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A Scalable Route to the SMO Receptor Antagonist SEN826: Benzimidazole Synthesis via Enhanced in Situ Formation of the Bisulfite−Aldehyde Complex

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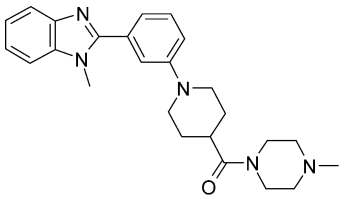
Supporting Information

ABSTRACT: A practical and scalable route to the SMO antagonist SEN826 **1** is described herein, including the discussion of an alternative approach to the synthesis of the target molecule. The optimized route consists of five chemical steps. A new and efficient access to the key intermediate **6** via the bisulfite−aldehyde complex was developed, significantly enhancing the yields and reducing costs. As a result, a synthetic procedure for preparation of multihundred gram quantities of the final product has been developed.

INTRODUCTION

The SMO receptor mediates Hedgehog (Hh) signaling critical to development, differentiation, growth, and cell migration.[1] In 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, Gli2 and Gli3. 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 unmet medical need with regard to tumours in the CNS, Siena Biotech has designed and investigated selective antagonists of the SMO receptor. The newly designed API development candidate SEN826 **1** (Figure 1) is part of a group of potent antagonists of the Hedgehog pathway.[5]



1
SEN826

Figure 1. SMO receptor antagonist SEN826.

RESULTS AND DISCUSSIONS

MedChem Synthesis. The first synthesis of SEN826, carried out in our Medicinal Chemistry laboratories, delivered a few grams of product to support in vitro testing (Scheme 1).

The synthesis starts with the formation of the 2-arylbenzimidazole derivative **6** which can be carried out starting from *N*-methylphenylenediamine **2** (Method A; blue path in Scheme 1) or employing *o*-phenylenediamine **4** in the ring closure reaction followed by *N*-methylation (Method B; orange path in Scheme 1). Sodium hydrogen sulfite is used to promote the condensation of the corresponding *o*-phenylenediamine with the Br-aromatic aldehyde **3**.[6b] The next step is the coupling of the aryl bromide with isonipecotic ethyl ester in Buchwald conditions. After acidic hydrolysis with HCl under microwave irradiation, the final amide **1** was synthesized with CDI as coupling agent. The major issues of this pathway for a multihundred gram scale are:

(a) poor yield in the synthesis of the bromobenzene intermediate **6**;
(b) poor reproducibility (in terms of conversion, impurity profile, reaction time) of the Buchwald coupling when increasing the scale;
(c) silica gel purification of each intermediate;
(d) final product **1** as free base is an amorphous solid, which is difficult to handle.

Evaluation of Synthetic Alternatives. At first we decided to investigate an alternative scalable synthetic pathway. This new route to SEN826 **1** is shown in Scheme 2. Preliminary attempts were carried out on gram scale (1−2 g) in order to

