rinsing, and drying of this material. Experiments were pursued to identify other crystalline forms of the product that might crystallize from other solvent systems and offer improved filtrations. With no clear leads identified from these experiments, we chose to pursue a telescoped process in which **5** would not be isolated, but instead taken directly into the piperidine coupling. This would allow us to bypass the problematic filtration of **5** altogether, and was ultimately chosen as the best solution to this problem (*vide infra*).

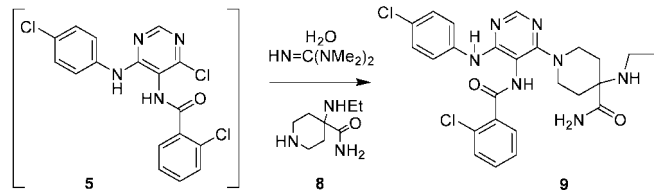


2.3. Preparation of Piperidine-Substituted Pyrimidine 9. A screen of several solvents and bases found that this piperidine−chloropyrimidine coupling was conveniently effected with organic amine bases in alcohol solvents. Triethylamine and isopropanol were used initially. We later changed conditions to *i*-Pr_2EtN (Hünig's base) in *n*-propanol, which offered a modest increase in reaction rate. Upon development of the telescoped process, we returned to NMP so as to be compatible with the acylation (*vide infra*).

The kinetics of this reaction were also studied and were found to be second order overall, first order in both chloropyrimidine (**5**) and piperidine (**8**). As with the acylation, this meant that the reaction slowed dramatically as it approached completion, and use of an excess of one reactant was required to drive the reaction to completion in reasonable times. Because the piperidine is commercially available (albeit more expensive than the acid chloride),[13] it was used in slight excess (1.2−1.3 equiv).



4 • HCl



2.4. Development of a Telescoped Process: Single-Pot Conversion of 4·HCl to 9. Due to the long filtration and drying times encountered with isolation of amide **5**, we sought to develop a telescoped process in which this intermediate was not isolated. Two obvious challenges were apparent: first, identification of a suitable solvent for both reactions, as the *n*-propanol solvent used in the piperidine coupling was clearly not suitable for the acylation. A solvent screen was performed for the piperidine coupling (**5** + **8** → **9**), and NMP was identified as a suitable solvent for this reaction, providing comparable yields, purities, and reaction times as *n*-propanol. Other solvents examined included THF, 2-methyl-THF, acetonitrile and toluene; none of these were suitable due to the limited solubility of **4**·HCl in these solvents. The second challenge was to quench the excess acid chloride present following the acylation, as this would react with piperidine **8** if present during its addition. This was easily achieved by addition of a small volume of water to the NMP solution upon complete acylation.

Selection of a suitable base turned out to be more challenging. The amine bases used in the previous piperidine coupling (e.g., triethylamine or *i*-Pr_2NEt) were of limited utility in the telescoped process, as the piperidine coupling stalled after 75−80% conversion, even with use of excess piperidine. This is presumably due to formation of the hydrochloride salt of the piperidine, which is of comparable basicity to these amines (note that by the end of the piperidine coupling, 3 equiv of HCl are present in the reaction mixture). Some success was realized with stronger, inorganic bases such as NaOH or Na_2CO_3 in aqueous−organic solvent mixtures such as *tert*-amyl alcohol, NMP, or THF. However, reproducibility on scales >5 g and filtration rates were problematic. The best results were obtained with organic amines that were more basic than triethylamine. 1,4-Diazabicyclo[2.2.2]octane (DABCO) and tetramethylguanidine (TMG, $Me_2NC(=NH)NMe_2$) were both effective in this regard, providing >98% conversions. TMG was chosen for further optimization. The optimized process involved dissolution of **4**·HCl in NMP (5 L/kg) and addition of 1.2 equiv of 2-chlorobenzoyl chloride (2-CBC). Upon complete reaction (typically 3−4 h), water was added to quench the excess acid chloride (0.75 L/kg, which is a 10-fold excess relative to the 0.2 equiv of excess acid chloride). This addition was somewhat

(13) Griffith, D. A. WO Patent 2004037823, 2004.

exothermic, and was done at a rate to keep the reaction temperature below 25 °C. Kinetic studies showed that the acid chloride hydrolysis was very fast under these conditions; the solution would be held for 60−90 min to ensure complete hydrolysis. TMG (3.5 equiv) was then added, followed by piperidine **8**. The resulting solution was then heated to 90−100 °C for 4−6 h.

Although this telescoped process worked extremely well in terms of effecting the desired bond formations, we were now faced with a complex solution containing the desired product as well as numerous salts (e.g., TMG-hydrochloride, TMG-2-chlorobenzoate, and some piperidine (**8**)-hydrochloride). Our first solution to this was an extractive workup, in which the reaction solution was diluted with THF and water. At this point a homogeneous solution was observed. Addition of toluene led to phase separation, with much of the NMP residing in the lower, aqueous phase. The product-rich toluene phase was separated, and a second portion of toluene was added to the organic phase, inducing a second separation of residual water and NMP. Finally, the organic phase (consisting primarily of product **9**, some of the excess piperidine **8**, toluene, and THF) was distilled to remove the THF. During this distillation the product began to crystallize from solution. Upon cooling, the product could be isolated as an easily filtered white solid. Subsequent analysis showed that significant levels (15−20%) of piperidine **8** were also present in this material (due to its lack of chromophores, this impurity could not be detected by HPLC, but NMR and GC/MS were able to quantify its levels). We found that a simple reslurry in 10 L/kg of isopropanol at reflux was effective at removing this impurity, and also offered significant purges for several other process-related impurities (see Table 2).

