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Overall Synthesis of GSK356278: Quick Delivery of a PDE4 Inhibitor Using a Fit-for-Purpose Approach

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Abstract:

The family of phosphodiesterase (PDE) enzymes hydrolyse cyclic nucleotides, cAMP and cGMP, leading to their inactivation as intracellular second messengers. Inhibition of these enzymes leads to an elevation of levels of cyclic nucleotides in the cell and prolongs their action on downstream signaling pathways. PDE4, of which there are four subtypes, is widely expressed throughout the brain but is also abundant in the periphery in inflammatory and immune cells, in the gastrointestinal tract, and in cardiac myocytes. GSK356278 1 is a potent, selective, and competitive inhibitor of PDE4 enzymes currently under investigation for the treatment of CNS disorders. The initial synthetic route developed by Medicinal Chemistry Department, used several hazardous and/or expensive reagents and harsh conditions and gave relatively low yields. By targeted process of research and development plus application of analytical techniques to identify byproduct and extensive route scouting, a novel synthetic route for 1 has been developed. This contribution reports the optimisation of the chemical synthesis of 1 to develop a large-scale process suitable for its synthesis.

1. Introduction

The family of phosphodiesterase (PDE) enzymes hydrolyse cyclic nucleotides, cAMP and cGMP, leading to their inactivation as intracellular second messengers. Inhibition of these enzymes leads to an elevation of levels of cyclic nucleotides in the cell and prolongs their action on downstream signaling pathways. PDE4, of which there are four subtypes, is widely expressed throughout the brain, but is also abundant in the periphery in inflammatory and immune cells, in the gastrointestinal tract, and cardiac myocytes.

Signaling through cAMP has been implicated in the pathophysiology of major depressive disorder (MDD)[1,2] and in the therapeutic action of existing antidepressant drugs.[3,4] Central inhibition of PDE4 may lead to an antidepressant effect in patients with MDD. Clinical evidence for the efficacy of PDE4 inhibitors in MDD comes from seven studies conducted with rolipram in which the drug proved as effective as existing antidepressant medications at reducing symptoms of depression.[5] However, rolipram was not progressed due to poor tolerability.

PDE4 inhibitors are also potent neuroprotective, neuroregenerative, and antiinflammatory agents. The preclinical profile of **1** is consistent with a potential efficacy in mood disorders, anxiety, autistic spectrum disorders, cognitive disorders, and inflammation.

Herein we describe the successful efforts to define a synthetic route for the large-scale manufacturing of **1**.

2. Initial Synthetic Route

The synthetic route employed to synthesise the first small batches of **1** is shown in Scheme 1.

2.1. Evaluation of the Route. The initial route[6] consists of a seven-step process with an overall molar yield between 15 and 18%. A preliminary analysis of the synthesis allowed identifying the steps involving harsh conditions, low yields, and hazardous and/or expensive reagents. In particular the steps critical for scale-up were:

- step 1, performed at 160 °C in 25 volumes of $POCl_3$. The purification of the product was achieved *via* a chromatography;[7]
- steps 2 and 3 involved solvent removal to dryness and gave variable yields;
- step 4 used HOBt, a reagent reported having risk of explosion by shock, friction, fire, or other sources of ignition;[8]
- step 5 used dioxane, a class 2 solvent;
- steps 6 and 7 used expensive reagents and gave nonreproducible yields;
- no recrystallisation process was available;
- side chain thiazolyl acetic acid **8** was very expensive;

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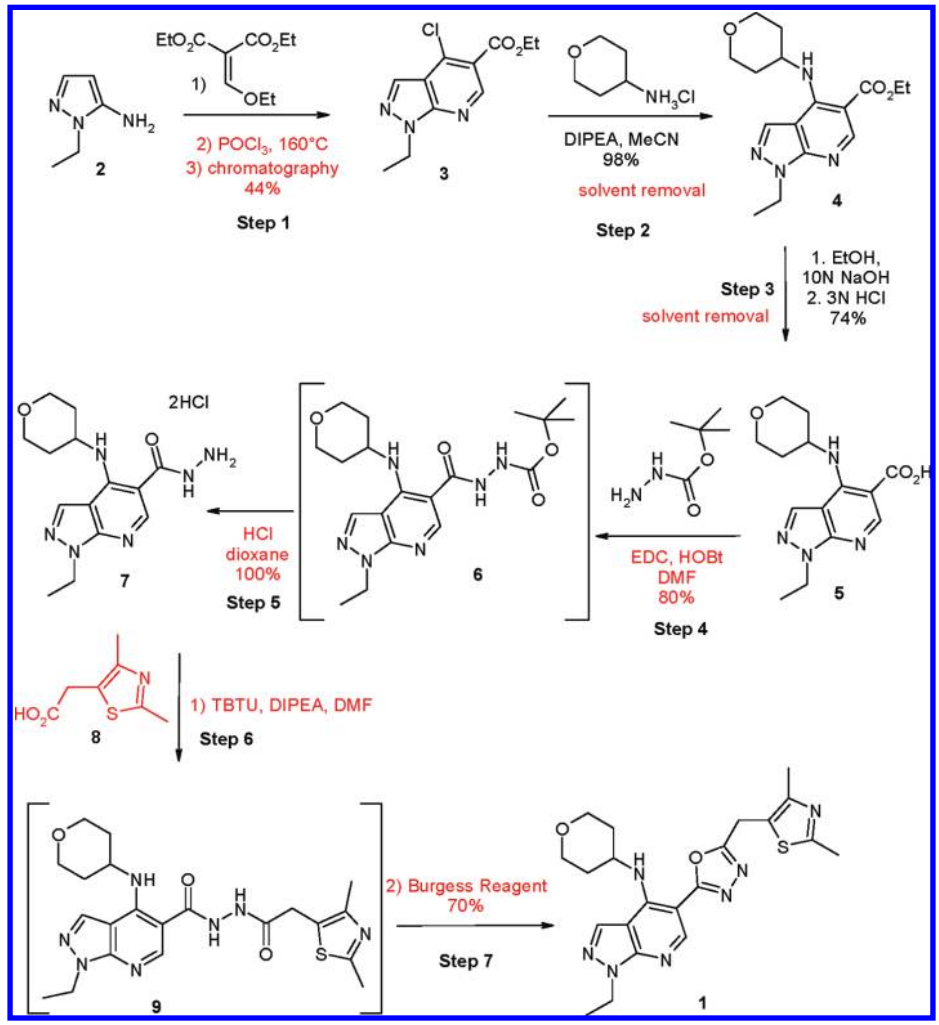
Scheme 1. **Initial synthetic route**



