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Development of a Scalable Route to the SMO Receptor Antagonist SEN794

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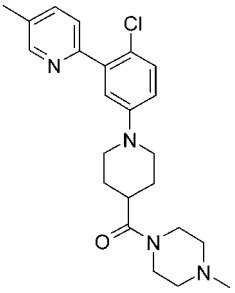
Supporting Information

ABSTRACT: A practical and scalable route to the SMO receptor antagonist SEN794 **1** is described herein. A new and efficient access to the key intermediate **7** via the Kröhnke reaction was developed, significantly simplifying the synthesis and reducing costs. The optimized route consists of six chemical steps plus a palladium scavenging step. The intermediates are solids and were isolated by filtrations, except for ester **9**, which was telescoped as the crude oil into the subsequent step. In the final amide formation step, target compound **1** was conveniently crystallized from the reaction mixture in high purity.

INTRODUCTION

The Smoothened (SMO) receptor mediates Hedgehog (Hh) signaling critical to development, differentiation, growth, and cell migration.[1] Under normal conditions, activation of the pathway is induced by binding of specific endogenous ligands (i.e., Sonic Hh) to its receptor Patched (Ptch), which in turns reverts the Ptch inhibitory effect on SMO. SMO activation ultimately determines specific target genes activation through a family of three transcription factors, Gli1/2 and 3. Although Hh signaling is significantly curtailed in adults, it retains functional roles in stem cell maintenance and aberrant Hh signaling has been described in a range of tumours.[2] Mutational inactivation of the inhibitory pathway components results in a constitutive ligand-independent activation seen in tumours such as basal cell carcinoma (BCC) and medulloblastoma. Ligand-dependent activation is seen in tumours such as prostate cancer, pancreatic cancer, gastrointestinal malignancies, melanoma, gliomas, breast cancer, ovarian cancer, leukemia, and B-cell lymphomas. A significant body of evidence supports the conclusion that SMO receptor antagonism will block the downstream signaling events.[3,4]

As part of a program to address the unmet medical need with regard to tumours in the CNS, Siena Biotech has designed and investigated selective antagonists of the SMO receptor. The brain-penetrant SEN794 (**1**, Figure 1) is part of a group of potent antagonists of the Hedgehog pathway.[5]



1
SEN794

Figure 1. SMO receptor antagonist SEN794.

RESULTS AND DISCUSSIONS

MedChem Synthesis. The first synthesis of SEN794, carried out in our Medicinal Chemistry laboratories, delivered ca. 1 g to support in vitro testing and is shown in Scheme 1.

It entails 7 linear steps with an overall yield of 7%, including two Pd-catalysed coupling reactions and two diazotizations. We felt that most of the transformations could be modified and made amenable for scale-up, such as replacing the $SnCl_2$-nitroreduction and the poor-yielding and—as a result of the use of TBTU—expensive final amidation. Nevertheless, the route suffered from two principal drawbacks: (1) use of two potentially hazardous diazotizations; and (2) the Negishi coupling in step 2, which gave poor yields and which is unfavorable due to the high cost of the 5-methyl-2-pyridylzinc bromide.

First Generation Optimisation. Most of the problematic steps of the MedChem route are located in the initial part of the synthesis. Consequently, we were keen on redesigning the synthetic route to identify an alternative route to the key intermediate **7**. Rather than disconnecting the heteroaryl−aryl system **7** via metal-catalysed cross coupling,[6] we considered constructing the pyridine ring via classical heterocyclic chemistry. The method described by Kröhnke[7a] to prepare substituted arylpyridines struck us as highly attractive, as it starts from commercially available raw materials and does not require a dehydrogenation step as in the conventional Hantzsch pyridine synthesis.

Mechanistically, the pyridine ring is formed through a series of steps (Scheme 2). The pyridinium salt **13** is generated via halogenation of **12** and *in situ* substitution with pyridine. The methylene group in **13** is highly activated for the Michael addition to methacrolein **14**, thus generating the 1,5-dicarbonyl species **15**, which is cyclised with NH_4OAc and gives the key intermediate **7** after elimination of pyridine.

While the literature precedent[7b] employed pyridine as solvent for the one-pot iodination and displacement with