This telescoped process was incorporated into a campaign conducted in the Sandwich pilot plant, and offered a dramatic improvement in processing times. In contrast to the worst filtration encountered on 76 kg scale (14 days for isolation of the acylation product), the telescoped process provided a *two day* processing time for both the acylation and piperidine coupling on 80 kg scale, a time savings of 12 days.

While the telescoped process offered considerable improvement in throughput, it became apparent during planning meetings for process optimization and design of experiment (DoE) work that we had an intimidating number of process parameters to consider during the reaction workup (e.g., addition volumes of water, THF, toluene addition #1, toluene addition #2, rate of heating during distillation, etc.). Having such a large number of parameters suggested that we could face challenges in technology transfer to our commercial manufacturing site, and could have an intrinsically nonrobust process. Additionally, the phase separation was quite difficult to observe during the extractive workup, and a large volume of toluene (38 L/kg) was required. We knew that a more attractive product isolation method would involve addition of an antisolvent to the reaction solution such that the product crystallized directly and could be isolated without requiring the multiple operations in the extractive workup.

Several antisolvents were screened, and we ultimately focused on water/THF mixtures. Optimization of the volumes and addition rates led to a process in which the crude reaction solution was diluted with a 75:25 (v/v) THF/water solution at ambient temperature, followed by slow addition of water to induce crystallization. This procedure worked well on laboratory-scale (see Experimental Section), but upon a pilot scale-up in the kilo laboratory we encountered a very slow filtration (>24 h on 2 kg scale). We also noted a difference in the crystallization induction during this run: in our laboratory pilots, crystallization typically initiated about one-third of the way through the water addition, whereas in the kilo laboratory campaign, crystallization did not occur until complete water addition, cool down, and seeding (by mechanical scratching of an aliquot). These observations were consistent with the use of equipment which was not seeded (i.e., the reactor was scrupulously clean and had not previously been used for this chemistry), whereas in our laboratory pilots we were in glassware and hoods that had seen this chemistry many times. It appeared that we had produced a supersaturated solution of product in the kilo laboratory campaign, and by the time seed crystals were introduced, a rapid and uncontrolled crystallization resulted.

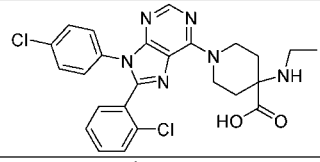
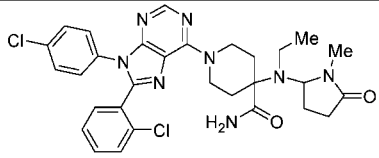
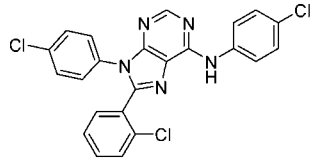
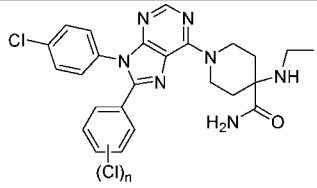
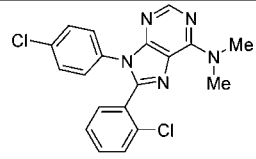
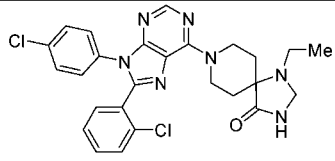
Solubility measurements provided further clarity around what had occurred. Figure 4 shows the thermodynamic solubility (right-hand, solid line) and kinetic solubility (left-hand, dotted line) at 30% water composition. These data were generated by slowly heating a defined concentration of **9** (Form D) in THF/water and recording the temperature at which dissolution was complete; this is represented by the thermodynamic solubility curve. The solution was then slowly cooled, and the temperature at which crystallization occurred was noted as the kinetic solubility (these experiments were performed in laboratories and equipment that had previously been used to run this process, so fall into the "seeded" category relative to the dichotomy discussed above). The red point indicates the region in which seed addition should lead to a controlled crystallization and good filtration rates.

In contrast, Figure 5 shows the situation in the Sandwich kilo laboratory. At the point of complete addition of water we were at 42% water composition and 22 °C. At this point, our mechanical induction of crystallization (by scratching the solution aliquot) was well to the left of the metastable zone that lies between thermodynamic and kinetic solubilities. Thus, the solution was significantly oversaturated, and when crystallization was initiated, it occurred in a rapid and uncontrolled fashion.

The difference in filtration rates was also reflected in photomicrographic analysis of the slow-filtering solids from the kilo laboratory campaign versus a representative, fast-filtering laboratory sample (Figure 6).

On the basis of this analysis, we decided to modify our process to incorporate a seeding protocol, such that we could ensure that crystallization would occur while the solution was in the metastable zone. Four solid-state forms of **9** had been characterized: Form A (anhydrous), Form B (*n*-propanol solvate, not relevant in the current process), Form C (dihydrate), and Form D (THF solvate). It was determined that Forms A and C were soluble in the 30% aq THF system, and thus were not suitable as seed crystals. Form D was less soluble, and could