- limited analytical data for intermediates and final drug substance were available.

3. Development of a Practical Synthesis

3.1. Synthetic Strategy. Due to the compressed project timeline it was decided to maintain the same chemical approach for the production of the required batches and to work only on the points identified as the most critical for scalability and cost.

3.2. Steps 1−3 Improvements. In step 1, our first objective was to find alternative milder conditions in which the reaction could be performed working at a temperature lower than 160 °C. Moreover, the removal *via* distillation of several volumes of the corrosive $POCl_3$ and the chromatographic purification, both feasible on a small scale, needed also to be addressed. As a result of a process optimization work, step 1 was divided into two substeps.[9] First, a thermal condensation of amino-pyrazole **2** and diethyl[(ethyloxy)methylidene]propanedioate was performed at 100 °C. Then, the removal by distillation of the ethanol formed allowed the subsequent intramolecular cyclisation to work at a lower temperature (110 °C) and with significantly less $POCl_3$. Pouring the reaction mixture into water to quench the excess of $POCl_3$ led to the crystallization of the product **3** in an improved yield and quality (typically above 98% a/a by HPLC), avoiding also the chromatographic purification.

The issues of step 2 were the removal of acetonitrile at the end of the reaction to allow an aqueous workup and the need to develop a purification step for intermediate **4**. A solvent screening identified 2-propanol (IPA) as a better choice for the chloride displacement by tetrahydro-2*H*-pyran-4-ylamine: the reaction reached completion after 16 h at reflux, and then the desired intermediate **4** crystallized on cooling in high purity (typically above 99% a/a by HPLC).

In step 3, the presence of ethanol as a cosolvent and the large excess of sodium hydroxide used for the hydrolysis of ester **4** prevented the crystallization of the acid **5** from the reaction mixture after the treatment with aqueous HCl. For these reasons, the hydrolysis was performed in water, and the potassium hydroxide was decreased to an almost stoichiometric amount. The acidification of the reaction mixture with 3 N HCl to pH 1.5−2 led to the precipitation of the intermediate **5** in excellent purity (typically above 99% a/a by HPLC). The improvements described above and the presence of crystallised intermediates mean that stages 1−3 now replace steps 1−3 (Scheme 2).

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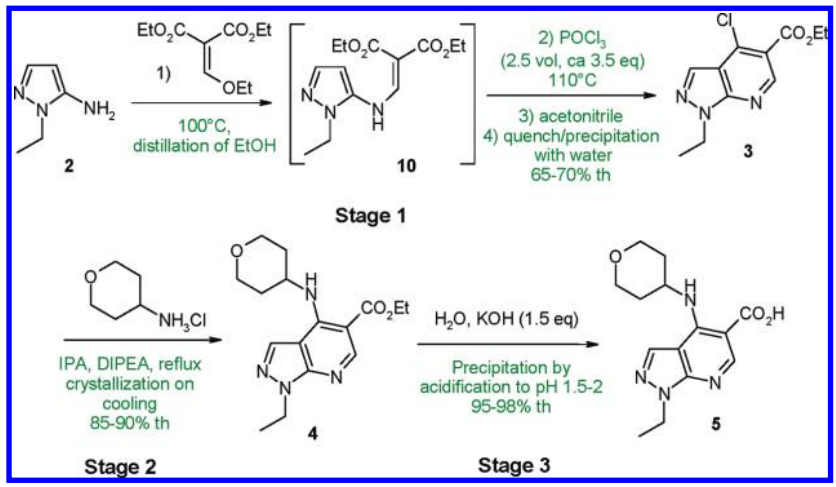
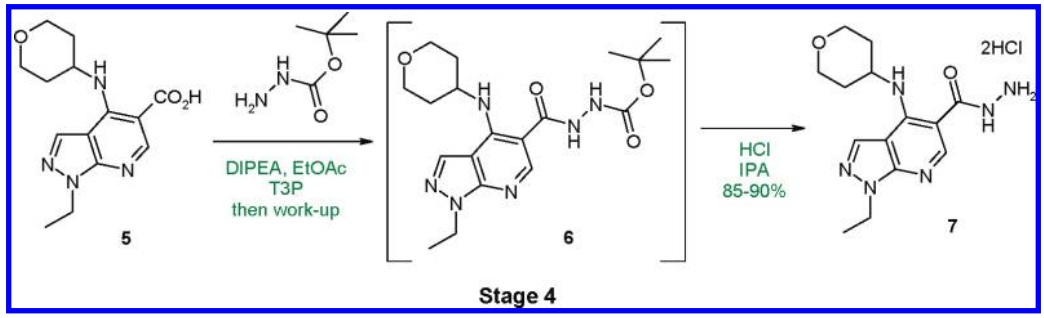
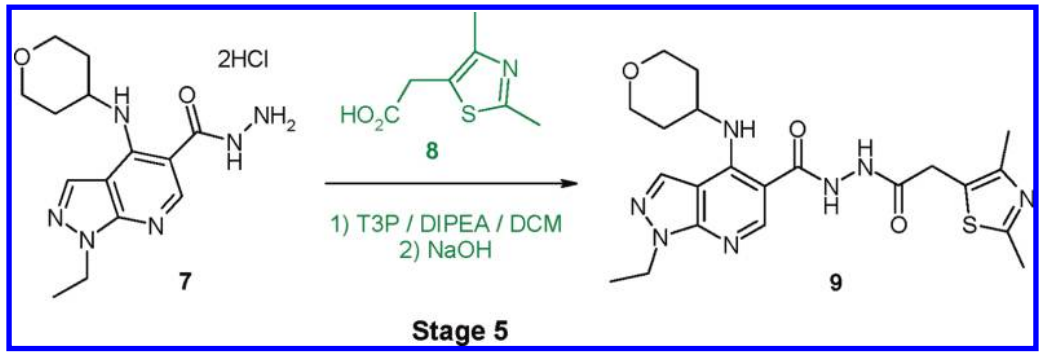
Scheme 2. **Stages 1−3**



