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Development of a robust synthesis of dactolisib at the commercial manufacturing scale

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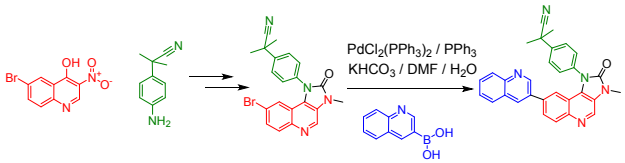

key steps: Suzuki coupling
purification and
Pd removal

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ABSTRACT: The development of the robust synthesis of 2-methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl]-phenyl]propionitrile (dactolisib) at the commercial scale is described. The key step is a Pd-catalyzed Suzuki coupling of 2-[4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile to 3-quinoline boronic acid. A special focus is placed on reducing the amount of Pd catalyst used in the Suzuki coupling and purifying the crude drug substance, including removing traces of Pd.

KEYWORDS: Pd-catalyzed Suzuki coupling; large scale; Pd removal; Smopex-234

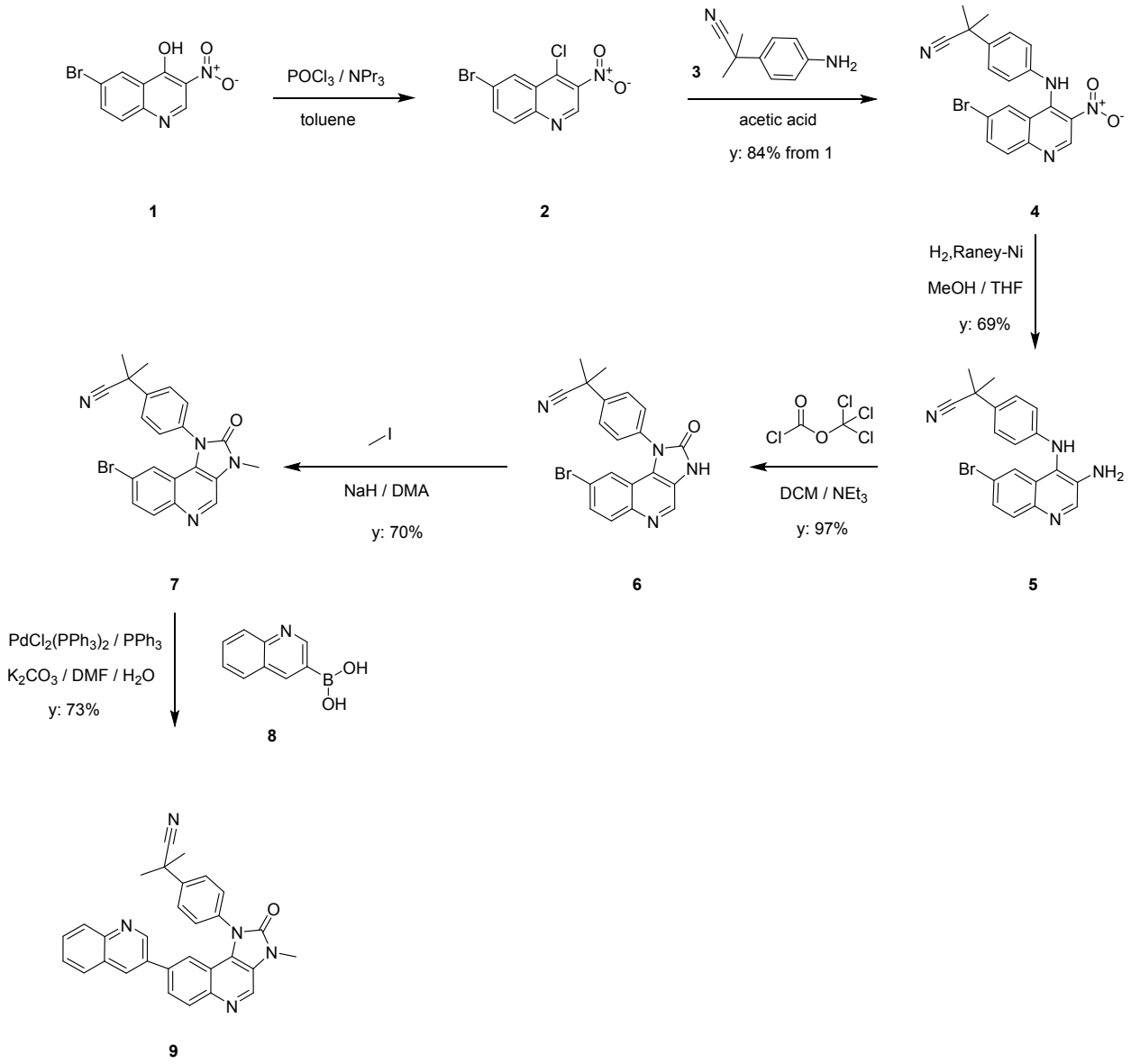
INTRODUCTION

2-methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl]-phenyl]propionitrile (dactolisib; compound **pure 9**, Scheme 4) is a dual kinase inhibitor of phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR).[1] Dactolisib is currently investigated to treat several solid tumor forms[2] and has activity against *Plasmodium falciparum* (malaria)[3] and trypanosomiasis (sleeping sickness), as structural analogs of dactolisib have been reported to show efficacy.[4] Several syntheses of the target dactolisib have been described in the literature.[4,5]

Herein, we report and discuss the synthesis development of dactolisib towards a commercial-scale process that was executed on a several hundred kg scale.

The route to dactolisib starts from the commercially available intermediates 6-bromo-4-hydroxy-3-nitro quinoline (**1**)[5c] and 2-(4-amino-phenyl)-2-methyl propionitrile (**3**)[6]. The free base drug substance was manufactured in 6 steps according to the early phase batch synthesis shown in scheme 1.

In the first early development batch following the research route, intermediate **2** was isolated as an evaporation residue from toluene. The conversion of intermediate **2** with starting material **3** to product **4** was then performed in acetic acid, and product **4** was isolated at an 84 % yield over 2 steps. In the next step, the nitro group of intermediate **4** was hydrogenated with a Raney Ni catalyst at normal pressure to the diamine product **5**, which was isolated and purified via column chromatography at a 69 % yield. Intermediate **5** was converted to product **6** with diphosgene at a 97 % yield. Methylation of intermediate **6** to product **7** with methyl iodide in N,N-dimethylacetamide and NaH as the base resulted in a 70 % isolated yield. The coupling of intermediate **7** with 3-quinoline boronic acid (**8**) required 6 mol % $PdCl_2(PPh_3)_2$ catalyst. The product **9** was then extracted with dichloromethane and purified by several precipitation steps from aqueous media to obtain a purity of > 99 % HPLC area at a 73 % isolated yield (scheme 1).



Scheme 1: First generation synthesis

This synthesis route was considered suitable for further development and a subsequent commercial process. The disconnection strategy to build the structure of dactolisib with three fragments, **1**, **3** and **8**, seemed to be logical and straightforward. The synthetic route is atom economic and does not require protecting groups. All of the intermediates are solids and can be crystallized, which is another advantage of the syntheses shown in schemes 2 and 4. The major

anticipated challenge was to obtain the required purity of the drug substance due to the very low solubility of dactolisib in most organic solvents and to remove the residual Pd to reach the low level of < 2 ppm required for subsequent commercial processes. We also focused on avoiding any column chromatography for purification and replacing undesired solvents, e.g., dichloromethane, or very toxic raw materials, e.g., diphosgene.