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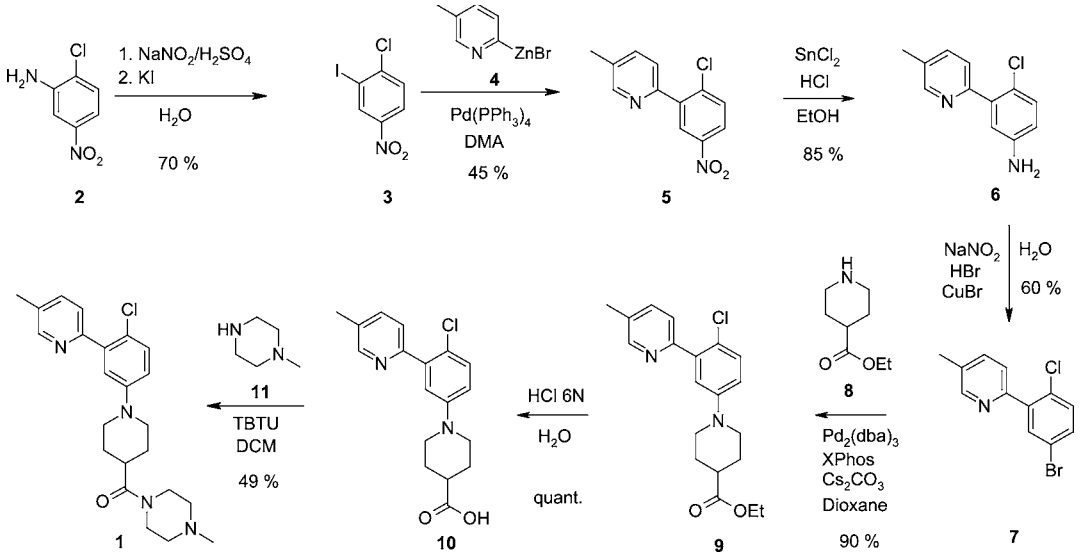
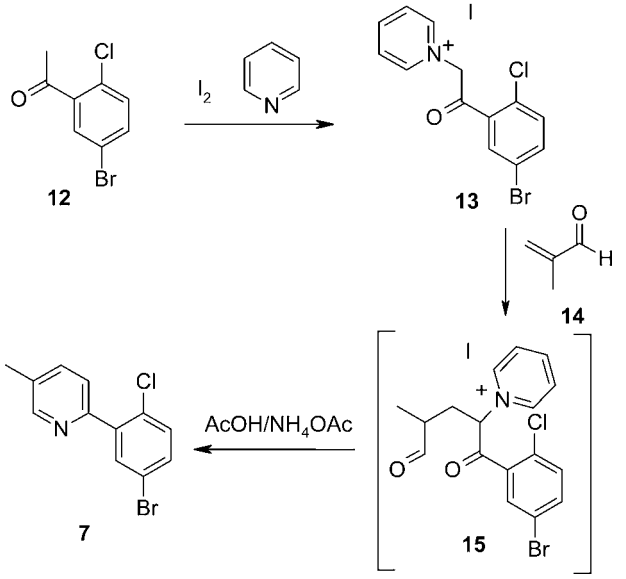
Scheme 1. MedChem Route to Compound 1



Scheme 2. Access to Key Intermediate 7 from Acetophenone 12



pyridine, we were able to reduce the excess pyridine to 5 equiv, using EtOH or iPrOH at reflux as reaction solvents. The desired pyridinium salt **13** precipitated when cooling the reaction mixture and was isolated by filtration. For scale-up to 250 g, iPrOH was preferred due to the lower solubility of the salt **13** in iPrOH and hence the better recovery (70−74% yield, at 98 area % HPLC purity).

Pyridinium salt **13** was then heated with methacrolein and ammonium acetate in MeOH. Disappointingly, the desired pyridine **7** was formed only in traces, with the unconverted starting material being the main product (Table 1, entry 1). The addition of acetic acid to the reaction mixture turned out to be key to improving the conversion (Table 1, entry 2). Furthermore, by increasing the reaction temperature (EtOH at reflux), the reaction was accelerated to give complete conversion after 4 h and a 66% isolated yield after chromatography on a 5 g scale (Table 1, entry 4).

Table 1. Optimisation of the Kröhnke Pyridine Formation

entry	reagents	solvent	yield
1	methacrolein (2 equiv), NH_4OAc (10 equiv)	MeOH, reflux, 18 h	trace[a]
2	methacrolein (2 equiv), NH_4OAc (10 equiv), AcOH (10 equiv)	MeOH, reflux, 18 h	68%[b]
3	methacrolein (1.5 equiv), NH_4OAc (5 equiv), AcOH (5 equiv)	MeOH, reflux, 20 h	67%[b]
4	methacrolein (1.5 equiv), NH_4OAc (5 equiv), AcOH (5 equiv)	EtOH, reflux, 4 h	66%[b]

[a]Main product: unconverted starting material **13**. [b]Isolated yield after chromatographic purification.

At the same time, it was demonstrated that the equivalents of methacrolein/ammonium acetate/acetic acid could be reduced from 2/10/10 to 1.5/5/5 without adverse effect on reaction rate and reaction profile (Table 1, entries 3 and 4). These conditions proved to be robust in the scale-up, furnishing 152 g of pyridine **7** in 71% yield with excellent purity (99 area % HPLC) after recrystallisation from iPrOH/H_2O 1:4 (Scheme 3).

With the aryl bromide **7** in hand, we turned our attention to the Buchwald−Hartwig coupling with ethyl isonipecotate **8**. In the past, we had obtained good results for the N-arylation of similar substrates with the catalyst system $Pd(OAc)_2$/BINAP in toluene. BINAP as ligand is desirable, as its use is not covered by patents.

With ca. 6 mol % of catalyst and ligand, complete conversion was reached in 3−18 h in toluene at reflux. The hydrodechlorinated product **16** (Figure 2), however, was always observed as side product at about 4 area % HPLC, increasing to 8 area % when reaction times were extended. It was found that the corresponding acid of **16** could be reduced to 1−1.5 area % when crystallizing acid **10** in the subsequent step. Nevertheless, with a view to maximizing the yield of the Buchwald−Hartwig coupling and eliminating potential purity issues downstream, we sought to minimize the formation of impurity **16.**

We reasoned that reducing the reaction time was crucial to suppress the presumed Pd-mediated hydrodechlorination side reaction. A significant improvement was obtained when Cs_2CO_3 from a different supplier was used. Literature precedent[8] indicates a strong influence of the Cs_2CO_3 particle