Table 2. **Impurity summary and control strategy**

Structure	Common Name	Control Strategy	Comments
	Hydrolysis product (**12**)	Specified in API at NMT 0.5%, controlled in crystallization of free base and HCl salt of **1**.	Active metabolite (forms *in vivo*).
	NMP adduct	Qualified in tox studies, specified at NMT 0.5% in API. Controlled in crystallization of free base and HCl salt of **1**.	Appears to form in Step 4 through an undefined oxidative mechanism. Levels of formation are modest (<0.5%) and do not vary by introduction of oxygen or nitrogen.
	Bis-adduct	50-fold purge of initial bis-adduct (**10**, Fig. 3) demonstrated in Step 2/3 and 3R. Controlled by specifying NMT 0.3% of bis-adduct **10** in **4** • HCl.	See Figure 3 and associated discussion.
	Mono-chloro benzoyl chloride isomers (n=1)	4-chloro and 3-chloro isomers show modest purge in Step 3R and are controlled through purchase specs for 2-CBC of NMT 0.2% of each isomer.	Numerous commercial suppliers have successfully met these purchase specs.
	Dichloro benzoyl chloride isomers (n=2)	2,3- and 2,5-dichloro isomers show very little purge in downstream chemistry, and are controlled through a tight purchase spec (NMT 0.1%).	Several commercial suppliers have successfully met these purchase specs.
	Dimethyl-amine adduct	Good purge demonstrated in Step 3R and in Steps 4/5. Controlled in Step 3R through specification of NMT 0.2% for uncyclized precursor.	Formed during piperidine coupling in presence of TMG (Step 3), presumably from *in situ* hydrolysis of TMG to generate dimethylamine.
	M+12	Qualified in tox studies up to 0.5%, not specified in API because current chemistry controls to levels below detection limit.	Forms in Step 4 when run in DMSO (Pummerer-type mechanism). Not observed when NMP is solvent.

be formed from Forms A and/or C by reslurrying in THF. The material from the Sandwich kilo laboratory campaign (ca. 2 kg) was used to generate Form D seed crystals for the commercial pilot campaign in Ireland.

As reflected in Figures 4 and 5, solubility ranges varied with both temperature and $\%H_2O$ composition. Through laboratory experiments and DoE work, we settled on a water content of 30% and a temperature of 40−50 °C (target 45 °C) as our target metastable range in which seed crystals could be introduced without redissolving, and well to the right of the metastable zone limit (i.e., the point at which an uncontrolled crystallization could occur).

This modified, seeded process was incorporated during the first run in our commercial manufacturing pilot plant on 75 kg scale. Upon completion of the telescoped reaction sequence, 3:1 THF/water was added, the solution was heated to 45 °C, and the appropriate volume of water was added to bring the solution to 30%. Form D seed crystals (0.5 wt %) were then added, followed by gradual cooling to 5 °C over 3 h. Using this protocol, reasonable filtration and rinse times were realized, with the caveat that cleaning of the filter-dryer between batches was necessary to prevent blinding of the filter (i.e., a "heel effect" was observed).

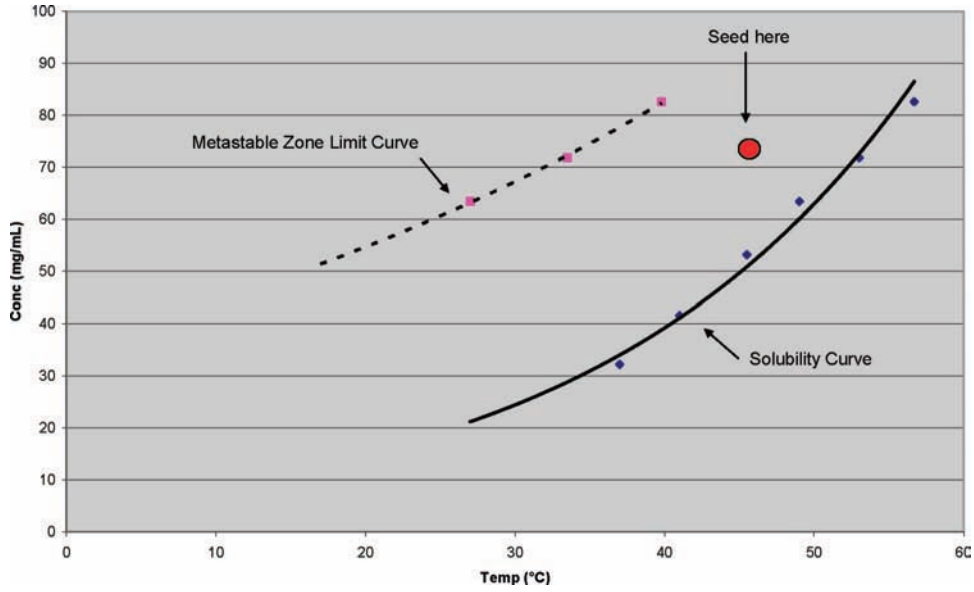


Figure 4. **Kinetic vs thermodynamic solubilities of 9 (Form D) in 30% aq THF.**

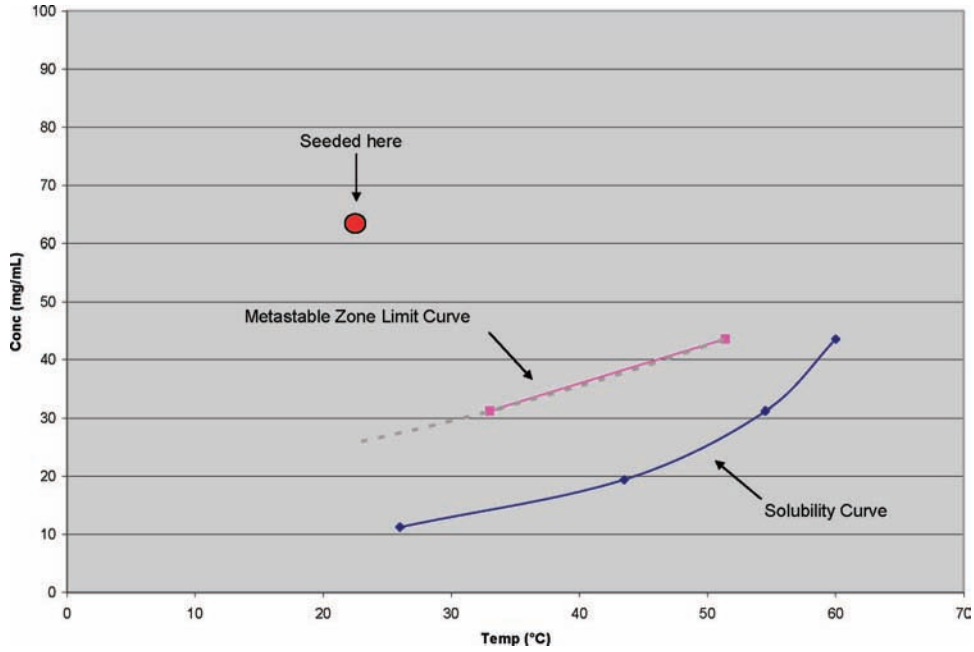
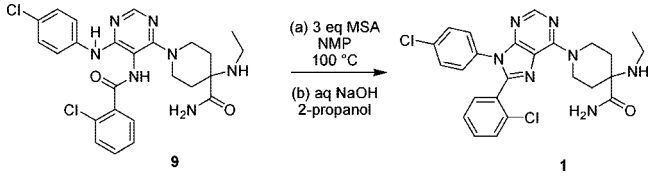