RESULTS AND DISCUSSION

Development of the synthesis

In the first step, 6-bromo-4-hydroxy-3-nitro quinoline (**1**) is converted into the 6-bromo-4-chloro-3-nitro quinoline (**2**) with $POCl_3$ as the chlorinating reagent.[7] The aim of our development work was to telescope the two steps from **1** to **4** without isolating unstable intermediate **2** as an evaporation residue as done in previous research and early tox batch synthesis. The intermediate (**2**) is not isolated and directly reacts with starting material **3** to yield product **4**.[8] Hence, starting material **1** was reacted in toluene with 2 equiv of $POCl_3$ in the presence of 1.5 equiv tripropylamine. The reaction was controlled by $POCl_3$ addition, and after the starting material **1** was consumed, toluene and an excess of $POCl_3$ were distilled off. In the first tox batch, 3 equiv of $POCl_3$ had to be used mainly due to the approximately 20 % H_2O present in starting material **1**. Later, the H_2O in starting material **1** was controlled to < 1 % (m/m). A reaction temperature of > 90 °C was necessary to ensure complete and addition-controlled conversion from **1** → **2**; therefore, the higher boiling point tripropylamine (b.p. 156 °C) was used instead of triethylamine (b.p. 89 °C). Water quenching of the reaction mixture was not feasible since intermediate **2** would immediately hydrolyze back to starting material **1**. Therefore, an excess of $POCl_3$ was distilled off

after complete conversion of **1** → **2** by partial evaporation and the addition of toluene, followed by a second partial evaporation. Then, the solvent was switched to acetonitrile. During these distillations, concentration to dryness was avoided. The residual $POCl_3$ (b.p. 106 °C) was not quantified in the reaction mixture after the distillations. The thermal stability of the reaction mixture was carefully examined by the DSC (differential scanning calorimetry) and RC1 (reaction calorimetry) tests, and a strong thermal decomposition started from 180 °C. To assure safe handling, the following safety measures were undertaken: Evaporation of the solvent never proceeded to dryness and was performed at a jacket temperature < 70 °C; in case of an internal temperature increase, the mixture was diluted with cold toluene or acetonitrile. In the initial tox batch, the conversion of intermediate **2** → **4** was performed in acetic acid; however, it was found that intermediate **2** hydrolyzed back to starting material **1** in acetic acid. Intermediate **2** was sufficiently stable in acetonitrile. During the addition of starting material **3** (1.05 equiv), the product **4** started to precipitate., However, after complete addition of **3**, an HPLC check showed that approximately 23 % of **3** was still present in the reaction mixture. Therefore, the reaction was stirred for additional 18 h. The product **4** was isolated after the addition of H_2O and NaOH (aq) at a yield of 90 – 98 % with a purity of 90 – 98 % (HPLC area %) and could be conveniently used in the next step without further purification. In a resupply campaign, the reaction of intermediate **2** with starting material **3** was performed in toluene after distilling off excess $POCl_3$. After complete conversion to intermediate **4**, a solvent switch to 2-propanol was performed and product **4** was precipitated by the addition of H_2O. At the laboratory scale and in the plant, crust formation and an inhomogeneous batch product were observed. This process variant was not pursued in subsequent development batches. The $POCl_3$ in the toluene distillate was safely quenched by

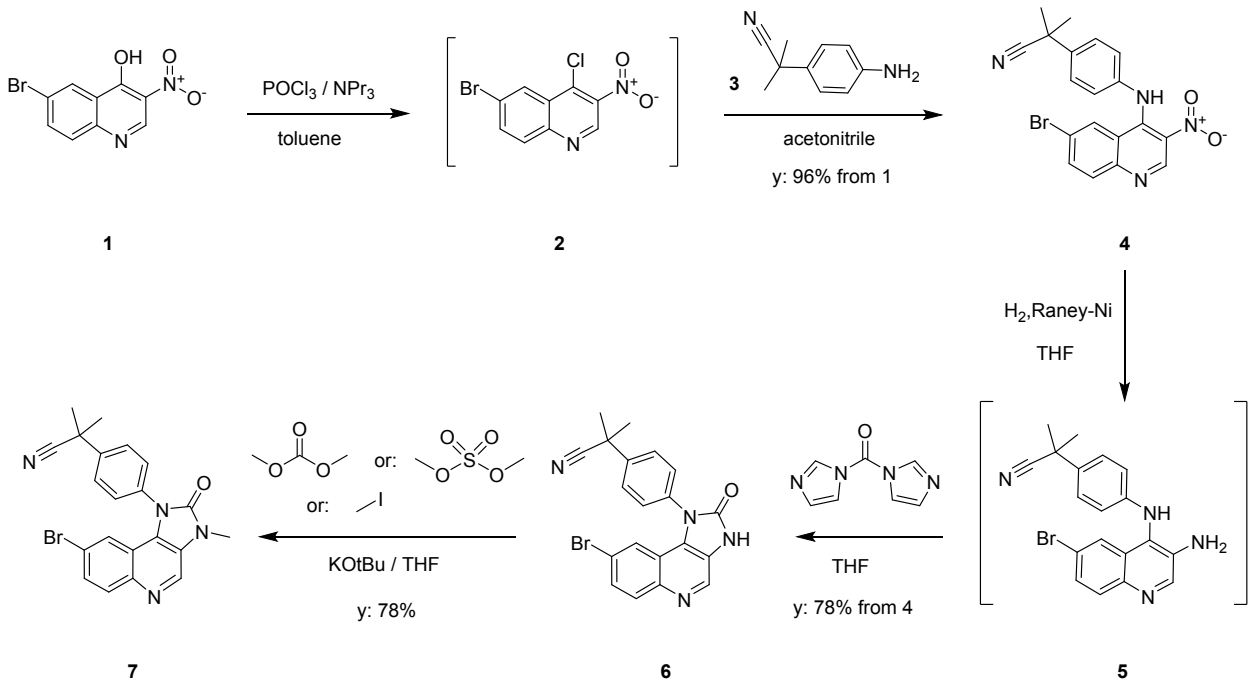
adding the distillate to hot water at 60 °C and stirring for 3 h at 60 °C, followed by neutralization with an aqueous NaOH solution.