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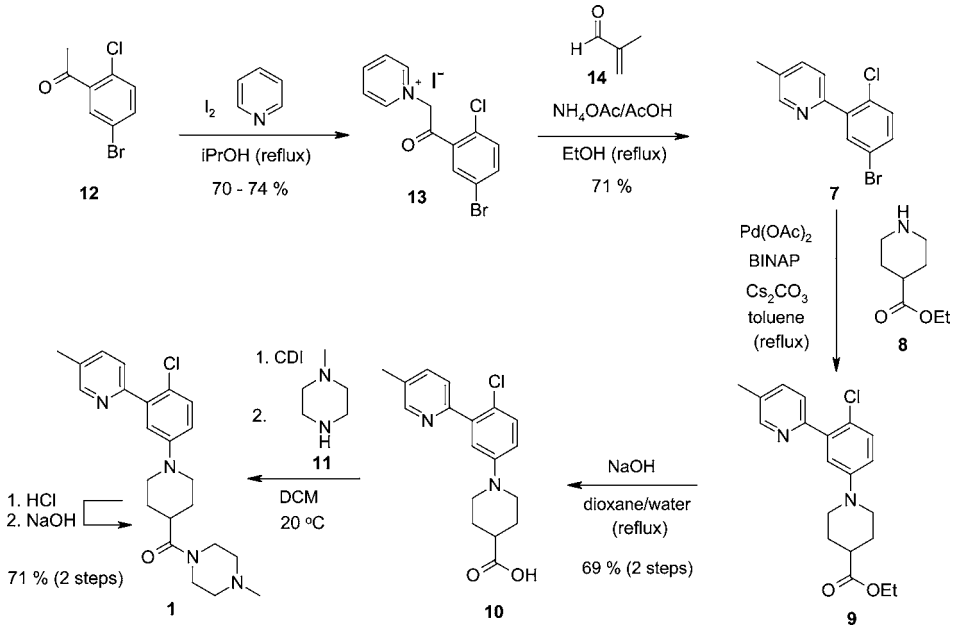
Scheme 3. First Generation Optimisation



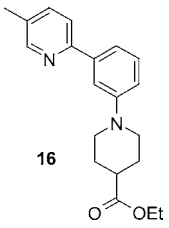


Figure 2. Hydrodechlorinated impurity **16**.

size on the reaction rate of Pd-catalysed N-arylations. In fact, we observed that when using a batch of Cs_2CO_3 with a smaller particle size,[9] the coupling reaction was fast, and on both 10 and 330 g scale complete conversion was obtained in 2−3 h.

Gratifyingly, also less than 0.5% of product **16** was formed in these reactions. The coupling product **9**, even when at high purity, was found to be an oil. Therefore, the crude product **9** (80−85 area % HPLC purity) was telescoped into the next step, where the crystalline acid **10** would allow an efficient purification.

The saponification went smoothly with aqueous NaOH in dioxane. Nonacidic impurities were removed by extraction with iPrOAc. Then adjustment of the reaction mixture to pH 5 precipitated the acid **10**. The purity could be enhanced from 95 to 98 HPLC area % by triturating the solid with hot EtOH.

For the amidation, we replaced TBTU as coupling agent with the more cost- and atom-efficient 1,1′-carbonyldiimidazole (CDI). In dichloromethane as solvent, the activation and coupling steps proceeded at room temperature. On a 5 g scale, the reaction was complete within 3 h, while conversion was slower on larger scale, requiring up to 3 days for nearly complete conversion. It is likely that differences in the quality of the acid **10**, in particular a higher water content in the larger scale reaction, caused the slow conversion. At this point, time constraints to deliver the final compound did not allow further investigations to resolve this issue. In the workup, excess N-methylpiperazine, imidazole, and residual acid were purged by washing the dichloromethane product solution with aqueous NaOH. Crude product **1** (HPLC purity of 98 area %) was obtained as a foam. We did not succeed in converting the foam into a crystalline solid, and therefore, we decided to purify **1** by formation and crystallization of a suitable salt.

A brief screen of acids and solvents revealed that, with aqueous HCl in acetone, the HCl salt could be obtained in good purity (98 area %), yield (85% for amidation and salt formation), and physical form (crystalline powder confirmed by X-ray powder diffraction). Subsequently, liberating the free base **1** initially gave an oil, which however was transformed into a filterable solid by cooling a hot EtOAc solution of the free base. The salt formation/free basing gave the final compound **1** with a purity of 99 area % as a partially crystalline powder, as determined by X-ray powder diffraction.

In summary, the first generation optimisation delivered a scaleable route, with the Kröhnke reaction providing an efficient access to the key intermediate **7**. The new route delivered 122 g of **1** and features a significantly improved overall yield of 26% vs 7% of the MedChem synthesis and six synthetic steps, without any chromatographic purification.

Second Generation Optimisation. The requirement for more SEN794 **1** for further in vivo tests gave us the opportunity to re-examine and improve the synthesis with the intention to carry out the major part of the campaign in a 10 L jacketed reactor. In particular, we were interested in optimizing three issues that we encountered in the work described above: (1) Replace I_2 and reduce the excess pyridine in the formation of the pyridinium salt **13**. (2) Better understand and control the reaction stages in the Kröhnke reaction. (3) Simplify the isolation and purification of the final material **1**.