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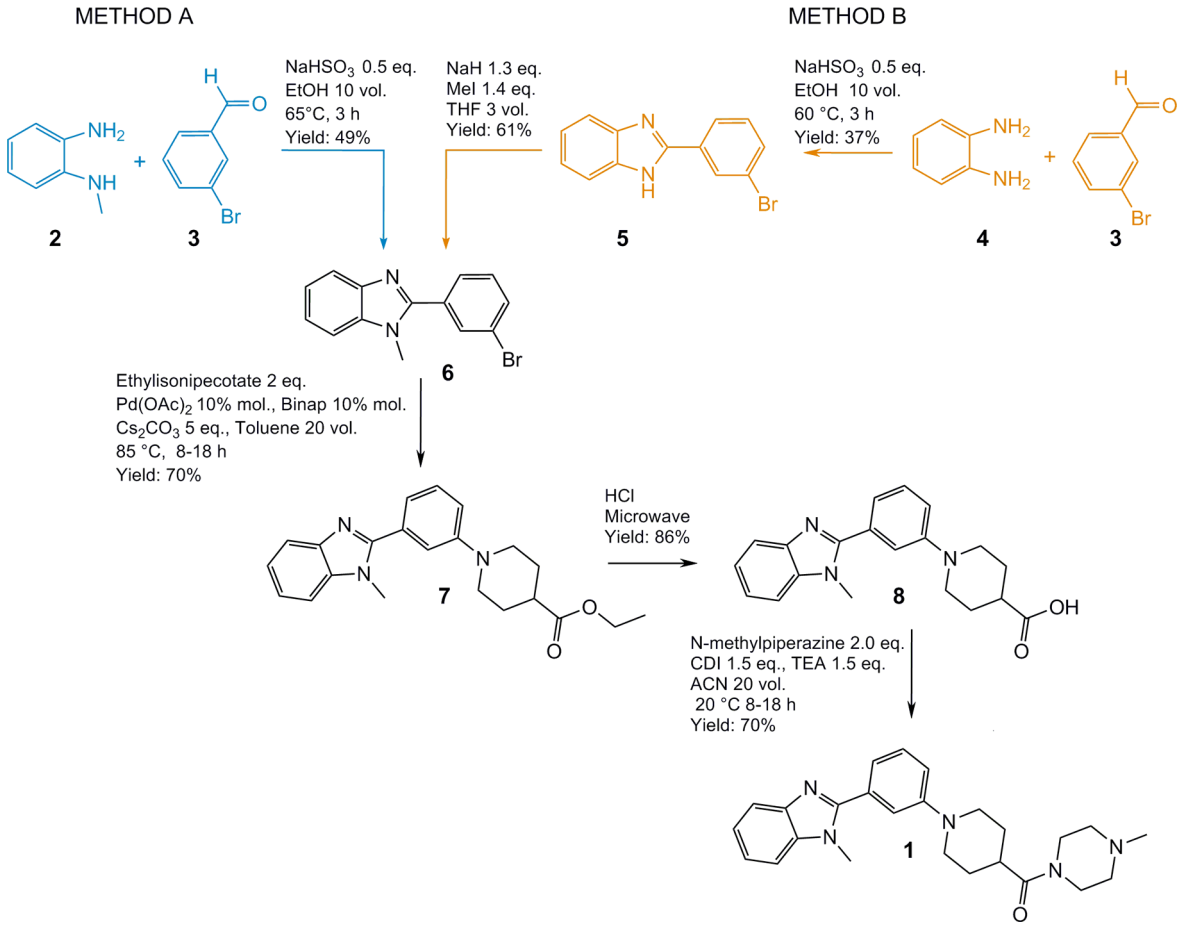
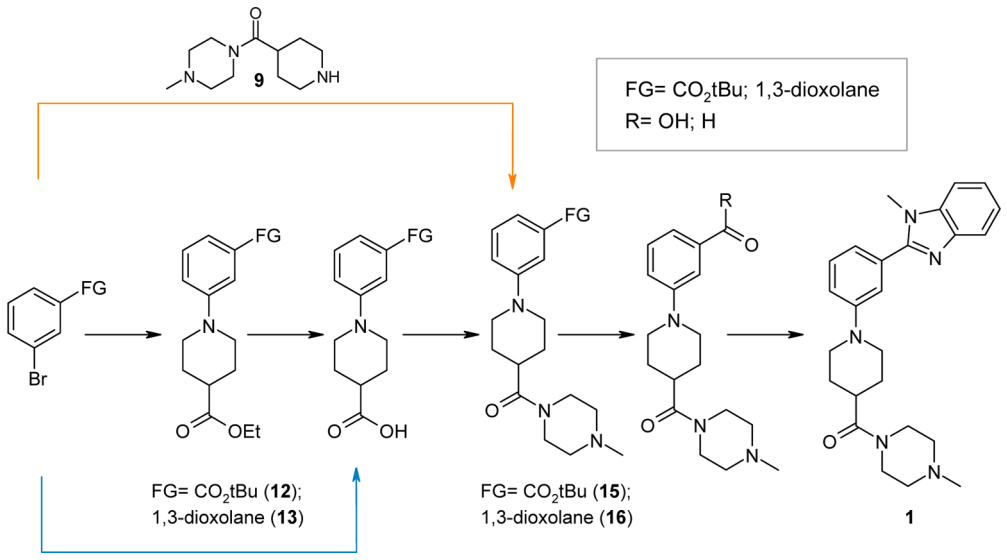
Scheme 1. MedChem Route to compound 1



Scheme 2. Alternative synthetic pathway to compound 1



evaluate HPLC profile (time of conversion, major impurities) and feasibility of each reaction.