For the hydrogenation of the nitro group in compound **4**, the following catalysts were screened: Pt/Al_2O_3, Pt/C, Rh/Al_2O_3, and Raney-Ni. These catalysts showed similar selectivity; however, the least expensive catalyst, Raney Ni,[9] was selected. With this catalyst, formation of only 0.5 – 2 % of desbromo impurity **10** was observed (HPLC area % at 210 nm; scheme 3). This amount of impurity **10** can be tolerated and still guarantees the proper quality of product **pure 9**. Impurity **10** can be cleanly synthesized by Pd/C hydrogenolysis of intermediate **5** in 2-methyl-THF in the presence of triethylamine. Moreover, the daughter impurity of impurity **10** in subsequent downstream processes leads to impurity **11**, which can be tolerated up to 10 % in intermediate **crude 9** to obtain qualified product **pure 9**. Due to catalyst poisoning by the residual NaH_2PO_4 (originating from the residual $POCl_3$ in the reaction of **2** → **3**) present in intermediate **4**, Na_2CO_3 was added to neutralize the sodium dihydrogen phosphate in the hydrogenation mixture. Under these conditions, hydrogenation ran smoothly. This nitro group hydrogenation could either be performed at normal pressure or up to a pressure of 5 bar in THF. The water that formed in the nitro group reduction and that was introduced with the Raney Ni catalyst had to be removed via azeotropic distillation in the presence of the reaction solvent THF and monitored by an in-process steering control via Karl Fisher titration with a limit of < 1000 ppm. The goal for future development was to avoid column chromatography and not to isolate the Ames positive intermediate **5**. In the first generation research synthesis, diphosgene[5a] was used to generate the cyclic urea intermediate **6**. Diphosgene is toxic, was used in chemical weapons in World War I and is not readily commercially available at a large scale. Moreover, the transport regulations of large quantities of diphosgene are quite strict. We found that the nontoxic phosgene equivalent

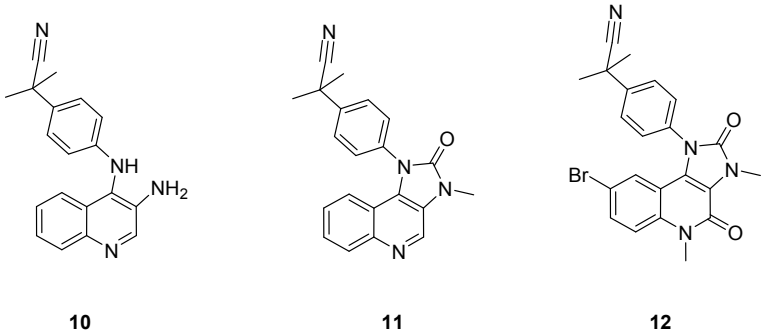
carbonyldiimidazole[10] worked nicely in this transformation. The use of triphosgene was not evaluated further. After azeotropic distillation of water, carbonyldiimidazole (1.9 – 2 equiv) was added; product **6** precipitated from the reaction mixture and was isolated by filtration at a yield of 75 – 85 %. Adding a sacrificial amount of carbonyldiimidazole to remove H_2O was not tested.

Methylation of **6** to **7** was performed in THF[11]. In the first generation research synthesis, NaH was used as a base. On pilot plant scale, the base was changed to a solution of KOtBu in THF, which was easier to handle than solid NaH. Methyl iodide was used as a methylating agent in the first development batches, and precipitated product **7** was isolated by filtration after the addition of H_2O at a 70 – 75 % yield. Product **7** was then carried onwards in the synthesis as a crude product. In the late phase of development, the methylating agent was changed to dimethyl sulfate, which has the advantage of being less volatile than methyl iodide; however, both methylating agents are carcinogens. Crude product **7** was recrystallized in late phase development batches. The methylation could be performed at room temperature using both methylating agents. Based on RC1 experiments, the reaction was assessed as non-critical. No further optimization of the addition rate of dimethyl sulfate (standard rate 2.5 h) was investigated. The quaternization of the quinoline nitrogen was not monitored. Dimethyl carbonate could also be used for this methylation as a methylating agent in DMF at 130 °C for 3 h in the presence of K_2CO_3; however, a significant amount of impurity **12** (up to 1 area % by HPLC at 210 nm; scheme 3) was formed under these conditions. This impurity **12** and its corresponding daughter impurity after Suzuki coupling with 3-quinoline boronic acid **8** did not meet the specification of < 0.1 area % by HPLC in **pure 9**. Furthermore, use of dimethyl carbonate as a methylating agent yielded dark-colored intermediate **7,** and even the color of **pure 9** derived from this material did not meet our internal specifications. Therefore, intermediate **7** originating from the dimethyl carbonate process had to be purified,

which was achieved using a slurry in pyridine, followed by recrystallization from anisole at an 84 % yield. In this purification step, the critical impurity **12** (scheme 3) was reduced to 0.1 %. Due to these findings and the necessity of performing an extra laborious purification of intermediate **7**, we decided to use dimethyl sulfate as a methylating agent for subsequent production batches. At a large scale, the **6** → **7** step can be performed with an average yield of 70 – 75 % after recrystallization from DMF. The critical impurity **12** was consistently present at no more than 0.2 % (HPLC area % at 210 nm). In the isolated intermediate **7**, dimethyl sulfate was determined to be < 1 ppm. This late phase development synthesis of intermediate **7** is outlined in scheme 2.



Scheme 2: Development synthesis of key intermediate 7



10 11 12

Scheme 3: Key impurities in the synthesis of dactolisib

Development of the key step, a Suzuki coupling reaction, to form intermediate crude 9[12]

In the manufacturing of the first development batch, 6 mol % of $PdCl_2(PPh_3)_2$ (the same catalyst used in the research synthesis) was used. The reaction was performed in a DMF / H_2O mixture using K_2CO_3 as the base. At the completion of the reaction, the product was isolated after tedious extractions with methylene chloride, followed by multiple precipitations / crystallizations. In the first GMP development batch, $KHCO_3$ was used as a base to avoid possible corrosion of the glass-lined vessels in the plant by the more basic K_2CO_3 at elevated temperatures, as observed in the corrosion testing lab. Hence, quinoline-3-boronic acid (**8**) was dissolved in a solution of DMF and aqueous $KHCO_3$ and added to compound **7** and the $PdCl_2(PPh_3)_2$ catalyst (3 mol %) in DMF. During the addition, the internal temperature of the reaction mixture had to be kept above 95 °C (usually the IT (internal temperature) was in the range from 96 °C to 102 °C and the jacket temperature was 110 °C – 115 °C) to keep the catalytic cycle active and to run the reaction in an addition-controlled manner. If the internal temperature during the addition dropped to < 95 °C, a significant amount of the desbromo impurity **11** formed. Under the ideal operating conditions outlined above, impurity **11** usually formed at 0.5 % - 3 % area % (HPLC at 210 nm). An HPLC

check immediately after the complete addition of **8** showed < 5 % of compound **7**. The reaction mixture was then stirred at > 95 °C for additional 2 h. To ensure the complete removal of residual compound **7** in the purification process of **crude 9** → **pure 9**, the limit of residual **7** in the process control (IPC) of the step **crude 9** was set to < 2 % (area % HPLC). The addition time of compound **8** was set at 0.5 h – 2 h. The starting material 3-quinoline boronic acid **8** began to exothermally decompose at 116 °C with a decomposition energy of 427 J / g. To ensure the thermal safety of the process, an addition-controlled reaction to **crude 9** and a high dilution of starting material **8** to approximately 5 % in DMF / $KHCO_3$ (aq) were necessary.