In the first generation optimisation, the pyridinium species **13** was formed through in situ iodination of the acetophenone by the pyridine−iodine complex, followed by nucleophilic substitution of the iodide with pyridine. We felt that separating the two stages and replacing the iodination with a bromination would be advantageous (Scheme 4). Bromine is easier to dose than iodine, and carrying out the nucleophilic substitution with pyridine in a separate step should allow using just 1 equiv of pyridine. We also found that employing CH_3CN as reaction

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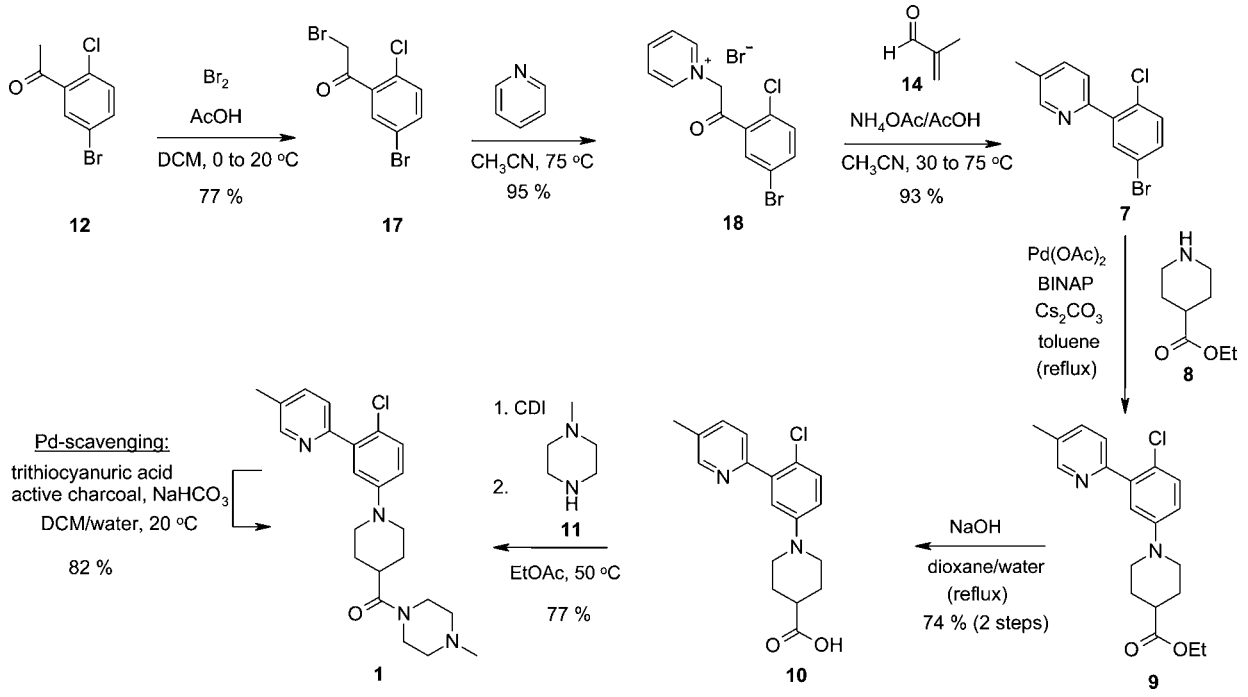
Scheme 4. Second Generation Optimisation



solvent both in the pyridinium salt formation as well as in the Kröhnke reaction was advantageous because of (1) better recovery of pyridinium salt **18** due to its lower solubility in CH_3CN vs. iPrOH and (2) a cleaner profile in the Kröhnke reaction with CH_3CN vs. EtOH.

Satisfyingly, these modifications worked well in practice. A bromine solution in dichloromethane was added over 2 h to the acetophenone **12** in dichloromethane, thus controlling the exotherm. After aqueous workup and solvent swap to cyclohexane, impurities including traces of unreacted starting material were purged efficiently by recrystallisation from cyclohexane, giving the bromide **17** as a white crystalline solid (1.36 kg). Upon reaction with pyridine in CH_3CN at reflux (Method A in the experimental part), the insoluble pyridinium salt **18** formed as an off-white solid in high purity (98% area HPLC) and was simply filtered off.

Alternatively, it was demonstrated on a 40 g scale that the bromoketone **17** did not need to be isolated but could be telescoped into the next step (Method B in the Experimental Part). To that end, the dichloromethane solution of crude **17** was solvent-swapped to acetonitrile and reacted with pyridine to give pyridinium salt **18** of equivalent quality and with a comparable yield (76% vs 73%) to Method A.

For the subsequent Kröhnke reaction, the excess of the reagents was further decreased without adverse effect to 1.1 equiv with regard to the methacrolein **14** and 2.5 equiv each for the ammonium acetate and acetic acid. Evidence for the stepwise mechanism of the pyridine formation was provided by UPLC-MS, documenting the formation of the 1,5-dicarbonyl intermediate **15** (see Scheme 2). The Kröhnke reaction actually gave a cleaner profile when the reaction was carried out stepwise to initially form the intermediate **15** at 30 °C (1.5−2 h), with subsequent heating to reflux to afford the cyclisation/elimination. For workup, the acetonitrile was partially evaporated, and then water was added and the precipitate recovered by filtration, giving an excellent yield (200 g, 93% vs 71% obtained previously) of **7** at high purity (98 area % HPLC).

No changes were made to the conditions for the Buchwald reaction and the saponification, and the results of the earlier campaign were reproduced.

With regard to the formation of final product **1**, we aimed at (1) reducing the long reaction times required in the first generation optimisation and (2) streamlining the workup procedure and avoiding the salt formation/free base liberation to purify the product.

We envisaged that replacing dichloromethane with a higher boiling solvent such as CH_3CN or EtOAc would speed up the reaction. This was confirmed experimentally: in both solvents at 50 °C, the activation of the acid **10** and the coupling with the *N*-methylpiperazine went to completion in 1 and 3 h, respectively.

Our preferred choice was EtOAc, as we had previously observed that the reaction product **1** was poorly soluble in EtOAc, and we hoped that it would be possible to crystallize it directly from the reaction mixture, leaving impurities and byproducts in solution. In practice, with 5 volumes of EtOAc at 50 °C, the activation (1 h) and amidation (2 h) were fast, and gratifyingly, upon cooling to −5 to 0 °C the desired product **1** crystallized and was recovered in good yield (74%, 92g) and excellent purity (99 area %) in a single crop.