Scheme 3. **Stage 4**



Scheme 4. **Stage 5**



3.3. Steps 4−5 Improvements. The coupling between acid **5** and 1,1-dimethylethyl hydrazinecarboxylate initially used 1-hydroxybenzotriazole (HOBt) as a coupling agent. However, HOBt is a rather expensive reagent and suffers from risk of explosion by shock, friction, fire, or other sources of ignition, posing issues with the safety of the process. Based on previous experience on other compounds, commercial propane phosphonic acid anhydride (T3P) solution in ethyl acetate could be used effectively in place of HOBt, increasing also the safety of the process. Indeed, the addition of T3P to a solution of **5** and 1,1-dimethylethyl hydrazinecarboxylate in ethyl acetate in the presence of DIPEA led to the formation of the desired intermediate **6**. Key to reach complete conversion was the slow addition of T3P to a cold solution of acid **5**, hydrazinecarboxylate, and DIPEA. In fact, this procedure allowed minimizing the degradation of the coupling agent due to the interaction with hydrazinecarboxylate.

The cleavage of the Boc group in compound **6** was initially performed with HCl in dioxane, a class 2 solvent. However, since HCl in 2-propanol gave similar results, it was used to replace dioxane. Both changes were combined in a new step called stage 4 (Scheme 3).

3.4. Steps 6−7 Improvements. Similarly to stage 4, T3P in ethyl acetate was tested for the coupling between intermediate **7** and the acid **8** in step 6, thus replacing TBTU. The new conditions allowed improving the yield, avoided the use of toxic dimethylformamide and led to the isolation of compound **9** with a high HPLC purity (typically above 98% a/a HPLC).

Of note, as the new conditions led to the isolation of intermediate **9**, a new stage 5 was introduced in the process (see Scheme 4).

However, unexpected issues came up in the following step 7 due to the formation of a new impurity not detectable by HPLC and presumably formed during the workup of the

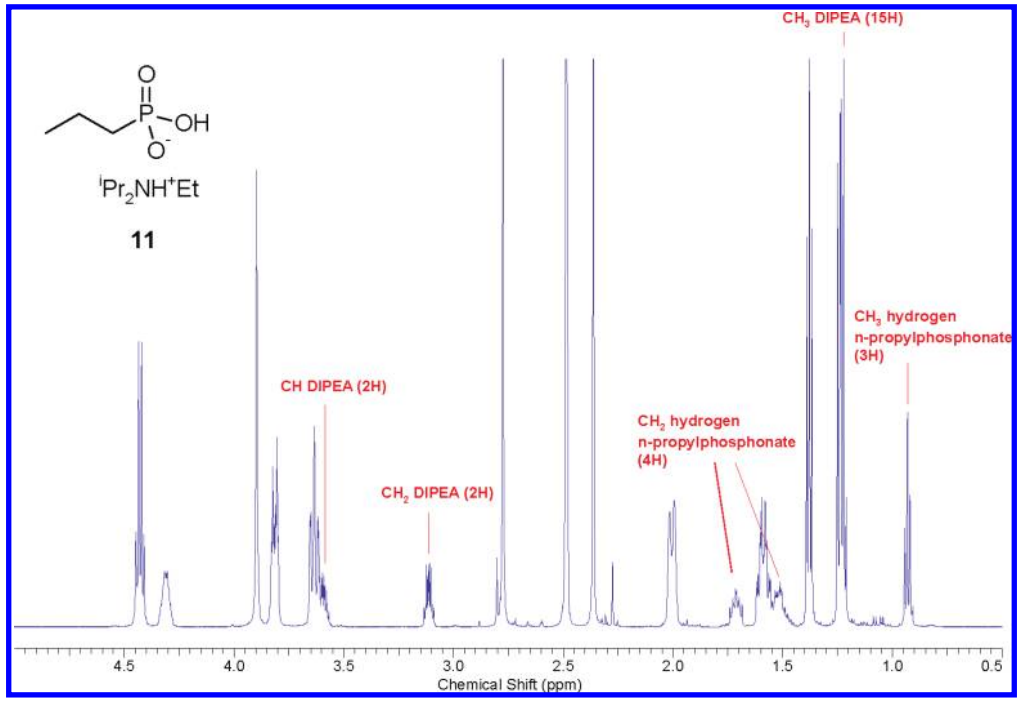


Figure 1. **Proposed structure of the impurity. Note: DMSO-d_6, 600 MHz. The impurity's signals are highlighted.**