The product **crude 9** was isolated by filtration after precipitation by the addition of water. The product **crude 9** was isolated at a 90 – 97 % yield with a purity of > 90 % (HPLC, area %) and contained 6000 – 7000 ppm Pd and 30 – 200 ppm Ni. However, this purity and the Pd and Ni levels were not acceptable for API quality. To achieve the required level of purity of the drug substance of > 99 % (HPLC area %) and residual Pd and Ni levels of < 2 ppm, further purification steps were necessary. The low tolerable level of Pd (< 2 ppm) in API was due to the high projected daily dose of dactolisib. Furthermore, starting materials **1**, **3**, and **8** and intermediates **4** and **5** had positive Ames test results. The limits of the Ames-positive starting materials and intermediates were checked based on the ICH guideline for product **pure 9** or the corresponding tosylate salt of **pure 9** at a level of 1.9 ppm for each of these impurities. This level can be achieved for each impurity and for the methylating agent dimethyl sulfate, which was used in the conversion of intermediate **6** → **7**. Potential byproducts or intermediates of the nitro group reduction (hydroxylamine, etc.) were not considered in this genotoxic evaluation.

For subsequent development batches, the goal was to further reduce the amount of the Pd catalyst to decrease the catalyst cost and the level of residual Pd contamination in the isolated product

crude 9. Initially, we tested a range of Pd / C catalysts with or without the addition of PPh_3.[13] Reactions were performed in DMF / H_2O or in NMP / H_2O. In all cases, the target product **crude 9** was formed as the major reaction product; however, a significant amount of impurity **11** (> 10 % area %; HPLC) was present in the reaction mixture. Therefore, the reaction to **crude 9** with the $PdCl_2(PPh_3)_2$ catalyst was further investigated. We tried to reduce catalyst loading while simultaneously adding 2 Pd equiv of PPh_3 to the reaction mixture. The Pd catalyst levels could be reduced to 0.3 mol %, and the reaction remained addition-controlled with regard to **8** (see Table 1)**.** Other homogeneous catalysts than $PdCl_2(PPh_3)_2$ were not considered due to the air stability of this catalyst and cost considerations. In laboratory experiments, we were able to reduce the catalyst amount to < 0.2 mol % by adding 2 Pd equiv of PPh_3 and achieve an acceptable yield and purity of **crude 9**. Without the addition of PPh_3, the Suzuki coupling did not work at these low catalyst loads. We hypothesized that adding 2 equiv PPh_3 could help to stabilize the catalytically active Pd(0) complex and that PPh_3 might act as a reducing agent for the Pd(II) to Pd(0) conversion.

Table 1: Key experiments for the Suzuki coupling to product crude 9

Catalyst	Reaction Products by HPLC	Yield of isolated crude 9
Pd / C 5 % (20 % m/m of **7**) type 39 paste (Johnson Matthey)	72.3 % **(9)**; 1 % **(7)**; 23.8 % **(11)**	Not isolated
$PdCl_2(PPh_3)_2$; 3 mol %	94.7 % **(9)**; 2.6 **(7)**; 2.6 **(11)**	95 %
$PdCl_2(PPh_3)_2$; 0.3 mol % + 0.6 mol % PPh_3	96.3 % **(9)**; 1.6 % **(7)**; 1.5 % **(11)**	97 %

The reaction was finally run in the following manner: starting material **7** and the Pd catalyst in DMF were placed in a reactor, and a solution of **8** in DMF / $KHCO_3$ (aq) was added at 90 – 95 °C.

The reaction mixture was stirred for 2 h and then checked by HPLC. The product was precipitated by the addition of H_2O and isolated via filtration. According to this optimization, the amount of Pd could be reduced by a factor of 10 to a level of < 700 ppm in the isolated product **crude 9**. The yield of the crude product remained approximately same (90 – 95 %) with a purity of > 98 % (HPLC area %). Starting material **8** was only soluble in this DMF / $KHCO_3$ (aq) solution at > 60 °C. However, when this solution was aged for a prolonged period of time (≥ at 60 °C; > 5 h) prior to the addition to compound **7** / catalyst mixture, a significantly higher amount of the desbromo impurity **11** was formed, probably due to the hydrolysis of DMF under these conditions. The ^{1}H-NMR data indicated that stirring a solution of compound **8** in DMF /$KHCO_3$ (aq; D_2O) at a jacket temperature of 70 °C resulted in the formation of 0.6 mol % potassium formate versus DMF after 4 h and that after 19 h, 2.6 mol % potassium formate formed. Based on this result, in another laboratory experiment, we added 65 mol % of potassium formate (corresponding to 2.6 mol % potassium formate versus DMF) to the solution of **8** in DMF / $KHCO_3$ (aq). After reaction with the starting material **7** under normal Pd-catalyzed conditions, the IPC of the reaction mixture showed < 2 % of residual **7** and the formation of 3.1 % of impurity **11**, which was depleted to < 1% (HPLC area %) in the isolated product **crude 9**. Potassium formate presumably serves as a reducing agent for the reaction **7** → **11**. This hypothesis was further supported by a control experiment in which a mixture of compound **7** together with the catalyst in the presence of an aqueous $KHCO_3$ solution but in the absence of starting material **8** was stirred for several hours at an internal temperature (IT) of > 95 °C. After 4 h at > 95 °C, 23 % of impurity **11** formed. Furthermore, in another control experiment, DMF was replaced by N,N-dimethylacetamide as the reaction solvent; after 4 h stirring at > 95 °C without the addition of starting material **8**, only approximately 1 % of desbromo **11** formed. Then, 3-quinoline boronic acid (**8**) was added, and the

reaction to the product **crude 9** proceeded smoothly providing product **9** at > 96 % area % and desbromo **11** at approximately 1.5 % (HPLC area %) in the in-process control 2 h after the addition of **8**. Usually, the solution of starting material **8** was maintained for a maximum of 2 h before addition to the reaction mixture of **7**. In an experiment in which the solution of starting material **8** in DMF / $KHCO_3$ was stirred for 7 h at a jacket temperature of 70 °C, 8 % of impurity **11** was observed in the product **crude 9**. This amount of impurity **11** could be depleted in the purification step to **pure 9**; however, a concomitant yield loss was observed. Excess 3-quinoline boronic acid (**8**) was initially set at 1.2 equiv; however, in larger batches, it could be successfully reduced to 1.1 equiv and even to 1.05 equiv. However, the optimal amount of the starting material **8** appeared to be 1.1 equiv versus **7**.

In the initial development batches, the product **crude 9** was isolated after drying, which had an impact on the throughput of the process since the water wet product **crude 9** had to be dried, resulting in long cycle times. However, the quality of the isolated product **crude 9** did not meet the quality requirements for the drug substance with regards to HPLC purity and residual Pd, resulting in the need for a recrystallization / purification step. For the initial development batches, the dried intermediate **crude 9** was recrystallized in a formic acid /methanol system. Later, it was found that purification could be performed in acetic acid / H_2O, and the drying step at intermediate **crude 9** was omitted. These alterations yielded a satisfactory purity of the product **pure 9** with regard to HPLC purity and residual Pd.