Figure 5. **Kinetic vs thermodynamic solubilities of 9 (Form D) in 42% aq THF.**



2.5. Preparation of CP-945,598 (1). The first two campaigns using the reordered bond-forming sequence (Scheme 2) effected this cyclization with sulfuric acid in hot DMSO. Subsequent studies of a wider range of acids and solvents determined that methanesulfonic acid (MSA) in NMP provided a faster reaction with lower levels of hydrolysis impurity **12** (Figure 7). This impurity was not of tremendous concern, as it purges relatively well in the isolation of **1** (both as free base and again in the salt formation). Additionally, it is an active metabolite formed postdosing in human plasma, and our toxicology studies had qualified it at levels of NMT 0.5% in final API. Nevertheless, the modest reduction in hydrolysis product in NMP relative to DMSO (from 1 to 2% to <0.2%) offered an improvement in product yield. It also raised the interesting possibility that NMP is acting as a "dummy amide hydrolysis substrate" for the equivalent of water generated in the cyclization, and is in effect serving as a mild dehydrating agent. The acid-mediated hydrolysis of NMP is known (complete hydrolysis is realized by refluxing NMP in concd HCl for 8 h, and product is isolated as the hydrochloride salt of 3-*N*-methylaminobutyric acid).[14] Although we did not observe this ring-opened NMP hydrolysis product, it is possible that upon neutralization and product isolation this material would cyclize to regenerate NMP, or would simply remain dissolved in the basic aqueous mother liquors.

(14) McElvain, S. M.; Vozza, J. F. *J. Am. Chem. Soc.* **1949**, *71*, 896–900.

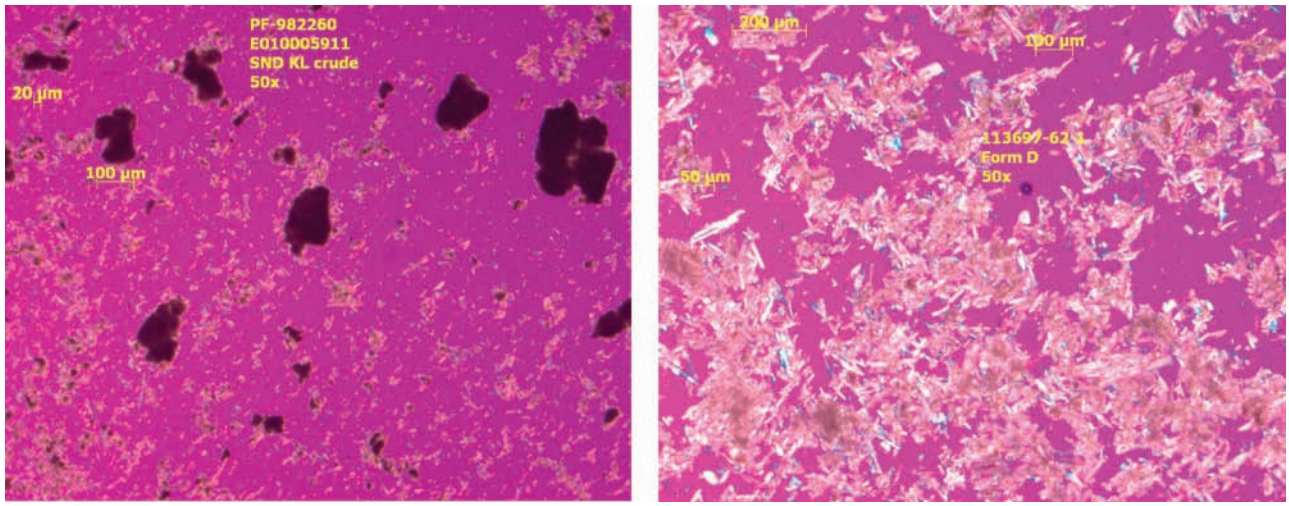
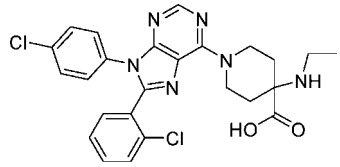


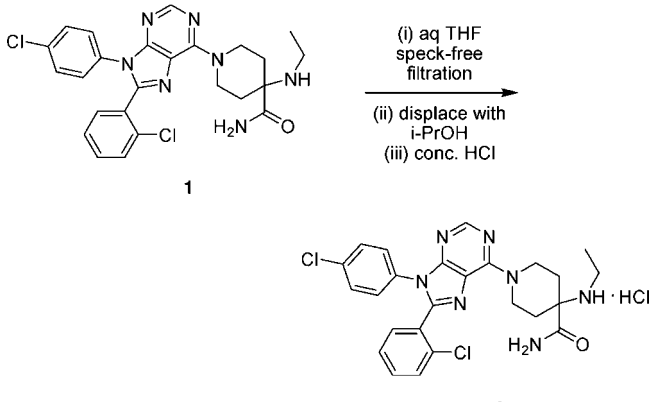
Figure 6. **Photomicrographs of slow (left) and fast (right) filtering solids (both images are at 50× magnification).**