Table 1. **Impact of amount of impurity 11 on conversion of step 7**

work-up method	amount of **11** (mol % by NMR)[a]	total impurities containing phosphorus (mol % by NMR)	conversion in step 7 (a/a % by HPLC)
quench with 3 vol $NaHCO_3$ 2% w/w wash with water	23	28	60
quench with 4 vol $NaHCO_3$ 2% w/w wash with water	8	12	85
quench with 5 vol NaOH 2 N reslurry with $NaHCO_3$ 2% w/w	n.d.	3	99
quench with 5 vol $NaHCO_3$ 2% w/w reslurry with water	1	2	98
quench with 5 vol NaOH 2 N reslurry with water	n.d.	8	92

[a] n.d.= not detected.

reaction in stage 5. This impurity, indeed, prevented the cyclization of the open compound **9** to the 1,3,4-oxadiazole **1** from reaching complete conversion. A combination of ^{1}H and ^{31}P NMR experiments led to its identification and to the development of an alternative basic workup for its removal. In particular, the impurity was assigned as the *N*-ethyl-*N*-(1-methylethyl)-2-propanaminium salt of the hydrogen propylphosphonate (**11**, see Figure 1).

This impurity was formed during the quench/hydrolysis of the excess of T3P with diluted sodium hydroxide, and it was not removed during the isolation of the intermediate **9** which followed the water addition. In fact, product **9** showed a poor solubility in all the considered solvents, thus rendering impossible any workup different from the direct precipitation from the reaction mixture.

The presence of impurity **11** affected the conversion of the subsequent cyclization to **1** promoted by Burgess reagent,[10] presumably by interacting with it (see Table 1).

After several attempts, a workup able to minimize (if not completely remove) the impurity **11** was developed. After the quench of the reaction mixture with 2 N NaOH, leading to the precipitation of the product, the solid was collected and washed by reslurry with a 2% w/w $NaHCO_3$ solution. To note: a dramatic change in the appearance of the wet cake was observed in the first reslurry of the solid, from a sticky to a powdery granular solid (purity typically above 98% a/a by HPLC).

As previously mentioned, the cyclization of intermediate **9** to **1** (step 7) in the original synthetic route, was performed with Burgess reagent, which is not only expensive but also unstable and requires storing at about −20 °C to avoid degradation. Trying to find some alternative conditions was fundamental, not only because of the risk associated with its incompatibility to impurity **11** but also because one additional issue arose from the analysis of one of the first toxicological batches prepared using the Burgess reagent. A not negligible amount of an unidentified impurity was present, and this could potentially put at risk the quality of the clinical batch if the same chemistry was applied. Moreover, some dedicated investigations highlighted the existence of a clear link to the usage of the Burgess reagent. However, since it was not possible to elucidate the nature of the impurity in a short time, we decided in line with a fit-for-purpose approach that a change in the chemical method could be a quick win for the timely clinical batch delivery.

As a consequence, after having tested some alternatives, which proved less efficient, tosyl chloride[11] in the presence of DIPEA was selected to promote the cyclization step that was

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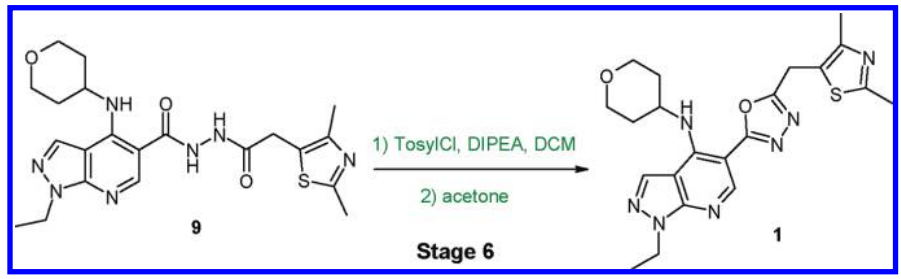
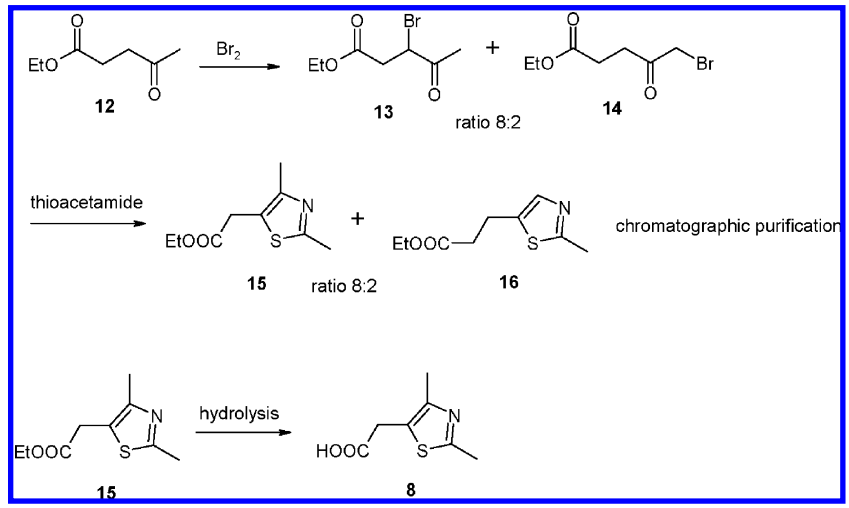
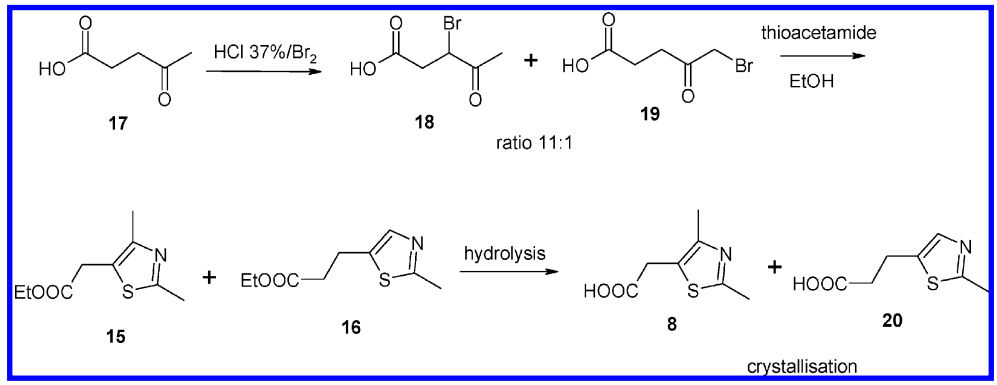
Scheme 5. **Stage 6**