Recrystallization of the crude drug substance and removal of Pd

Crude 9 is almost completely insoluble in most organic solvents, making it very difficult to design a feasible recrystallization system. Formic acid was identified as a good solvent for product **9,** which probably forms a soluble formate salt. We therefore designed a recrystallization process that involved the dissolution of **crude 9** in formic acid and the addition of activated charcoal (NORIT C EXTRA USP grade) to reduce Pd and Ni. Additionally, charcoal served as a decolorizing agent. In addition to Smopex-234[14], a Pd and Ni scavenger was added to further reduce the levels of heavy metals. This mixture was stirred at room temperature; charcoal and Smopex-234 were filtered off and MeOH was finally added at 60 °C. Under these conditions, methyl formate formed; the purified product **pure 9** precipitated and could be isolated by filtration. To enhance the purity of the drug substance to the required level of > 99 % (HPLC area %) and reduce the residual Pd and Ni levels to < 2 ppm, the preceding purification method had to be repeated a second time. In the first cycle, approximately 80 % of the Pd initially present in **crude 9** was removed by charcoal and Smopex-234; approximately 12 % of Pd ended up in the mother liquor and 5 % of the initial Pd amount remained in the precipitated product. In the second cycle, approximately 90 % of the remaining Pd was removed by charcoal and Smopex-234. Thus, the purified drug substance was isolated at a > 90 % yield with an HPLC purity of > 99 % and Pd and Ni levels of < 2 ppm. After the first recrystallization cycle, the Pd level was in the range from 20 to 100 ppm. When only charcoal was used, the once-precipitated product **pure 9** still contained approximately 200 ppm Pd, which was too high. Therefore, a combination of charcoal and Smopex-234 was used as a Pd scavenger in the subsequent development. QuadraSil MP and 3-mercaptopropyl ethyl sulphide silica were also investigated as Pd scavengers, and their efficacy for Pd removal was similar to that of Smopex-234. Then, Smopex-234 was used as a scavenger in combination with charcoal. Experiments using only Smopex-234 were not performed since the

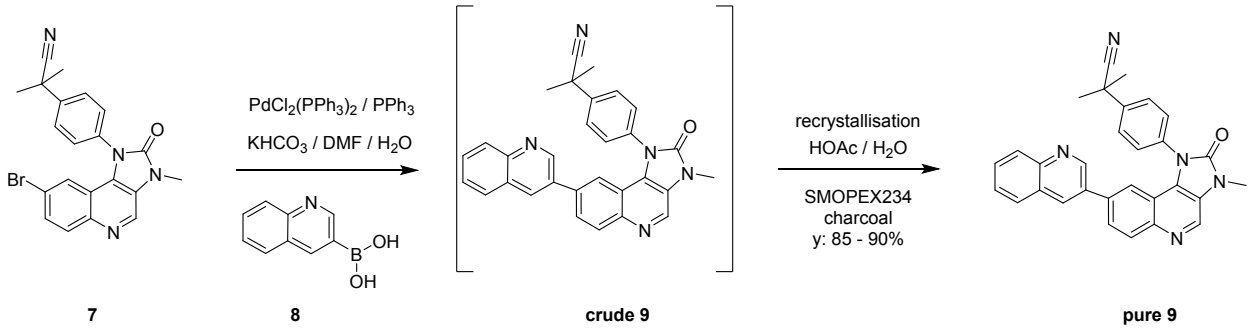
addition of charcoal proved to be necessary to remove the color from product **pure 9**. Recrystallization and an investigation of Pd removal without the addition of charcoal and Smopex-234 were not performed. The problem of H_2 and CO_2 release due to Pd-catalyzed decomposition of formic acid was addressed in the scale-up campaign, and safety measures were implemented. The exhaust of the reactor was passed through a vessel filled with water and was then directly released over the roof. The mother and washing liquor tanks were immediately sent to an incineration plant without intermittent storage.

However, this process has the following four disadvantages:

- Product **crude 9** originates from a precipitation process from DMF / H_2O containing salts (K_2CO_3 and $KHCO_3$). The purification procedure from intermediate **crude 9** to product **pure 9** is performed under anhydrous conditions (methanol, formic acid, and methyl formate), and thus, residual salts from the previous Suzuki coupling are not removed, which may lead to a potential risk of elevated sulfated ash levels in the drug substance.
- Intermediate **crude 9** has to be dried; otherwise, the formation of formic acid methyl ester with concomitant precipitation of **pure 9** is not complete due to the presence of water, which will result in a large yield loss after isolation of **pure 9**.
- The presence of a significant residual amount of Pd in **crude 9** may result in H_2 and CO_2 formation due to the catalytic decomposition of formic acid. Indeed, in a pilot plant campaign, pressure was formed in a drum of mother liquor, which can lead to a potentially dangerous situation, especially since H_2 is formed. Special safety measures had to be implemented, and these measures are not acceptable for a commercial process.
- The volume changes in this step are not favorable for the plant. Intermediate **crude 9** is dissolved in 5 volumes of formic acid and then concentrated to a low volume (2-fold) with

regard to the starting intermediate **crude 9**. Then, 8 volumes of methanol are added. Due to these disadvantages, an alternative purification method had to be sought.

An alternative solution using an acetic acid / H_2O mixture was found. To further reduce the levels of Pd in **crude 9**, cysteine was added to the H_2O used for precipitation of the product **crude 9**. The Pd levels in isolated and dried product **crude 9** were consistently < 500 ppm using a final loading of 0.3 mol % $PdCl_2(PPh_3)_2$. However, on the plant scale, the product **crude 9** was not dried and was dissolved as a water-wet filter cake in acetic acid; Smopex-234 and charcoal were added, and the mixture was stirred at 90 °C for 1 h. Then, charcoal and Smopex-234 were removed via filtration, and charcoal and Smopex-234 were added again to the filtrate; the mixture was stirred for 1 h at 90 °C, and the solids were filtered off. The filtrate was evaporated to a volume of approximately 5 – 5.5-fold versus the theoretical yield. The purified product was precipitated by the addition of 16.4 volumes of deionized H_2O. The yield of these two-telescoped steps was approximately 85 % - 90 % and the purity was usually > 99.5 % HPLC (area %). The product **pure 9** was dried at 80 °C until AcOH was < 1 % (m/m). The final step of the late phase synthesis of dactolisib is outlined in scheme 4.



Scheme 4: Synthesis of dactolisib from the key intermediate 7

The isolated product **crude 9** contained a variable amount of H_2O. In the lab (filtration over a nutsch filter), the water levels were usually up to approximately 30 – 50 % of the theoretical amount of the product **crude 9**, and in the plant (centrifugation), the water levels were 20 – 50 % of the theoretical amount of the product **crude 9**. The solubility of the product **pure 9** in the AcOH / H_2O system reaches a maximum at a ratio of about 4:1 (AcOH : H_2O) either at RT as well as 90 °C, see Figure 1.