12

Figure 7. **Structure of API hydrolysis product.**

In the H_2SO_4/DMSO reaction, product was isolated by basification with aq NaOH and extraction of free base **1** into Me-THF. Concentration of the organic phase and displacement with toluene brought about crystallization of **1** as the free base in satisfactory yields (e.g., 78% on 50 kg scale). Although effective, this extractive isolation procedure suffered from the requirement for large volumes of organic solvents (up to 50 L/kg), reducing the efficiency and environmental sustainability of the process. We addressed this concern when we switched to the MSA-NMP conditions through identification of a direct crystallization protocol in which the reaction mixture was diluted with isopropanol (5 L/kg) and neutralized with aq NaOH (10 volumes, 3.5 equiv). This induced crystallization of **1** as its free base, and reduced the solvent usage from 50 to 16 L/kg. The isolated yield for this process was typically 90−95%.



1 **1 • HCl**

2.6. Preparation of CP-945,598-01 (1·HCl). Several protocols were developed to deliver the hydrochloride salt as the desired polymorph (Form A); these procedures changed over time, reflecting the scale of API manufacture, equipment train utilized, and stage of development. The early campaigns utilized a two-stage salt formation: addition of concd HCl to the free base in THF generated the HCl salt as a mixture of three less stable polymorphs. A reslurry in aq isopropanol converted this mixture to Form A, the desired, thermodynamically stable polymorph.

Although reliable, this two-stage salt formation was less preferred than a single-pot method, which would improve throughput and decrease solvent waste streams. We found that salt formation in aq isopropanol reliably delivered Form A in a slurry (to solution)-to-slurry conversion. The free base was combined with isopropanol (30 L/kg) and water (2 L/kg) and heated to 60 °C, at which point a slurry was observed. Hydrochloric acid (12 N, 1.3 equiv) was then added, at which point dissolution occurred. After 15−30 min, the HCl salt began to crystallize from solution, which was then cooled gradually to 20 °C over 1−2 h, and the product was collected by filtration.

It is standard cGMP practice to perform a final filtration of the API (or a near precursor) to remove any fibers or particulate matter that may have been introduced in earlier operations. We refer to this as a "speck-free filtration." In the salt formation described above, the speck-free filtration was performed during a recrystallization of the free base (**1**) from THF and toluene. The free base was dissolved in THF and water, passed through a microfilter, and then displaced with toluene to precipitate the anhydrous free base. This material was then handled under speck-free conditions prior to being used in the isopropanol salt formation. It bears noting that all solvents introduced after the speck-free filtration must themselves be speck-free filtered prior to use.

During tech transfer discussions with our colleagues in Pfizer's commercial manufacturing pilot plant in Ringaskiddy, Ireland, they expressed a strong desire to move the speck-free filtration to a point during the final salt formation, thus avoiding the need to handle a solid intermediate under speck-free conditions. This change was also driven by the fact that the free base recrystallization was no longer needed as a purity control point, as the Step 3R isopropanol reslurry was now our primary control gate for impurities. Thus, we developed a third salt formation procedure in which the free base hydrate (the product of Step 4 prior to the THF/toluene recrystallization) was dissolved in aq THF and heated to effect dissolution. Speck-

Table 3. **Commercial pilot plant campaign in Ringaskiddy, Ireland**

step number (product)	yield (%)
1 (**4**·HCl)	86
2/3 (**9**)	80
3R (**9**)	89
4 (**1**)	94
5 (**1**·HCl)	95
overall yield	**55**

free filtration was done at this stage, followed by a solvent displacement with isopropanol to a defined specification of residual THF and water (determined by NMR and Karl Fischer titration, respectively). The appropriate volume of water was then reintroduced, followed by concd HCl. Seed crystals were also introduced to ensure formation of the desired polymorph. This procedure represents the current salt formation and is included in the Experimental Section.

2.7. Impurity Control. Detection, identification, and control of impurities in the API are of primary importance during the development of any drug candidate. Table 2 summarizes several key impurities that have been identified during the development process. It is interesting to note that most of the impurities shown are formed at some point in the synthesis, with the exception of the chloro and bis-chloro isomers introduced with the 2-chlorobenzoyl chloride. Because a rather modest purge of these impurities was observed in the isopropanol reslurry (Step 3R), our control strategy requires controlling the isomer levels at point of purchase through well-defined purchase specifications.

3. Conclusions

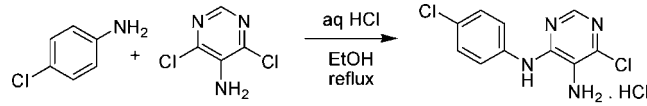
Although the current bond-forming sequence was defined quite early in the development process, numerous changes to the reaction conditions and isolation strategies occurred during the course of the project, as described in this paper. The identification of key issues that require experimental redesign was very much an interactive process involving continuous dialogue among process chemists, analytical chemists, material scientists, supply chain personnel, and Pfizer's commercial manufacturing group. Each of these groups had their own perspective on the project and the associated bulk campaigns, and the optimal solution for one group may present significant technical challenges for another group. Maintaining an open dialogue was critical for arriving at a process that best met the needs of all the groups involved in the project. This optimization strategy has also led to a final API process that is robust and consistently delivers a high-quality API.

Our largest bulk campaign to date was completed in Pfizer's commercial manufacturing pilot plant in Ringaskiddy, Ireland. The outcome of this campaign was quite successful, as summarized in Table 3. A total of 371 kg of API was delivered in four batches, utilizing the route shown in Scheme 4.