3-Br-benzoic-*tert*-butyl ester and 3-Br-phenyl-1,3-dioxolane were considered to be suitable starting materials, as they contain a masked group (respectively a carboxylic acid or an aldehyde) that would allow selective basic hydrolysis of the ethyl ester moiety and, later in the synthesis, would represent a suitable functional group for the ring-closure step to SEN826.[7] Moreover, Buchwald couplings on this compound with primary amines have already been described.[8] The reactivity between the 3-Br-phenyl derivatives and isonipecotic ethyl ester or amine **9** (Scheme 2, orange arrow) was tested using the same conditions of the original Medchem procedure (Scheme 1).[9] All the experiments gave clean HPLC profile but lower yields

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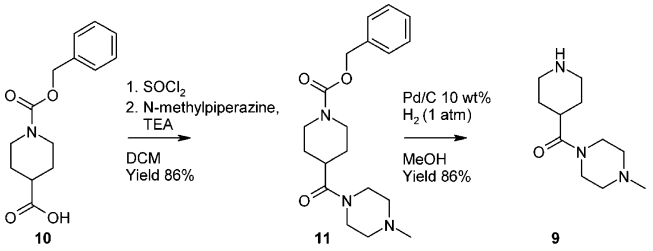
(60%) with respect to the original route. Buchwald coupling between Br-phenyl derivatives and isonipecotic acid (Scheme 2, blue arrow) gave only poor conversion and was not pursued any further.

Next, the direct amidation of the ester (**12** or **13**, Scheme 2) with *N*-methyl-piperazine was examined. By carrying out the reaction in neat conditions, only low conversions (25% a/a by HPLC) were observed. NaH and LDA as strong bases to deprotonate the amine did not improve conversion in this case. Running the reaction with DABCO−$AlMe_3$ complex,[12] an air-stable adduct of trimethyl aluminum, also resulted in low conversion (35% a/a by HPLC), although with a very clean HPLC reaction profile. The ester hydrolysis with aqueous NaOH in dioxane followed by CDI-mediated amidation in acetonitrile worked with moderate yields (yield on two steps: 40−45%) and turned out to be, in our opinion, the best way to obtain the desired amide **15** or **16** (Scheme 2).

At this point, under time and resource limitations the final ring-closure step of the alternative sequence was not tried, and the Medchem pathway was selected for the optimization. The original synthesis appeared much more attractive because of its higher yields in Buchwald coupling, hydrolysis, and amidation stages. However, a useful indication for the design of a new synthetic approach was found: amine **9** underwent the desired cross-coupling and would be an interesting intermediate for an alternative approach. Because of its high cost, a two-step lab synthesis of **9** was developed with an overall yield of 74% giving 50 g of **9** as free base in excellent NMR purity after distillation under reduced pressure (Scheme 3).

Scheme 3. Two-step synthesis of amine 9



The convergent route via amine **9** could be worth considering, provided that the Cbz-protected amine **10** can be sourced at a reasonable price.[11]

Process Optimization. Two campaigns were carried out to synthesize SEN826 batches for preclinical studies (Figure 2). The first one furnished 250 g of the final compound **1** as HBr salt and included some reaction optimization work; the aim of the second campaign, which furnished 500 g of final product as HBr salt, was to improve the yield of the initial stages of the synthesis. The achieved results are described in detail in the corresponding section.