Scheme 6. **Original side-chain 8 synthesis**



Scheme 7. **Current side-chain 8 synthesis**



performed at reflux in dichloromethane. This modification represented a considerable improvement both for the strong cost reduction and for the increased quality of the final API (see Table 4), since the aforementioned byproduct was not formed (Scheme 5).

3.5. Side-Chain 8 Synthesis. A careful optimization of the synthesis of the thiazolyl acetic acid **8** was also carried out. Indeed the original synthetic route (Scheme 6) suffered from poor selectivity in the first step, i.e. the bromination of ethyl levulinate **12** which afforded the two regioisomeric α-bromoketones **13** and **14** in a ratio 8:2 in favor of the desired product **13**. This rendered the synthesis poorly efficient as, after reaction with thioacetamide, a chromatographic purification was required to separate the desired thiazole **15** from the unwanted isomer **16**.

After some literature searches,[12] it was found that starting from levulinic acid **17** instead of ester **12**, not only could a better selectivity in the bromination step be obtained, but also the desired acid **8** could be later selectively crystallized from the reaction mixture, thus avoiding the chromatographic purification and simplifying the process (Scheme 7).

3.6. Recrystallization. A solubility screening was performed in short times to find the appropriate solvents for recrystallization. From the first experiments it was clear that **1** was characterized by a very low solubility in most solvents (Table 2). Solubility was evaluated by HPLC method in pure solvents.

Additional data were obtained in different mixtures of solvents, and at the end of the screening, the results showed that the product could be obtained by a cooling crystallization from anisole or by an antisolvent crystallization at room

(11) Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. *Org. Lett.* **2005**, 4539.

(12) Gouault, N.; Cupif, J.-F.; Amoros, M.; David, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, *20*, 2234.

Table 2. **Solubility of 1 in pure solvent**

	solubility (mg/mL)		
solvent	20 °C	50 °C	80 °C
anisole	14	40	126
toluene	7	20	
cumene	3		13
DMSO	3	9	
acetone	3	7	
MEK	4	16	
MIBK	2	5	
MeOH	3	8	
ethanol	1	10	
1-propanol	2	7	
2-propanol	1	3	
EtOAc	3	7	
iPrOAc	2	4	
water	0	0	
THF	19	44	
DCM	157		

Table 3. **Solubility of 1 in mixture of solvents**

solvent mixtures	(v/v)	solubility (mg/mL) 20 °C
DCM/EtOH	(20/80)	31
DCM/acetone	(20/80)	6
DCM/EtOAc	(20/80)	5

temperature, employing DCM as solvent. Ethanol, acetone, and ethyl acetate were selected as possible antisolvents to be employed with DCM (Table 3).

After several crystallization trials in the lead solvents, the DCM/acetone system came out as the best choice, both for reaction conditions in stage 6 and for recrystallization in stage 7.

3.7. Analytical Methods. Two test batches were fully characterised to evaluate the quality of the material produced by the new fit-for-purpose route. The following analytical techniques were applied: compound identification by nuclear magnetic resonance (NMR), residual solvents by headspace-gas chromatography-flame ionisation detection (HS-GC-FID), water content by Coulometric Karl Fischer titration, inorganic content by residue on ignition, and organic impurities by reversed-phase high performance liquid chromatography (RP-HPLC). The latter method was able to indicate stability and to separate process impurities, degradants, and the main compound.