Experimental Section

All reactions were run in standard air-dried glassware with magnetic stirring under a static atmosphere of nitrogen unless otherwise noted. Mass spectral data were obtained on a Micromass ZMD mass spectrometer with flow injection analysis and atmospheric pressure chemical ionization (APCI). Reactions were monitored by HPLC analysis using an Agilent 1100 series HPLC equipped with a Zorbax SB-C18 column (4.6 mm × 50 mm), gradient elution from 95:5 to 20:80 (0.5% $HClO_4$ in water)/(acetonitrile) over 11 min, hold for 1 min, then gradient from 20:80 to 95:5 over 5 min; flow rate = 1.0 mL/min, 40 °C, 210 nm detection. Retention times: **4** (6.7 min), **5** (8.9 min), **9** (6.3 min), **1** (7.1 min).

Reagents were purchased from commercial suppliers and used as received. 4-Chloroaniline, 2-chlorobenzoyl chloride, TMG, methanesulfonic acid, and *N*-methylpyrrolidinone were purchased from Aldrich. 5-Amino-4,6-dichloropyrimidine was purchased from Fluka. 4-Ethylamino-4-carboxamidopiperidine (**8**)[15,16] was purchased from Fontarome Chemicals, Milwaukeee, Wisconsin.



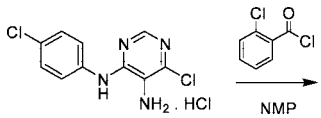
4 • HCl

Step 1: Preparation of 6-Chloro-*N* $_4$ -(4-chlorophenyl)-4,5-pyrimidinediamine Hydrochloride (4·HCl) from 4-Chloroaniline. A three-neck, 12 L round-bottom flask equipped with an overhead stirrer, nitrogen inlet, and reflux condenser was charged with 5-amino-4,6-dichloropyrimidine (1.0 kg, 6.1 mol), 4-chloroaniline (930 g, 7.3 mol, 1.2 equiv) and 2B ethanol (5.8 L) (2B ethanol is anhydrous ethanol denatured from toluene). A portion of 3 N hydrochloric acid (4.0 L, 12 mol, 2.0 equiv) was added, and the slurry was heated to reflux for 36 h. The reaction mixture was cooled, and the solids were collected by filtration, rinsing with 3.75 L of ethyl acetate. After vacuum drying overnight at 40 °C, the product was obtained as a white-to-tan solid, mp 192−196 °C dec (1.5 kg, 84% yield).

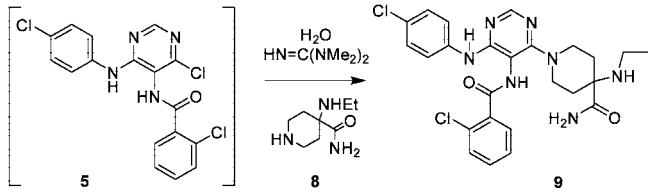
IR (thin film): cm^{-1} 3316, 3224, 2632, 1650, 1604, 1586, 1558, 1491, 1231; ^1H (DMSO-d_6): δ 9.29 (s, 1H), 8.2−7.9 (br s, 2H), 7.88 (s, 1H), 7.80 (d, J = 9, 2H), 7.35 (d, J = 9, 2H). ^{13}C NMR (DMSO-d_6): δ 149.2, 144.7, 139.4, 138.1, 129.0, 127.0, 126.0, 122.8. MS (EI): 255 (100). Anal. Calcd for $C_{10}H_9Cl_3N_4$: C, 41.19; H, 3.11; N, 19.22; Cl, 36.48. Found: C, 41.35; H, 3.00; N, 19.23; Cl, 36.34.

Preparation of 6-Chloro-*N* $_4$-(4-chlorophenyl)-4,5-pyrimidinediamine Hydrochloride (4·HCl) from 4-Chloroaniline Hydrochloride. A single-neck, 25-mL flask equipped with a reflux condenser and nitrogen inlet was charged with 4,6-dichloropyrimidine (2.02 g, 12.3 mmol), 4-chloroaniline hydrochloride (2.45 g, 14.9 mmol, 1.2 equiv), and 2B ethanol (11.7 mL). A portion of 3 N hydrochloric acid (8.1 mL, 24 mmol, 2.0 equiv) was added, and the reaction mixture was heated to reflux for 24 h. The slurry was cooled, filtered, and rinsed with water. After drying in a vacuum oven for 4 h, the product was obtained as a white-to-tan solid (3.15 g, 88% yield). Physical and spectral data matched that of the material prepared by the aniline free base method (above).

(15) Dow, R. L. U.S. Patent 2004110453, 2004.
(16) Ragan, J. A. WO Patent 2006043175, 2006.