We were aware that palladium residues from the Buchwald reaction might contaminate the final product, and in fact, various batches of the amide **1** were found to contain between 1200 and 2200 ppm palladium (determined by ICP-MS).

We opted for inserting a palladium-removal step[10] at the stage of the amide **1** rather than the coupling product **9**, as we believed that the crystallizations of the acid **10** and the amide **1** would have already taken out the major part of the palladium, thus requiring less of the scavenging agent. Indeed, the palladium content was reduced by a factor of 5 going from the coupling product **9** to amide **1**, but it was still far too high for our specifications. We screened various scavengers (Table

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2): trithiocyanuric acid/activated carbon,[11] activated carbon,[12] polymer-bound tris(aminoethyl)amine,[13] and $NaHSO_3$.[14]

Table 2. Palladium Scavenging Experiments

entry	compd	scavenger	palladium content[a]
1	ester **9**	no scavenger	8500 ppm
2	amide **1**	no scavenger	1843 ppm
3	amide **1**	trithiocyanuric acid/activated charcoal[b]	61 ppm
4	amide **1**	$NaHSO_3$[c]	190 ppm
5	amide **1**	activated charcoal[d]	379 ppm
6	amide **1**	polymer-bound tris(aminomethyl) amine[e]	704 ppm

[a]Determined by ICP-MS. [b]20 mol % trithiocyanuric acid, 20% w/w activated charcoal, dichloromethane, 20 °C, 2 h. [c]$NaHSO_3$ (4 equiv), dichloromethane/H_2O (1:1), reflux, 2 h. [d]10% w/w activated charcoal, dichloromethane, 20 °C, 16 h. [e]50% w/w polymer-bound tris-(aminomethyl)amine (3.5−5.0 mmol/(g N loading)), dichloromethane, 20 °C, 16 h.

On scale, amide **1** was treated with trithiocyanuric acid (20 mol %) and active charcoal (20% w/w) and stirred vigorously in a two-phase dichloromethane/aqueous $NaHCO_3$ system. After filtration and washing the dichloromethane phase with aqueous NaOH to remove excess trithiocyanuric acid, dichloromethane was solvent swapped to acetone, leading to the precipitation of **1** as a white crystalline solid. The Pd-content was reduced to 20 ppm (from 2239 ppm in crude **1**). Final product **1** was obtained with a yield of 82% and a purity of 98% area (HPLC).

CONCLUSIONS

A practical route for the SMO antagonist SEN794 **1** was developed. A new and efficient access to the key intermediate **7** via the Kröhnke reaction was found, significantly simplifying the synthesis and reducing costs. The overall yield was increased from 7% in the original medicinal chemistry route to 26% in the first optimization and further to 31% in the second optimization. The optimized route consists of six chemical steps plus a palladium scavenging step. The intermediates are solids and were isolated by filtrations, except for ester **7**, which was telescoped as the crude oil into the subsequent step. In the final amide formation step, target compound **1** was conveniently crystallized from the reaction mixture in high purity. The route described herein should be scalable with only minor adjustments in the work-ups. Due to the urgency to deliver final product **1** for in vivo studies, it was not possible to carry out all steps on scale under the optimized reaction and workup conditions.

EXPERIMENTAL PART

The reported yields are corrected for purity and water/solvent content of the products. Generally, the reactions were monitored by HPLC and purities/conversions quoted refer to HPLC area % at 254 nm. HPLC method: Waters Symmetry C18 3.5 μm 4.6 × 75 mm column, flow rate 0.8 mL/min, mobile phase A 0.76% aq K_2HPO_4 buffer or 0.1% aq formic acid, mobile phase B acetonitrile, gradient (18 min) 95:5 A/B to 20:80 A/B over 10 min, then 5 min equilibration at 20:80 A/B.

UPLC-MS analyses were run using a Acquity Waters UPLC equipped with a Waters SQD (ES ionization) and a Waters Acquity PDA detector, using a column BEH C18 1.7 μm, 2.1 mm × 50 mm. Gradients were run using 0.1% NH_4HCO_3 water/acetonitrile 95/5 and acetonitrile with a gradient 95/5 to 15/85, flow: 0.8 mL/min over 3 min or 0.05% formic acid water/acetonitrile 95/5 and acetonitrile with a gradient 95/5 to 100, flow: 0.8 mL/min as stated in the examples. Retention times are expressed in minutes. Temperature: 40 °C. UV Detection at 215 and 254 nm. ESI+ detection in the 80−1000 m/z range.

Synthesis of 2-Bromo-1-(5-bromo-2-chloro-phenyl)-ethanone (17). 2-Chloro-5-bromoacetophenone (**12**, 1345 g, 5.7 mol, 1 equiv) was charged under a blanket of nitrogen to a jacketed reactor, equipped with 2% aq sodium thiosulfate and a 1 N aq NaOH trap for scrubbing the off-gases. Dichloromethane (2.5 L) was added, followed by AcOH (32.7 mL, 0.57 mol, 0.1 equiv) and by another 2.5 L of dichloromethane, and the mixture was stirred for 20 min at +5 °C.

A solution of Br_2 (959 g, 6 mol, 1.05 equiv) in dichloromethane (5 L) was then added dropwise over 2 h, maintaining the temperature between 0 and 5 °C. After complete addition, the mixture was stirred for 1 h at 20 °C, when HPLC indicated 90 area % conversion of the starting material, corresponding to a conversion of >97% w/w due to the stronger UV absorbance of the starting material **12**.