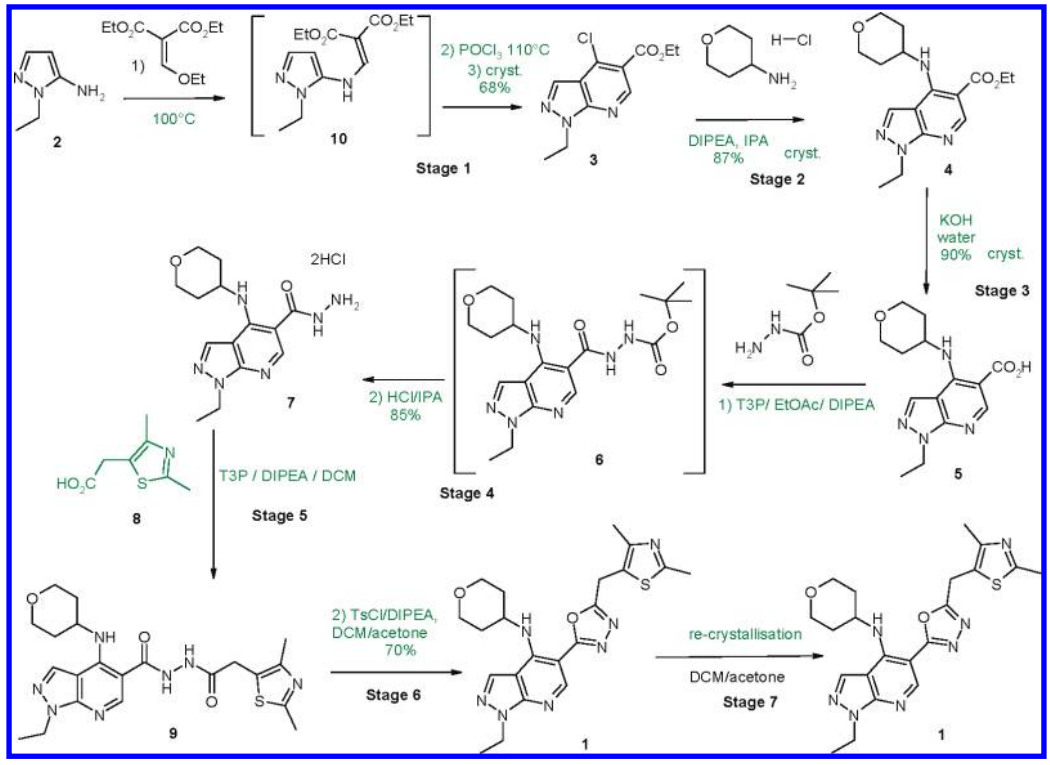
Table 4. **Analytical data overview of two test batches produced with the fit-for-purpose route**

analytical test	batch 1	batch 2
identity by NMR	confirmed	confirmed
content by HPLC (% w/w, water and solvent free basis)	99.8	99.9
total impurities by HPLC (% a/a)	0.14	0.12
residual solvents by GC (% w/w)		
total	0.80	0.40
individual[a]		
dichloromethane (DCM)	0.66	0.33
acetone	0.12	0.06
diisopropylethylamine (DIPEA)	0.02	0.01
water content by KF (% w/w)	<0.10	<0.10
inorganic content by residue on ignition (% w/w)	<0.10	<0.10

[a] Individual solvent contents do not exceed the Permitted Daily Exposure limit permitted by ICH Q3C based on the maximum daily dose of GSK356278 administered.

The analytical data obtained for both batches demonstrated that the newly developed synthetic route was reproducible, all major impurities were identified and under control (Table 4). The fit-for-purpose route allowed production of highly pure material suitable to support clinical trials.

Scheme 8. **Optimized synthetic route to 1**



4. Conclusions

The current process comprises simpler conditions, no chromatographic purifications, no solvent swaps, cheaper and safer reagents, reproducible and robust conditions, higher yield, and better analytical control, in particular:

- overall yield doubled to about 30%
- mass productivity (amount of product obtained divided by amount of all reagents/solvents used) increased from 0.18% to 0.7%
- current material cost decreased by more than 50%, reaching the target cost of goods

All the optimisation studies were completed in approximately two months with a limited number of resources.

The new process (Scheme 8) appeared reliable and was successfully scaled up twice on kilogram scale of final API **1** in high yield and excellent purity to support clinical studies, and it could be further scaled up to support future project needs.

Experimental Section

All materials were obtained from commercial suppliers and used without further purification. All reactions were carried out under nitrogen atmosphere. HPLC measurements were performed on an Agilent 1200 series binary LC system, using the following generic acidic HPLC methods:

1. column type: Zorbax SB-C18, 3 mm × 50 mm, 1.8 μm; mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; linear gradient from 100% A to 95% B over 3 min at 60 °C; flow 1.5 mL/min; detector UV DAD @220 nm
2. column type: Luna C18; mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; linear gradient from 100% A to 95% B over 8 min at 40 °C; flow 1 mL/min; detector UV DAD @220 nm.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 600 spectrometer; ^{31}P NMR spectra were recorded on a Varian Inova 300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced to either $CDCl_3$ or DMSO-d_6 (7.27 and 2.50 ppm for ^{1}H NMR, and 77.00 and 39.51 ppm for ^{13}C NMR, respectively); ^{31}P NMR spectra were referenced to external H_3PO_4 85% (0 ppm).

IR spectra were recorded on a Bruker Vertex 70 spectrometer in attenuated total reflectance (ATR) mode with 2 cm^{-1} resolution.

Ethyl 4-Chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3). 1-Ethyl-1*H*-pyrazol-5-amine **2** (1 kg) and diethyl [(ethyloxy)methylidene]propanedioate (1.9 L) were heated to reflux (internal temperature ~100 °C) for 1.5 h; then ethanol was removed *via* vacuum distillation.

$POCl_3$ (2.5 L) was added and the mixture heated to reflux (internal temperature ~110 °C) for 3.5 h. The mixture was cooled to 20 °C, acetonitrile (1 L) was added, and then the solution was further cooled down to 10 °C.

The mixture was added dropwise to cold (about 10 °C) water (16 L), keeping the internal temperature below 20 °C. Acetonitrile (1 L) was used to wash the line.