4 • HCl



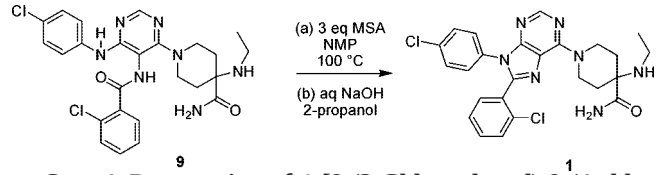
Step 2/3. Preparation of 1-[5-(2-Chlorobenzoylamino)-6-(4-chlorophenylamino)-4-pyrimidinyl]-4-ethylamino-4-piperidine Carboxamide (9). A four-neck, 300-mL round-bottom flask equipped with an overhead stirrer, addition funnel with rubber septum, temperature probe, and a reflux condenser with a nitrogen inlet was charged with NMP (100 mL) and 6-chloro-N_4-(4-chlorophenyl)-4,5-pyrimidinediamine hydrochloride (**4**•HCl) (20.0 g, 68.6 mmol). 2-Chlorobenzoyl chloride (10.4 mL, 14.4 g, 82.1 mmol, 1.20 equiv) was charged to the addition funnel. At ambient temperature, the acid chloride was added over 60 min, during which time the internal temperature remained at 20−25 °C. A 5 mL portion of NMP was used to rinse the addition funnel. The reaction mixture was stirred for 4 h after the addition, at which point HPLC analysis of an aliquot showed complete conversion to 4-chloro-5-(2-chlorobenzamido)-6-(4-chlorophenylamino)pyrimidine (**5**). Water (15 mL) was charged to the addition funnel, and added slowly to the reaction mixture such that the temperature remained <25 °C (addition required ~5 min). The reaction mixture was stirred for an additional 75 min and then treated with TMG (30.2 mL, 27.8 g, 241 mmol, 3.5 equiv), which was added from the addition funnel over 30 min. 4-Ethylamino-4-carboxamidopiperidine (**8**) (15.3 g, 89 mmol, 1.3 equiv) was added in a single portion, and the mixture was heated in an oil bath to an internal temperature of 95 °C for 5 h. Analysis of an aliquot by HPLC showed >98% conversion to 1-[5-(2-chlorobenzoylamino)-6-(4-chlorophenylamino)-4-pyrimidinyl]-4-ethylamino-4-piperidine carboxamide (**9**). The reaction mixture was cooled to ambient temperature. In a separate flask, a solution of THF (220 mL) and water (73 mL) was prepared.

Approximately half of this solution was added to the reaction mixture, which was then transferred to a 1 L Erlenmeyer flask equipped with a magnetic stir bar, rinsing with the remainder of the THF/water solution. The diluted reaction mixture was then treated with an additional 257 mL of water, added dropwise from an addition funnel. The resulting slurry was stirred for 4 h. The solids were collected by filtration, rinsing the flask and washing the filter cake with 1:1 THF/water (100 mL). After air-drying for 4 h, crude product was obtained as an off-white solid (37.8 g, 104%). This material was taken directly into the isopropanol reslurry (next procedure).

Data for 4-chloro-5-(2-chlorobenzamido)-6-(4-chlorophenylamino)pyrimdine (intermediate **5**, isolated in a different experiment): MS (CI): 393 (100); ^{1}H (DMSO-d_6): δ 10.0 (s, 1H), 9.11 (s, 1H), 8.40 (s, 1H), 7.93 (dd, J = 7, 2, 1H), 7.66−7.40 (m, 7H).

Step 3R: Reslurry Purification of 1-[5-(2-Chlorobenzoylamino)-6-(4-chlorophenylamino)-4-pyrimidinyl]-4-et hylamino-4-piperidine Carboxamide (9). A four-neck, 1-L round-bottom flask equipped with an overhead stirrer, reflux condenser with nitrogen inlet, and a temperature probe was charged with **9** (35.33 g) and isopropanol (353 mL, 10 mL/g). The slurry was heated in an oil bath to an internal temperature of 80 °C and held at that temperature for 22 h, after which it was then cooled to ambient temperature and stirred for 2 h. The solids were collected by filtration, rinsing with 200 mL of isopropanol. After drying in a vacuum oven at 25−30 mm and 46 °C, the product was obtained as a white powder, mp 218−221 °C (Form A, anhydrous) (29.61 g, 84%).

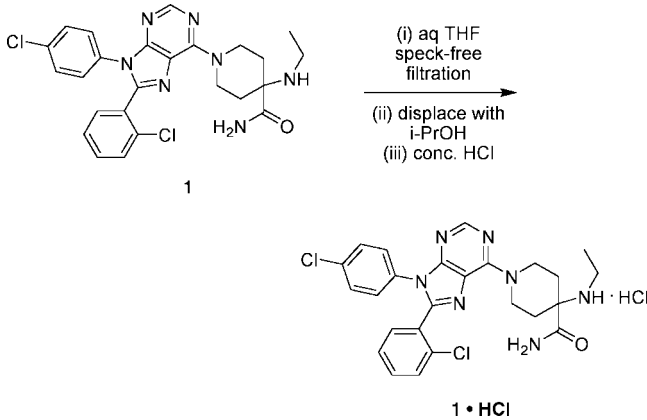
The following data are for Form D, the THF solvate of **9**, which is obtained by refluxing in 7:3 THF/water for 3−6 h: ^{1}H (DMSO-d_6): δ 9.70 (s, 1H), 8.17 (s, 1H), 7.99 (s, 1H), 7.67 (dd, J = 7, 2, 2H), 7.59−7.57 (m, 2H), 7.54−7.47 (m, 2H), 7.32 (dd, J = 7, 2, 2H), 7.26 (br s, 1H), 6.96 (s, 1H), 3.76−3.72 (m, 2H), 3.47 (br t, J = 10, 2H), 2.33 (t, J = 7, 2H), 2.01−1.98 (m, 1H), 1.87−1.82 (m, 2H), 1.56−1.52 (m, 2H), 0.99 (t, J = 7, 3H). ^{13C} NMR (DMSO-d_6): δ 178.5, 165.9, 160.8, 158.0, 155.3, 139.6, 136.4, 132.2, 131.0, 130.7, 129.7, 129.1, 128.0, 126.4, 122.5, 100.5, 59.8, 43.4, 37.5, 33.0, 16.4. MS (CI): 528 (100). Anal. Calcd for $C_{25}H_{27}Cl_2N_7O_2$•C_4H_8O: C, 58.00; H, 5.87; N, 16.33. Found: C, 57.58; H, 5.72; N, 16.72.