Then 4 L of the dichloromethane was removed by distillation at 600 mbar. The resulting mixture was washed with aqueous sodium thiosulphate (2% wt solution, 3 L), water (2 × 3 L), NaOH 0.2 M solution (3 L), and again water (2 × 3 L). To switch the solvent from dichloromethane to cyclohexane, another 1 L was distilled off the organic phase, and cyclohexane (2.5 L) was added. Then the residual dichloromethane was distilled off under reduced pressure (35 °C, 400 mbar) to give a clear yellow solution, which was cooled to 0 °C and stirred for 1 h, affording a white precipitate. After filtration via Buchner funnel and drying under vacuum for 16 h at room temperature, 1224 g (69% yield) of a white solid was obtained (HPLC purity 98.4%).

The mother liquor was concentrated under vacuum to half of its original volume, and the residue was cooled to 0 °C, filtered, and dried on the filter for 16 h, giving a second crop of **17** as a pale yellow amorphous solid (140 g, 8% yield). HPLC purity 90.2%. Total yield: 1364 g (77%). UPLC-MS: t_R = 1.64 min, no ionization. HPLC: t_R = 9.30 min. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.68 (d, J = 2.4 Hz, 1H); 7.56 (dd, J = 8.4 Hz, 2.4 Hz, 1H); 7.32 (d, J = 8.4 Hz, 1H); 4.48 (s, 2H). ^{13}C NMR (100 MHz $CDCl_3$): δ 192.9, 137.8, 135.8, 133.1, 132.2, 130.4, 121.2, 34.4.

Synthesis of 1-[2-(5-Bromo-2-chloro-phenyl)-2-oxo-ethyl]pyridinium Bromide (18), Method A. In a 3 L 4-neck round bottomed flask, equipped with and overhead stirrer, thermometer, and condenser, bromoacetophenone **17** (223 g, 715 mmol, 1 equiv) was dissolved in CH_3CN (1.5 L). Then pyridine (57.5 mL, 715 mmol, 1 equiv) was added in one portion. The mixture was stirred for 2 h at 75 °C when HPLC showed complete conversion. The reaction mixture was aged for 30 min in an ice bath (5 °C), and the precipitate was filtered off and washed with CH_3CN (2 × 500 mL). The solid was dried for 1 h under suction on the filter, giving 265 g (95% yield) of **18** as an off-white solid. UPLC-MS: t_R = 0.87 min, m/z = 310 $[M + H]^+$. HRMS calcd for $C_{13}H_{10}BrClNO$ $[M]^+$ 309.9629, found 309.9631. HPLC: t_R = 2.60 min; purity 97.5%. Mp (DSC): 269 °C. ^{1}H NMR (400 MHz DMSO-d6): δ 8.99 (d, J = 5.6 Hz, 2H); 8.75 (t, J = 8.0 Hz, 1H); 8.31−8.27 (m, 3H); 7.92 (dd, J = 8.8 Hz, 2.4 Hz, 1H); 7.66 (d, J = 8.8 Hz,

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1H); 6.42 (s, 2H). ^{13}C NMR (100 MHz $CDCl_3$): δ 190.7, 147.3, 146.8, 137.7, 137.6, 135.2, 134.0, 131.7, 128.5, 120.9, 68.4.

Synthesis of 1-[2-(5-Bromo-2-chloro-phenyl)-2-oxo-ethyl]pyridinium Bromide (18), Method B. In a 1 L 4-neck round bottomed flask, equipped with overhead stirrer, thermometer, and condenser, acetophenone **12** (40 g, 171.6 mmol, 1 equiv) was dissolved in dichloromethane (80 mL), followed by acetic acid (0.96 mL, 17 mmol, 0.1 equiv) and dichloromethane (80 mL).

The yellow solution was stirred for 20 min at 20 °C. Then 1 mL of a solution of Br_2 (27.5 g, 172 mmol, 1 equiv) in dichloromethane (160 mL) was added via dropping funnel. After disappearance of the orange colour, the remaining Br_2 solution was added dropwise over 30 min. The mixture was stirred at 20 °C; the reaction stalled at 86% conversion (by HPLC) after 14 h, and no further conversion was observed in the subsequent 3 h (total reaction time 17 h). N_2 was bubbled through the orange solution for 20 min to remove HBr (employing 2% aq sodium thiosulfate and 1 N NaOH traps), and then 160 mL of dichloromethane was removed at the rotary evaporator. The remaining solution was washed with 2% aq sodium thiosulfate solution (80 mL), water (2 × 80 mL), 0.1 M NaOH solution (80 mL), and again water (2 × 80 mL).

Then the dichloromethane was solvent swapped to CH_3CN, giving a solution of crude bromoketone **17** (HPLC purity 85.3%, assumed yield 46 g, 148 mmol).

To the CH_3CN solution of **17** in a 1 L 4-neck round bottomed flask, equipped with overhead stirrer, thermometer, and condenser, was added pyridine (11.8 mL, 148 mmol, 1 equiv) in one portion. Then the mixture was stirred for 2 h at 75 °C when HPLC indicated 99% conversion. The suspension was aged for 1 h in an ice bath and filtered and the solid washed with CH_3CN (3 × 80 mL) and dried for 30 min on the filter to give 51 g (76% yield over two steps) of **18** as an off-white solid. UPLC-MS: t_R = 0.87 min, m/z = 310 $[M + H]^+$. HPLC: t_R = 2.60 min; purity 98.3%.