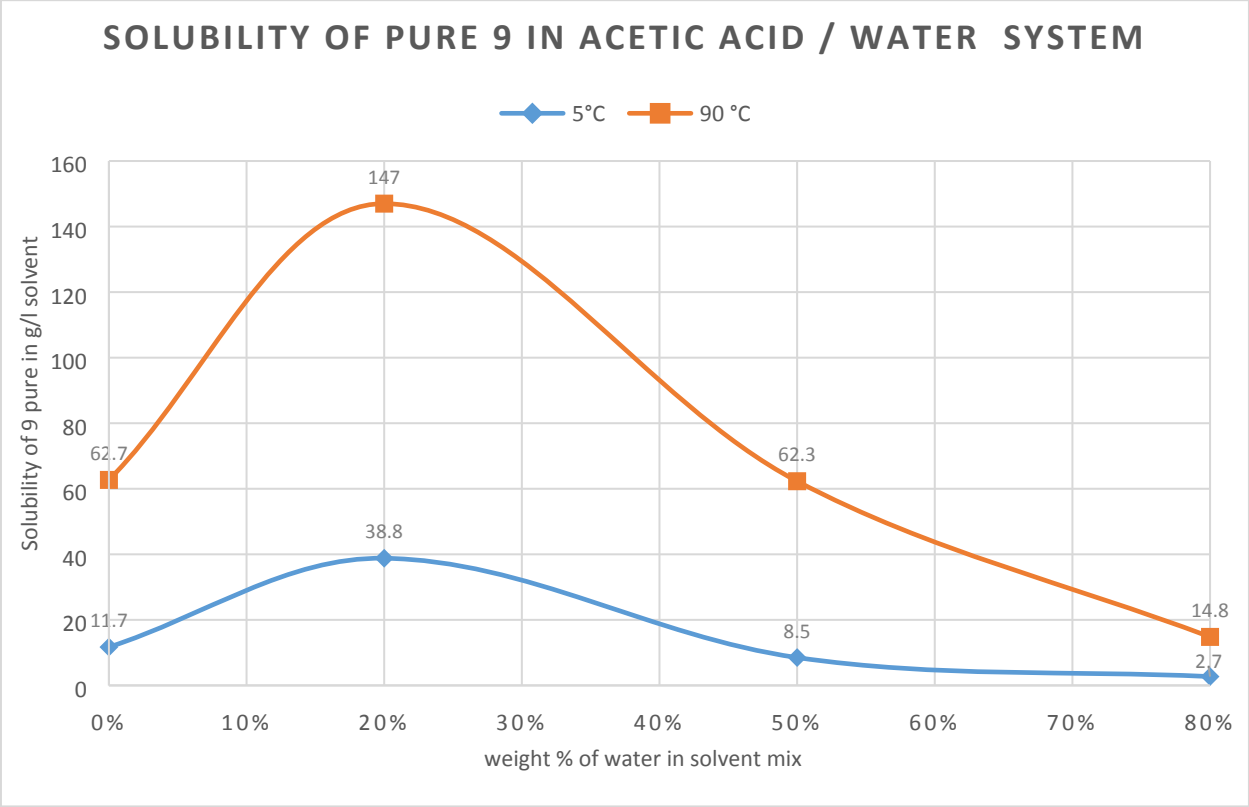


Figure 1: Solubility of pure 9 in AcOH / H_2O system

Some residual H_2O is beneficial to dissolve the **crude 9** in AcOH. The impact of various amounts of H_2O brought into the recrystallization process from **crude 9** → **pure 9** was investigated. The

results are summarized in the following Table 2. In all experiments listed in table 2, charcoal and Smopex-234 were used for the Pd removal.

H_2O content in crude 9 (g/g crude 9)	**Yield (%)**	**Residual Pd in pure 9 * (ppm)**	**HPLC purity (area %)****
10	92.9 %	< 1	99.9
20	92.9	< 1	99.9
50	93.6	< 1	99.7
100	93.6	< 1	99.8
200	95.7	< 1	99.4

* The starting material **crude 9** contained 342 ppm Pd.

** The starting material **crude 9** had an HPLC purity of 98.9 % (area %).

Table 2: Impact of the H_2O content in crude 9 on the quality and yield of isolated pure 9

The data indicate that the H_2O content in wet **crude 9** is independent of the Pd removal efficiency in this process. However, if > 100 % m/m H_2O is present in **crude 9** (calculated on dried basis), the efficiency of the depletion of byproducts is decreased. Higher levels of residual H_2O in wet **crude 9** slightly increase the yield, as expected.

With this final recrystallization process of dactolisib from acetic acid / H_2O, it is possible to easily remove up to 10 % of impurity **11** into the mother liquor; however, only approximately 2 % of the remaining starting material **7** is purged. Hence, the limit of residual starting **7** in the in-

process control of the reaction **7** + **8** → **crude 9** was set to < 2 %. The Pd levels in the isolated purified product **pure 9** were usually below 2 ppm.

CONCLUSION

We successfully developed a robust production process for the synthesis of dactolisib. The amount of Pd catalyst $PdCl_2(PPh_3)_2$ can be reduced to 0.3 mol % in the Suzuki coupling by the addition of triphenylphosphine as a supplementary ligand. The intermediate **crude 9** after the Suzuki coupling was not dried in the final process, thus improving the process throughput. Pd can be removed with charcoal / Smopex-234, and the final purified free base **pure 9** of dactolisib was isolated at an 85 – 90 % yield (Suzuki coupling and purification) with a purity of > 99.5 % (HPLC area %) and Pd and Ni < 2 ppm. The number of isolated products can be reduced from 6 in the first generation synthesis (scheme 1) to 4 in the final process (scheme 2 and 4).

EXPERIMENTAL SECTION

General:

All solvents and reagents used were of bulk quality.

The NMR spectra were recorded on a Bruker Avance 400 (^{1}H NMR: 400 MHz; ^{13}C NMR: 100 MHz) spectrometer in the indicated solvent. Coupling constants (J) are reported in hertz (Hz). The accuracy of the measurement of the coupling constants was within +/- 0.2 Hz.

HPLC was performed on an Agilent 1100 or 1200 machine. HR-LC/MS were measured on a Waters Acquity UPLC/Synapt G2 Q-TOF MS instrument and were performed by using electrospray ionization in the positive ion mode after separation by liquid chromatography (Nexera

from Shimadzu). The elemental composition was derived from the mass spectra acquired at a high resolution of approximately 30,000 on an LTQ Orbitrap XL mass spectrometer (Thermo Scientific). A high mass accuracy below 1 ppm was obtained by using a lock mass.

All reactions were carried out under inert atmosphere (N_2).

Synthesis of 2[4-(6-bromo-3-nitro-quinolin-4-yl amino)-phenyl]-2-methyl-propionitrile (4). 6-Bromo-4-hydroxy-3-nitroquinoline (78.5 kg; 292 mol) was placed in a reactor together with toluene (463 kg) at RT. Then, tripropylamine (62.7 kg; 438 mol; 1.5 equiv) was added. The suspension was then heated to 80 °C, and $POCl_3$ (89.4 kg; 584 mol; 2 equiv) was added within approximately 1 h. The reaction mixture was heated to 90 °C and stirred at 90 °C – 95 °C for 2 h, and the turnover of the reaction was checked by HPLC (requirement: < 1 % starting material). The reaction mixture was cooled to 65 – 70 °C, and 345 kg toluene was distilled off. Then, four times toluene (262 kg) was added, and the same amount of toluene was distilled off. The solvent was exchanged to acetonitrile. Four times acetonitrile (235 kg) was added, and the same amount of the solvent was distilled off. Finally, acetonitrile (628 kg) was added. The internal temperature was decreased to 25 °C, and a solution of 2-(4-amino-phenyl)-2-methyl propionitrile **(3)** (49 kg; 306 mol; 1.05 equiv) in 78.5 kg acetonitrile was added within 1.5 h. During the addition of starting material **3**, product **4** precipitates from the reaction mixture. The reaction mixture was stirred at RT for 18 h. The reaction was checked with HPLC (requirement: < 1.0 % area % intermediate **2**). Finally, H_2O (3,000 kg) was added, and 1,268 kg of the solvent was distilled off under vacuum at 70 °C. After the distillation of the first 700 l of the solvent, additional H_2O (900 kg) was added. When the distillation was stopped, the pH was adjusted to 5 – 6 by adding 30 % NaOH (93 kg). The reaction mixture was then cooled to 0 ° C within 7 h and stirred at that temperature for 2 h;