Step 4. Preparation of 1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-4-piperidine Carboxamide (1). A 50-L, glass-lined reactor was charged with 1-[5-(2-chlorobenzoylamino)-6-(4-chlorophenylamino)-4-pyrimidinyl]-4-ethylamino-4-piperidine carboxamide (**9**) (1.80 kg, 3.14 mol) and NMP (4.98 L). The resulting solution was stirred at 25 °C for 20 min. Methanesulfonic acid (906 g, 9.43 mol, 3.0 equiv) was then added in three equal portions of 302 g each over approximately 15 min. The reaction mixture was heated to 100 °C and held at that temperature for 4 h. The reaction mixture was then cooled to 35 °C over 45 min and sampled for HPLC analysis (acceptance criteria NMT 1.0% starting material, result was 0.36%). The reaction mixture was stirred at 25 °C for 2 h while the analysis was conducted. 2-Propanol (9 L) was then added over 25 min, followed by NaOH (377 g, 9.42 mol, 3.0 equiv) dissolved in 18 L of water. The caustic solution was added over 35 min. The pH of the solution was checked to ensure complete acid neutralization (pH was 8.5). The resulting slurry (solids precipitated during the base addition) was stirred for 2−4 h, then filtered on a 14-in. Nutsche filter fitted with a poly cloth. The solids were washed with 7:3 (v/v) isopropanol/H_2O (18 L) and pulled dry, then transferred to a vacuum oven (45 °C, 25−30 mm) to yield the product as a white to off-white solid, mp 141−143 °C (Form C, monohydrate) (1.4 kg, 84%).

IR (thin film) cm^{-1} 3475, 3286, 2976, 1678, 1495, 1334, 1265, 1091; ^{1}H (DMSO-d_6): δ 8.23 (s, 1H), 7.70 (dd, J = 8, 2, 1H), 7.51−7.41 (m, 4H), 7.33−7.30 (m, 2H), 7.00 (br s, 1H),

5.0−3.5 (br m, 4H), 2.39−2.36 (m, 2H), 2.11−2.09 (m, 1H), 1.89−1.84 (m, 2H), 1.65−1.62 (m, 2H), 1.02 (t, J = 7, 3H). ^{13C} NMR (DMSO-d_6): δ 178.4, 153.8, 153.5, 152.5, 146.0, 133.8, 133.72, 133.67, 133.6, 132.7, 130.1, 129.9, 129.7, 129.6, 128.0, 119.4, 60.0, 37.6, 33.0, 26.1, 16.4. MS (CI): 510 (100). Anal. Calcd for $C_{25}H_{25}Cl_2N_7O \cdot H_2O$: C, 56.82; H, 5.15; N, 18.55. Found: C, 56.86; H, 5.21; N, 18.36.



Step 5. Preparation of 1-[8-(2-Chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-4-piperidine Carboxamide Hydrochloride (1·HCl). To a clean, dry, and nitrogen-purged 100-L glass-lined reactor was charged THF (6.73 L), water (358 mL), and 1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-4-piperidine carboxamide (**1**) free base monohydrate (716 g, 1.35 mol). The solution was warmed to 35−45 °C until homogeneous and was then transferred to a clean, dry, and nitrogen-purged glass-lined 50 L reactor through an inline 0.5 μm Pall filter, rinsing with an additional portion of THF (1.43 L). Isopropanol (7.16 L) was added, and the mixture was heated to 80−90 °C to distill off THF to a pot volume of approximately 7 L. The reaction mixture was then cooled to 70 °C and an additional 7.16 L of isopropanol was added. The distillation process was repeated. A third portion of 7.16 L of isopropanol was added, and the distillation was repeated a third time. The reaction mixture was cooled to 70 °C, and a final portion of isopropanol (5.73 L) was added. In a 2 L Erlenmeyer flask, 3 N HCl was prepared by addition of water (859 mL) and concd HCl (152 mL). Approximately 20% (226 mL) of this HCl solution was added to the reaction vessel over 15−20 min. The reaction mixture was further cooled to 60 °C, and a sample was pulled for KF and residual THF analysis (^{1}H analysis showed a 172:1 (0.6%) molar ratio of isopropanol to THF; KF analysis showed 0.13% water). Seed material (**1**·HCl, Form A) (7 g, 1 wt %) was then added, followed by the remaining 3 N HCl (approximately 785 mL) over 15−20 min. The solution was stirred at 60 °C for 4 h, then cooled to 25 °C over 1.5−2 h. Solids were collected by filtration, rinsing with isopropanol (1.79 L). After drying for 16 h in a vacuum oven, the product was obtained as a white solid, mp 275−276 °C dec (676 g, 88%).

IR (thin film): cm^{-1} 3332, 2949, 1691, 1578, 1562, 1493, 1332, 1291, 1259, 1090; ^{1}H (DMSO-d_6): δ 9.47 (br s, 2H), 8.30 (s, 1H), 8.11 (s, 1H), 8.00 (s, 1H), 7.71 (dd, J = 7, 1, 1H), 7.53−7.43 (m, 4H), 7.34−7.30 (m, 2H), 5.2−3.5 (br m, 4H), 2.87−2.86 (m, 2H), 2.47−2.43 (m, 2H), 2.03−1.98 (m, 2H), 1.25 (t, J = 7, 3H). ^{13C} NMR (DMSO-d_6): δ 170.1, 153.7, 153.5, 152.6, 146.5, 133.9, 133.8, 133.5, 132.8, 130.2, 129.8, 129.7, 129.6, 128.1, 119.5, 112.5, 63.9, 38.5, 30.6, 12.3. MS (CI): 510 (100). Anal. Calcd for $C_{25}H_{25}Cl_2N_7O \cdot HCl$ (Form A, anhydrous): C, 54.91; H, 4.79; N, 17.93; Cl, 19.45. Found: C, 54.77; H, 4.66; N, 17.83; Cl, 19.54.

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