Synthesis of 2-(5-Bromo-2-chlorophenyl)-5-methyl-pyridine (7). In a 5 L 4-neck round bottomed flask, equipped with overhead stirrer, thermometer, and condenser, a suspension of pyridinium salt **18** (296 g, 0.757 mol, 1 equiv) in CH_3CN (2 L) was cooled to ca. 10 °C in an ice bath, and then acetic acid (108 mL, 1.89 mol, 2.5 equiv), NH_4OAc (147 g, 1.89 mol, 2.5 equiv), and methacrolein **14** (68.5 mL, 0.832 mol, 1.1 equiv) were added in one portion each. The reaction mixture was stirred for 1 h at 30 °C in order to complete Michael adduct formation (monitored by UPLC/MS), during which the suspension turned from white to orange. Then the reaction mixture was heated for 17 h at 75 °C.

The reaction mixture was filtered (removal of pyridinium hydrobromide) and then 1.5 L of CH_3CN was distilled off at the rotary evaporator. The mixture was stirred vigorously in an ice bath at ca. 5 °C, and then 2 L of water was added dropwise via dropping funnel. Precipitation of a tan solid started after addition of ca. 0.65 L. After complete addition of the water, the suspension was stirred for 1 h at 5 °C and then filtered, and the solid was washed twice with water. The solid was dried for 18 h in the vacuum oven at 35 °C to give 200 g (93% yield) of **7** as an amorphous tan solid. UPLC-MS: t_R = 1.66 min, m/z = 282 $[M + H]^+$. HRMS calcd for $C_{12}H_{10}BrClN$ $[M + H]^+$ 281.9680, found 281.9682. HPLC: t_R = 8.69 min; purity 97.8%. ^{1}H NMR (400 MHz DMSO-d_6): δ 8.53 (m, 1H); 7.75−7.70 (m, 2H); 7.73 (d, J = 2.4 Hz, 1H); 7.64 (dd, J = 8.0 Hz, 2.4 Hz, 1H); 7.60 (d, J = 8.0 Hz, 1H); 7.53 (d, J = 8.0 Hz, 1H); 2.36 (s, 3H). ^{13}C NMR (100 MHz $CDCl_3$): δ 152.8, 150.3, 140.9, 136.8, 134.5, 132.8, 132.5, 131.7, 131.4, 124.4, 120.9, 18.5.

Synthesis of 1-[4-Chloro-3-(5-methylpyridin-2-yl)-phenyl]piperidine-4-carboxylic Acid Ethyl Ester (9). In a 10 L jacketed reactor, $Pd(OAc)_2$ (31.8 g, 5.9 mol %) and BINAP (94.7 g, 6.3 mol %) were suspended in toluene (6.8 L), a nitrogen atmosphere was established by two cycles of vacuum (200 mbar) and nitrogen (atmospheric pressure), and the mixture was stirred for 45 min at 55 °C.

Cs_2CO_3 (2340 g, 7.2 mol, 3 equiv), followed by aryl bromide **7** (677 g, 2.4 mol, 1 equiv) and ethyl isonipecotate (**8**, 406 mL, 2.6 mol, 1.1 equiv) were added, and the mixture was heated for 2 h at 110 °C, when HPLC showed complete conversion. Then the mixture was cooled to room temperature and filtered through a Buchner funnel to remove the inorganic salts, which were washed with EtOAc (500 mL). The combined organics were washed with water (3 × 3 L) and then filtered. 4.5 L of the solvent was removed under vacuum, and the solution was stirred with activated charcoal (168 g, 25% wt) for 1.5 h at 25 °C. After filtration through a cellulose pad (300 g), the pad was washed with EtOAc (500 mL) and the combined organics were concentrated under vacuum to give 940 g of crude **9** as a brown oil. UPLC-MS: t_R = 1.58 min, m/z = 359 $[M + H]^+$. HRMS calcd for $C_{20}H_{24}ClN_2O_2$ $[M + H]^+$ 359.1521, found 359.1521. HPLC: t_R = 8.49 min; purity 80.6%. ^{1}H NMR (400 MHz $CDCl_3$): δ 8.53 (s, 1H); 7.56−7.52 (m, 2H); 7.30 (d, J = 9.2 Hz, 1H); 7.11 (d, J = 2.8 Hz, 1H); 6.89 (dd, J = 9.2 Hz, 2.8 Hz, 1H); 4.15 (q, J = 7.6 Hz, 2H); 3.65 (dt, J = 12.8 Hz, 4.0 Hz, 2H); 2.81 (td, J = 12 Hz, 2.4 Hz, 2H); 2.42 (m, 1H); 2.39 (s, 3H); 2.01 (m, 2H); 1.84 (m, 2H); 1.26 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$): δ 174.6, 154.5, 150.3, 149.8, 139.3, 136.3, 131.8, 130.4, 124.3, 122.1, 119.0, 117.7, 60.4, 49.0, 40.8, 27.9, 18.2, 14.2.

Synthesis of 1-[4-Chloro-3-(5-methylpyridin-2-yl)-phenyl]-piperidine-4-carboxylic Acid (10). In a 10 L jacketed reactor, crude ester **9** (850 g, 1.85 mol, HPLC purity 78%, 1 equiv) was suspended in mixture of 1,4-dioxane (4 L) and aqueous NaOH solution (170 g NaOH in 2 L of water, 4.25 mol, 2.3 equiv) and then refluxed under stirring for 15 h, when conversion was complete by HPLC.