product **4** was finally isolated via filtration. The filter cake was washed with acetonitrile : H_2O = 1:10 (240 kg). The wet product was dried at 60 °C in vacuum to give 115.4 kg of product **4**, which corresponded to a 96 % yield. The purity of the production batches were in the range from 90 to 98 % (HPLC area %). This product was used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.07 (s, 1H), 8.71 (d, J = 1.9 Hz, 1H), 7.98 (dd, J = 8.9, 1.9 Hz, 1H), 7.91 (d, J = 8.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 1.68 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 148.17, 147.72, 141.40, 140.59, 137.92, 135.58, 132.08, 130.19, 127.23, 126.49, 125.12, 123.02, 120.48, 120.42, 36.71, 28.77.

HR-LC MS: m/z $[M^+H]^+$ calcd for $C_{19}H_{16}N_4O_2Br$: 411.0457; found: 411.0350.

Synthesis of 2-[4-(8-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile (6).

Starting product **4** (113.9 kg, 277 mol) and Na_2CO_3 (5.7 kg) were combined with THF (1,481 kg) into an autoclave. The Raney nickel catalyst (21 kg) was added, and the mixture was hydrogenated under normal pressure of molecular hydrogen up to the uptake of 3 equiv of H_2 (usually, approximately 8 – 10 h). At this point, no significant consumption of H_2 was observed. The turnover of the reaction was checked by HPLC (< 1 % of intermediate **4**). The catalyst was then filtered off and washed four times with THF (122 kg). THF was distilled off under vacuum (1,400 kg). Then, twice THF (473 kg) was added and distilled off. More THF (1,416 kg) was added, and the H_2O content was measured (limit: 1000 ppm; KF-titration). Finally, carbonyldiimidazole (86 kg, 531 mol; 1.9 equiv) was added. The reaction mixture was heated to

60 °C within 1.5 h and was stirred at this temperature for 3 h. The reaction was checked by HPLC for completion (< 1 % of intermediate **5**; HPLC area %), and the suspension was cooled to 0 °C – 5 °C within 3 h and stirred for another 2 h; then, the crude product was filtered. The filter cake was washed with THF (471 kg). The crude THF wet product was charged into a reactor together with H_2O (439 kg) and suspended at IT 40 – 50 °C for 1 h. Then, the product was filtered, washed with H_2O and dried at 90 °C until the H_2O content (KF) was < 0.4 % to obtain 88 kg of intermediate **6** (78 % yield). The purity of the isolated product was in the range from 92 % to 97 % (HPLC area %) of the production batches.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.82 (s, 1H), 8.80 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.75 – 7.67 (m, 2H), 7.65 (dd, J = 9.1, 2.1 Hz, 1H), 6.97 (d, J = 2.1 Hz, 1H), 1.82 (s, 6H).

^{13}C NMR (101 MHz, DMSO-*d6*) δ 153.88, 143.76, 143.08, 135.16, 134.90, 132.86, 129.94, 129.91, 129.12, 127.25, 124.83, 122.80, 122.60, 119.30, 116.43, 37.32, 28.83.

HR-LC MS: m/z $[M^+H]^+$ calcd for $C_{20}H_{16}N_4OBr$: 407.0507; found 407.0530.

Intermediate **5** could be isolated after hydrogenation by evaporation of THF and crystallization from n-heptane. Analytical results of intermediate **5**:

^{1}H NMR (500 MHz, DMSO-*d6*; 100 °C) δ 8.67 (s, 1H), 7.95 – 7.85 (m, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 7.49 – 7.36 (m, 1H), 7.31 – 7.22 (m, 2H), 6.68 – 6.53 (m, 2H), 5.15 (br. s, 2H), 1.65 (s, 6H).

^{13}C NMR (126 MHz, DMSO-*d6*; 100 °C) δ 144.18, 143.97, 140.56, 137.30, 130.70, 130.65, 127.75, 126.43, 125.17, 124.26, 123.09, 121.48, 119.02, 113.83, 35.20, 28.00.

HR-LC MS: m/z $[M^+H]^+$ calcd for $C_{19}H_{18}N_4Br$: 381.0715; found 381.0746.

Synthesis of 2-(4-((3-aminoquinolin-4-yl)amino)phenyl)-2-methylpropanenitrile (10)

Intermediate **5** (5 g; 13.1 mmol) was dissolved in 100 ml 2-Me-THF together with 2 g (19.8 mmol; 1.5 equiv) triethylamine. Then, 0.5 g of Pd/C (10 %) catalyst was added, and the mixture was hydrogenated in an autoclave at RT with 1 bar overpressure for a total of 8 h. A LC/MS check of the reaction mixture showed complete consumption of starting material **5**. The catalyst was filtered off and washed with 2-Me-THF, and the 2-Me-THF product solution was washed with 50 ml 0.05 M citric acid, followed by two washes with 50 ml deionized H_2O. The 2-Me-THF solution of compound **10** was evaporated to dryness to obtain 3.5 g product **10** as a brown evaporation residue (88 % yield).

Analytical results of compound **10**

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.63 (s, 1H), 7.96 – 7.79 (m, 2H), 7.73 – 7.62 (m, 1H), 7.43 – 7.30 (m, 2H), 7.30 – 7.19 (m, 2H), 6.62 – 6.50 (m, 2H), 1.61 (s, 6H).

^{13}C NMR (101 MHz, DMSO-*d6*) δ 144.91, 143.99, 142.20, 137.31, 130.33, 129.04, 126.54, 126.10, 125.77, 125.11, 124.13, 122.68, 121.68, 114.00, 35.64, 28.41.

HR-LC MS: m/z $[M + H]^+$ calcd for $C_{19}H_{19}N_4$: 303.16042, found: 303.16068.

Synthesis of 2[4-(8-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl)-phenyl]2-methyl-propionitrile (7).

Intermediate **6** (166 kg; 408 mol) was placed together with THF (889 kg) in a reactor. Then, a solution of 20 % m/m KOtBu (343 kg; 611 mol; 1.5 equiv) in THF was added within 2 – 3 h under cooling at 20 °C – 25 °C. The addition tank was rinsed with THF (45 kg). The mixture was stirred

at 20 °C – 25 °C for 0.5 h, and dimethyl sulfate (77 kg; 610 mol; 1.5 equiv) was added within 2.5 h. The reaction mixture was stirred for 2 h at 25 ° - 30 °C. Then, the reaction was checked with HPLC (requirement < 2 % of **6**). A solution of 5 % NH_3 in H_2O (316.5 kg) was added, and the mixture was stirred for 0.5 h at 25 °C – 30 °C. Product **7** was filtered and washed with THF (182 kg) followed by a mixture of methanol (93 kg) and H_2O (93 kg). The crude wet product was charged in a reactor together with DMF (1717 kg) and activated charcoal (8.6 kg). The mixture was heated at 120 °C within 2.5 h and stirred at that temperature for 0.5 h. Then, the charcoal was filtered off and rinsed with DMF (345 kg). The filtrate was cooled within 5 h to 5 °C and stirred at that temperature for 1.5 h; then, the product was filtered and washed with TBME (452 kg). The product was dried in vacuum at 45 °C to obtain 133.8 kg product **7** (78 % yield). The purity level of the 9 production batches: > 99.0 % (area % HPLC); impurity **12** < 0.2 % (area % HPLC).