The obtained suspension was stirred for about 20 h, then the solid was collected by filtration, washed with water (4 × 3 L) and dried under vacuum at 50 °C overnight to obtain compound **3** as a pale-brown solid (1.6 kg), overall yield of 70% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.42 (s, 1H), 4.53 (q, J = 7.2 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H); HPLC purity typically above 98% a/a.

Ethyl 1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4). Compound **3** (1.6 kg), tetrahydro-2*H*-pyran-4-amine hydrochloride (0.918 kg) and iPr_2EtN (3.22 L) were combined in 2-propanol (4.830 L) and heated to reflux for 22 h.

The solution was cooled down to 50 °C and seeded with compound **4** (1.61 g).

After 1 h at 50 °C the slurry was cooled down to 0 °C in 2 h and stirred for about 4 h. The solid was collected by filtration, washed with cold 2-propanol (0 °C, 2 × 3.22 L), and dried under vacuum at 50 °C to obtain compound **4** as a white solid (1.735 kg); overall yield about 86% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.23 (d, J = 8.0 Hz, 1H), 8.72 (s, 1H), 8.24 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.24 (m, 1H), 3.85 (td, J = 3.7, 11.7 Hz, 2H), 3.64 (td, J = 2.2, 10.2 Hz, 2H), 2.03 (m, 2H), 1.57 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H); HPLC purity typically above 99% a/a.

1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (5). Solid **4** (1.735 kg) was suspended in water (8.67 L); solid KOH (0.451 kg) was then added and the suspension heated to 75 °C for about 1 h.

The mixture was cooled down to 20 °C, and HCl 3 N (2.6 L) was added until pH was 1.5−2. The slurry was aged for about 19 h, and then the solid was collected by filtration, washed with water (2 × 5.2 L), and dried under vacuum at 50 °C for 24 h to obtain compound **5** as a white solid (1.523 kg); overall yield 96% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 9.50 (d, J = 7.9 Hz, 1H), 8.71 (s, 1H), 8.22 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.24 (m, 1H), 3.85 (m, 2H), 3.64 (t, J = 10.2 Hz, 2H), 2.03 (d, J = 12.3 Hz, 2H), 1.55 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); HPLC purity typically above 99% a/a.

1-Ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide Dihydrochloride (7). Compound **5** (1.523 kg), 1,1-dimethylethyl hydrazinecarboxylate (0.838 kg), iPr_2EtN (4.11 L) and EtOAc (3.05 L) were charged in the vessel and cooled to 5−10 °C. Commercial T3P 50% w/w in EtOAc (6.85 L) was slowly added in about 1.5 h. The solution was then heated to 25 °C and stirred for 1 h. Aqueous potassium carbonate 10% w/w solution (7.6 L) was added, the mixture was stirred and then the phases were separated.

The aqueous phase was back-extracted twice with EtOAc (2 × 7.6 L), and then the combined organic layers were concentrated under vacuum to about 4.5 L. EtOAc (7.6 L) was added and the solution concentrated again under vacuum to about 4.5 L. The suspension was filtered to remove some

inorganic solid and washed with EtOAc (1.5 L). HCl 5−6 N in 2-propanol (7.6 L) was added, obtaining a thick suspension. The suspension was heated to 50−55 °C (internal temperature) for about 1.5 h, then cooled to 20 °C, and aged overnight. The solid was collected by filtration, washed with 2-propanol (2 × 4.5 L), and dried under vacuum at 50 °C for several hours to obtain compound **7** (1.93 kg) as a white solid, overall yield 97% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 11.81 (br s, 1H), 9.9 − 11.2 (br, 2H), 9.78 (d, J = 7.1 Hz, 1H), 8.73 (s, 1H), 8.36 (s, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.30 (m, 1H), 3.84 (m, 2H), 3.66 (m, 2H), 2.04 (m, 2H), 1.58 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H); HPLC purity typically above 98% a/a.

3-Bromolevulinic Acid (18). Levulinic acid **17** (1 kg, 8.61 mol, 0.885 L, 1 equiv) was dissolved in 37% HCl (2.5 L). Bromine (1.45 kg, 9.10 mol, 0.4665 L, 1.05 equiv) was added dropwise over 2 h at −5 °C, and the reaction mixture was slowly warmed up to room temperature (using a water bath). The dark-brown reaction mixture turned yellow at about 18 °C, and after stirring for additional 3−4 h (at room temperature) precipitation of a white solid was observed. After cooling to 0 °C, water (9−11 L) was added, and the white precipitate was filtered off over a P_2 glass funnel. The filtrate was extracted twice with TBME (2 × 4 L each) and dried over Na_2SO_4, and the solvent was evaporated at reduced pressure, affording crude 3-bromolevulinic acid **18** (1.23 kg, 6.31 mol, 73%, ratio 3- to 5-bromolevulinic acid 11:1). In total 11.65 kg of 3-bromolevulinic acid was prepared according to the above-described procedure.

Ethyl-2-(2,4-dimethylthiazol-5-yl)acetate (15). To a solution of 3-bromolevulinic acid **18** (6.2 kg, 31.79 mol, 1 equiv) in EtOH (40 L) was added ethanethioamide (2.6 kg, 36 mol, 1.1 equiv). The clear solution was heated to reflux for 2 h, and after cooling to room temperature the EtOH was evaporated under reduced pressure. The yellow semi-solid residue was dissolved in water (10 L) and extracted with TBME (15 L). The water layer was basified with 25% NH_3 solution (2 L), adjusting the pH to 8, and extracted with TBME (15 L). The organic layer was washed with brine (5 L) and concentrated *in vacuo*, affording crude **15** (3.77 kg, about 60%). The material was used in the next step without further purification.