Then 1,4-dioxane was distilled off under reduced pressure, 2 L of water was added, and the basic aqueous phase was extracted with iPrOAc (3 × 1.5 L). The aqueous phases were then acidified to pH 4.5 by adding HCl solution (360 mL of 37% HCl in 1.7 L of H_2O), and the resulting suspension was aged at 5 °C for 1.5 h. After filtration and washing the filter cake with water, 1180 g of crude **10** was isolated as a yellow solid. Crude **10** was suspended in 5 L of EtOH, heated at reflux for 1 h and then cooled to 20 °C, and filtered through a Buchner funnel, washing with cold EtOH (2 × 550 mL). The solid still contained BINAP derived impurities (3% by HPLC). It was resuspended in EtOH (1.5 L), stirred at 20 °C for 30 min, filtered, and dried for 4 h on the filter and for 16 h at 55 °C in the vacuum oven to give 590 g (73% yield for 2 steps) of **10** as a yellow solid. UPLC-MS: t_R = 1.12 min, m/z = 331 $[M + H]^+$. HRMS calcd for $C_{18}H_{20}ClN_2O_2$ $[M + H]^+$ 331.1208, found 331.1209. HPLC: t_R = 5.77 min; purity 98.3%. Mp (DSC): 263 °C. KF: 0.7% wt water. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H); 7.68 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 8.0 Hz, 1H); 7.32 (d, J = 8.8 Hz, 1H); 7.03−6.98 (m, 2H); 3.65 (d, J = 12.8 Hz, 2H); 2.78 (t, J = 11.6 Hz, 2H); 2.40 (m, 1H); 2.35 (s, 3H); 1.88 (d, J = 13.2 Hz, 2H); 1.62 (q, J = 11.6

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Hz, 2H). ^{13}C NMR (100 MHz $CDCl_3$): δ 176.6, 154.5, 150.5, 150.2, 139.7, 137.2, 132.6, 130.8, 124.6, 120.8, 118.8, 117.8, 48.5, 40.5, 28.0, 18.3.

Synthesis of {1-[4-Chloro-3-(5-methylpyridin-2-yl)-phenyl]piperidin-4-yl}-(4-methylpiperazin-1-yl)-methanone (1). In a 2 L 4-neck round bottomed flask, equipped with an overhead stirrer, condenser, thermometer, and dropping funnel, CDI (58.9 g, 364 mmol, 1.2 equiv) was suspended in EtOAc (400 mL). After the suspension was stirred for 10 min at 20 °C, acid **10** was added (100 g, 303 mmol, 1 equiv), and the reaction mixture was stirred for 1 h at 50 °C until imidazolide formation was complete (monitored by quench with butylamine and subsequent HPLC analysis). Then a solution of *N*-methylpiperazine **11** (37 mL, 333 mmol, 1.1 equiv) in EtOAc (100 mL) was added dropwise over 5 min. The reaction mixture was stirred for 2 h at 50 °C, when HPLC indicated complete conversion.

The mixture was allowed to reach 20 °C (ca.1 h), and then it was cooled to −5 °C (ice/NaCl bath) and aged for 2 h. The suspension was filtered, and the solid was washed twice with cold EtOAc. The off-white solid was dried for 30 min under suction on the filter, giving 92 g (77% yield) of **1**. UPLC-MS: t_R = 0.86 min, m/z = 413 $[M + H]^+$. HPLC: t_R = 2.57 min; purity 99.2%. Pd content (ICP/MS): 2239 ppm.

Palladium Scavenging. In a 2 L 4-neck round bottomed flask, equipped with condenser, overhead stirrer, and thermometer, amide **1** (92 g, 223 mmol), trithiocyanuric acid (8.4 g, 47.4 mol, 21 mol %), and activated charcoal (18.4 g, 20% weight) were suspended in dichloromethane (900 mL). A solution of $NaHCO_3$ (35 g) in water (350 mL) was added in one portion, and then the resulting mixture was vigorously stirred for 2.5 h at 20 °C and then for 1 h in an ice bath (ca. 5 °C). The aqueous−organic mixture was filtered through a cellulose pad, and after washing with dichloromethane (3 × 200 mL), the phases were separated, and then the organic phase was washed with 1 M NaOH (3 × 500 mL) and water (2 × 500 mL). Dichloromethane was solvent swapped to acetone by repeated addition of acetone and evaporation to give a suspension of a fine white powder. Filtration gave 75 g (82%) of **1** as a white crystalline solid. UPLC-MS: t_R = 0.86 min, m/z = 413 $[M + H]^+$. HRMS calcd for $C_{23}H_{30}ClN_4O$ $[M + H]^+$ 413.2103, found 413.2102. HPLC: t_R = 2.57 min; purity 99.1%. Mp (DSC): 173 °C. ^{1}H NMR (400 MHz DMSO-d_6): δ 8.50 (s, 1H); 7.69 (dd, J = 8.0 Hz, 2.4 Hz, 1H); 7.53 (d, J = 8.0 Hz, 1H); 7.32 (d, J = 8.8 Hz, 1H); 7.04−6.98 (m, 2H); 3.73 (d, J = 12.4 Hz, 2H); 3.52−3.42 (m, 4H); 2.84−2.75 (m, 3H); 2.35 (s, 3H); 2.33−2.20 (m, 4H); 2.18 (s, 3H); 1.69−1.61 (m, 4H). ^{13}C NMR (100 MHz $CDCl_3$): δ 173.0, 154.6, 150.4, 150.2, 139.7, 137.2, 132.6, 130.8, 124.6, 120.6, 118.7, 117.6, 55.8/55.2 (signals of 2 conformers), 48.6, 46.2/41.6 (signals of 2 conformers), 37.7, 28.5, 18.3. Pd content (ICP/MS): 20 ppm.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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

Notes

The authors declare no competing financial interest.

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