^{1}H NMR (400 MHz, acetic acid-*d4*) δ 9.20 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.02 – 7.88 (m, 2H), 7.81 (dd, J = 9.2, 2.0 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 2.0 Hz, 1H), 3.76 (s, 3H), 1.90 (s, 6H).

^{13}C NMR (101 MHz, acetic acid-d_4) δ 154.10, 144.79, 140.04, 133.67, 132.19, 130.97, 130.94, 129.25, 128.17, 127.10, 123.87, 123.67, 123.10, 120.87, 115.63, 37.24, 28.27, 27.71.

HR-LC MS: m/z $[M^+H]^+$ calcd for $C_{21}H_{18}N_4OBr$: 421.0664; found 421.0636.

Analytical data of compound **12**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 2H), 7.53 – 7.47 (m, 3H), 7.31 (d, J = 9.1 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 1.85 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.76, 153.71, 143.58, 136.00, 134.34, 130.99, 129.14, 126.96, 126.03, 124.18, 123.86, 116.97, 115.43, 115.12, 112.92, 37.36, 29.76, 29.49, 29.29.

HR-LC MS: m/z $[M^+ H]^+$ calcd for $C_{22}H_{20}N_4O_2Br$: 451.07642; found 451.07642.

Synthesis of 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl)-phenyl]propionitrile (crude 9; pure 9).

Intermediate **7** (155 kg; 368 mol) was placed in a reactor together with DMF (961 kg) at RT under N_2. The mixture was degassed by evacuating and flushing several times with N_2. Then, bis(triphenylphosphine) palladium dichloride (0.78 kg; 1.1 mol; 0.3 mol %) and triphenylphosphine (0.62 kg; 2.4 mol; 0.64 mol %) were added. In a second reactor, 3-quinoline boronic acid **8** (70 kg; 405 mol; 1.1 equiv) was dissolved in DMF (721 kg) at 60 °C. A solution of $KHCO_3$ (207 kg) in H_2O (1033 kg) was added at 60 °C, and the solution of **8** was degassed. Meanwhile, the first reactor was heated to 95 °C – 100 °C, and the hot solution of **8** was added within 1.5 h at > 95 °C to the starting **7**. The reaction mixture was stirred for 2– 6 h at this temperature and was checked by HPLC (requirement: < 2 % **7**; area %). A solution of L-cysteine (13.7 kg) in demineralized H_2O (115 kg) was added within 20 minutes. The mixture was stirred at > 95 °C for 2 h. Then, demineralized H_2O (712 kg) was added. The mixture was cooled within 9 h to 0 °C and was stirred at that temperature for 4 h. The product **crude 9** was filtered and washed with H_2O (2,296 kg),to obtain 209 kg wet **crude 9** (theoretical 100 % yield: 172 kg), which was directly converted to the product **pure 9**.

This crude product contained 151 ppm Pd and < 1 ppm Ni (after drying in the lab). The HPLC purity of this intermediate **crude 9** was 98.8 % (area % HPLC).

Acetic acid (1634 kg) was placed in a reactor together with the above crude product (209 kg). Then, Smopex-234 (17.5 kg) was added. The mixture was stirred at RT for 2 h; charcoal (17.5 kg)

was added, followed by AcOH (204 kg). The mixture was heated to 90 °C within 1.5 h and stirred at that temperature for 1 h. Then, charcoal and Smopex-234 were filtered off and washed with AcOH (369 kg). To the filtrate, Smopex-234 (17.5 kg) followed by charcoal (17.5 kg) and AcOH (89 kg) were added. The mixture was stirred for 1 h at 90 °C. Then, Smopex-234 and charcoal were removed by filtration. The filter cake was washed with AcOH (553 kg). AcOH was distilled off under vacuum at 70 °C to a residual volume of approximately 950 l in the vessel (measured by radar). Then, demineralized H_2O (2,888 kg) was added at 80 – 90 °C. The mixture was seeded (0.5 kg of **pure 9**). Stirring was continued for 0.5 h; the mixture was cooled within 7 – 10 h to 0 °C and stirred at that temperature for 4 h; then, the product **pure 9** was filtered and washed with a mixture of demineralized H_2O (368 kg) and AcOH (128 kg) followed by demineralized H_2O (2,943 kg). The wet product (253 kg) was dried in a paddle dryer at 80 °C under full vacuum (< 10 mbar) to obtain 152.2 kg purified product **pure 9** (88 % yield; based on intermediate **7**). The product contained < 1 ppm Pd and < 1 ppm Ni. HPLC purity 99.8 % area %. Assay AcOH < 1 % m/m.

^{1}H NMR (400 MHz, acetic acid-*d4*) δ 9.14 (s, 1H), 8.82 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.14 – 8.04 (m, 2H), 7.93 – 7.97 (m, 3H), 7.89 – 7.82 (m, 2H), 7.79 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.72 – 7.62 (m, 1H), 7.36 (d, J = 1.8 Hz, 1H), 3.79 (s, 3H), 1.81 (s, 6H).

^{13}C NMR (101 MHz, acetic acid-*d4*) δ 154.12, 147.17, 144.83, 144.78, 139.98, 135.59, 135.40, 133.84, 132.65, 131.96, 131.19, 130.04, 129.38, 128.54, 128.39, 128.03, 127.77, 127.17, 126.62, 126.40, 123.74, 123.71, 118.99, 114.57, 37.32, 28.31, 27.81.

Anal. calcd for $C_{30}H_{23}N_5O$: C, 76.74; H, 4.94; N, 14.92. Found: C, 76.34; H, 4.92; N, 14.82.

HR-LC MS: m/z $[M^+H]^+$ calcd for $C_{30}H_{24}N_5O$: 470.1981; found 470.2009.

Analytical data of compound **11**:

^{1}H NMR (400 MHz, acetic acid-d4) δ 9.32 (s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.86 (ddd, J = 8.5, 7.0, 1.1 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.57 – 7.48 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H), 1.89 (s, 6H).

^{13}C NMR (101 MHz, acetic acid-*d4*) δ 154.34, 144.62, 138.79, 134.50, 133.73, 130.77, 129.12, 128.27, 127.88, 127.16, 123.94, 123.73, 123.45, 121.09, 114.24, 37.16, 28.13, 27.86.

HR-LC MS: m/z $[M^{+}H]^{+}$ calcd for $C_{21}H_{19}N_4O$: 343.15534; found: 343.15552.

ASSOCIATED CONTENT

NMR data of intermediates of the synthesis are provided.

The following files are available free of charge.

NMR data of all intermediates and listed impurities (PDF)

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Notes

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