In total 6.67 kg of crude ethyl-2-(2,4-dimethylthiazol-5-yl)acetate was prepared according to the above-described procedure.

(2,4-Dimethyl-1,3-thiazole-5-yl)acetic Acid (8). Crude **15** (3.77 kg, 18.57 mol, 1 equiv) and KOH (pellets; 1.16 kg, 20.71 mol, 1.1 equiv) were dissolved in MeOH (18 L). The dark-brown reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and water (4 L) was added with stirring (pH = 10). The solution was acidified with 2 N HCl (3 L) to pH = 5.5 (a brown precipitate was formed at pH = 6). The solids were filtered over a P_2 glass funnel and stirred in water (2 L) for 2 h. Subsequently acetone (3 L) was added, and the white precipitate formed was filtered over a P_2 glass funnel. The white wet solids of the final product (3.1 kg) were dried at 45 °C (until water content below 0.5% w/w) affording compound **8** (1.658 kg, 9.34 mol, 64%). Preparation of a second batch according to the above-described procedure furnished **8** (1.55 kg, 9.06 mol, 62%). The filtrate of both batches (30 L) was concentrated and acidified to pH 5.5. The brown precipitate was filtered over a P_2 glass funnel. The solids were stirred in water (5 L) for 2 h and acetone (7 L) was added. After one hour the white precipitate was filtered over a P_2 glass funnel. The white wet solids of the final product (1.14 kg) were dried at 45 °C (until water content below 0.5% w/w), yielding additional compound **8** (0.605 kg, 24%). In total 3.73 kg of the final target was prepared according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 3.69 (s, 2H), 2.53 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 171.5, 162.1, 148.3, 123.0, 31.5, 18.5, 14.6; HPLC purity typically above 98% a/a.

***N′*-[(2,4-Dimethyl-1,3-thiazol-5-yl)acetyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbohydrazide (9).** Compound **7** (1.2 kg) was charged under nitrogen followed by dichloromethane (9.6 L) and iPr_2EtN (2.76 L). The mixture was stirred at 20 °C for about 15 min. Compound **8** (0.66 kg) was added to the suspension, and the mixture was cooled to 5 °C (internal temperature) to add slowly, in about 40 min, commercial T3P solution 50% w/w in EtOAc (2.4 L), keeping the temperature below 10 °C. The suspension was heated to 20 °C, and a solution of sodium hydroxide 2 N (6 L) was added. A solid immediately precipitated, and the suspension was heated to 40 °C for about 1 h, then cooled to 20 °C and aged overnight. The suspension was filtered, and the solid washed with sodium bicarbonate 2% w/w solution (4.8 L) and then three times with water (4.8 L). The solid was dried in the oven at 50 °C overnight to obtain 0.826 kg of the compound **9** as a white solid, overall yield 63% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.28 (s, 1H), 10.11 (s, 1H), 9.64 (d, J = 7.4 Hz, 1H), 8.58 (s, 1H), 8.20 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.20 (m, 1H), 3.83 (td, J = 3.7, 11.7 Hz, 2H), 3.68 (s, 2H), 3.63 (m, 2H), 2.54 (s, 3H), 2.28 (s, 3H), 2.01 (m, 2H), 1.52 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); HPLC purity typically above 98% a/a.

5-{5-[(2,4-Dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (1). Compound **9** (0.82 kg) was suspended in dichloromethane (8.2 L). iPr_2EtN (0.9 L) and tosyl chloride (0.508 kg) were added, and the mixture was heated to reflux for about 1.5 h. The mixture was cooled down to 20 °C, and sodium hydroxide 2 N (4.1 L) was added; the layers were separated, and the organic layer was washed with sodium hydroxide 2N (4.1 L) and water (2 × 4.1 L). The resulting organic layer was concentrated to about 4.9 L, dichloromethane (1.64 L) was added, and then the solution was filtered to remove inorganics, the filter was washed with dichloromethane (0.4 L), and the solution was concentrated again to about 4.9 L. The solution was seeded at 20 °C (4.1 g of **1** suspended in 82 mL of acetone), then acetone (10.66 L) was added in about 1 h and the slurry was aged for 2 h. The solid was collected by filtration, washed with acetone (3 × 2.4 L) and dried under vacuum at 50 °C for about 24 h to obtain 5-{5-[(2,4-dimethyl-

1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine **1** (0.581 kg) as a white solid, overall yield 74% theoretical. The process was repeated twice according to the above-described procedure.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (d, J = 6.7 Hz, 1H), 8.70 (s, 1H), 8.00 (s, 1H), 4.51 (q, J = 7.3 Hz, 2H), 4.36 (s, 2H), 4.23 (m, 1H), 4.07 (td, J = 4.1, 12.0 Hz, 2H), 3.66 (ddd, J = 2.5, 9.8, 12.0 Hz, 2H), 2.65 (s, 3H), 2.45 (s, 3H), 2.19 (m, 2H), 1.84 (m, 2H), 1.52 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 164.1, 161.7, 151.8, 150.0, 148.9, 147.2, 132.8, 121.4, 102.5, 94.8, 66.0, 50.3, 42.2, 33.0, 22.8, 19.1, 15.0, 14.8.

IR (ATR) cm^{-1}: 3261, 1162, 1592, 1524, 1472, 1340, 1252, 1237, 1139, 1087, 1009, 984, 956, 873, 778, 667.

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Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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