Stages 1 and 2 - Comparison between Methods A and B. *250 g Campaign.* Method A. Studies directed toward the synthesis of the benzimidazole ring began by exploring on gram scale the feasibility of employing 3-Br-benzaldehyde **3** (1.1 equiv), *N*-methylphenylenediamine **2** (1.0 equiv), and sodium hydrogen sulfite (0.5 equiv) in ethanol (10 vol) as solvent. After 3 h at 75 °C (T_{int}) we observed partial conversion (80% a/a by HPLC). On further addition of 0.2 or 0.3 equiv of compound **3**, the reaction was deemed to be complete by HPLC analysis (respectively in 3 or 2 h). The relative impurity

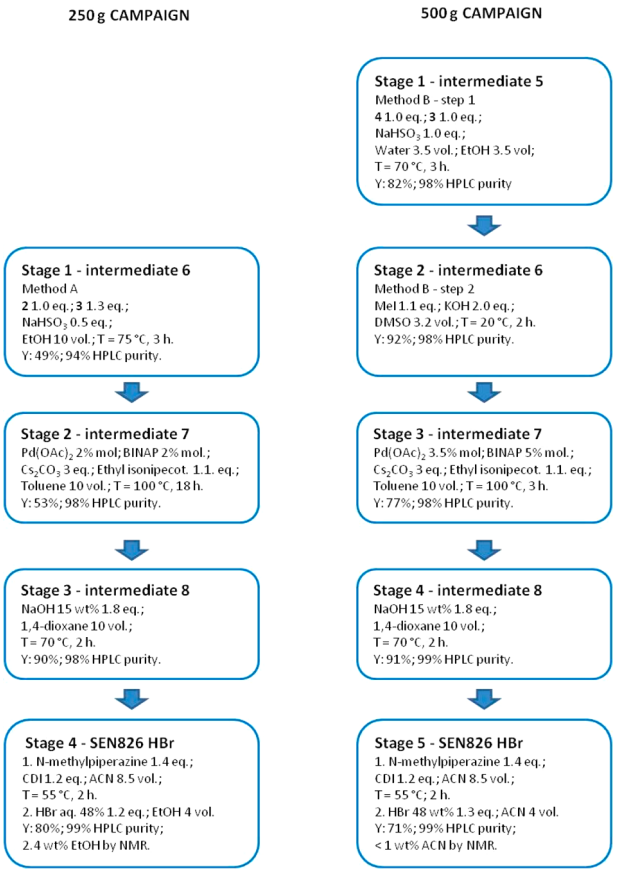


Figure 2. Workflow of 250 g and 500 g process campaigns.

profile determined by HPLC−MS analysis is reported below (Figure 3).

Starting amine **2** (<1% a/a) and 2% a/a of 3-Br-benzoic acid (peak 3 was the major impurity of the commercial aldehyde **3**) were detected together with the desired product **6** (peak 1, Figure 3) and two unidentified impurities (peaks 2 and 4, Figure 3). We hypothesized their structures solely by mass spectra interpretation (Figure 4).

In the next 20-g scale experiment a quite complex sequence of washes was necessary in order to eliminate these impurities (Figure 5).

Fortunately, during the scale up experiment of the first campaign (250 g scale) a solid precipitated while cooling the reaction mixture to room temperature. After filtration, a treatment with active charcoal followed by a trituration with cyclohexane (3 vol) was necessary to obtain the desired intermediate **6** as a brown solid in 94% HPLC purity but only in 49% yield. Method B. Starting from 1,2-phenylidenediamine **4**, the benzimidazole synthesis on gram scale gave a relatively low yield range (20−37%) and a messy HPLC profile under the same conditions employed in method A. Longer reaction time (18 h) or further addition of sodium hydrogen sulfite (up to 0.9 equiv) did not affect the yield or the reaction.[13] We observed a slight improvement in the HPLC profile of the condensation, maintaining the reaction temperature at 60 °C over 6 h (43% a/a of **5**) instead of 75 °C (35% a/a of **5**). The HPLC−MS check at the end of reaction is reported below (Figure 6).

As in method A, starting amine **4** (<1% a/a) and 3-Br-benzoic acid were detected. The latter (peak 2, m/z = 199 $[M - 1]^-$) had the same retention time of an unidentified oligomeric impurity with m/z = 547 $[M + 1]^+$. This explained

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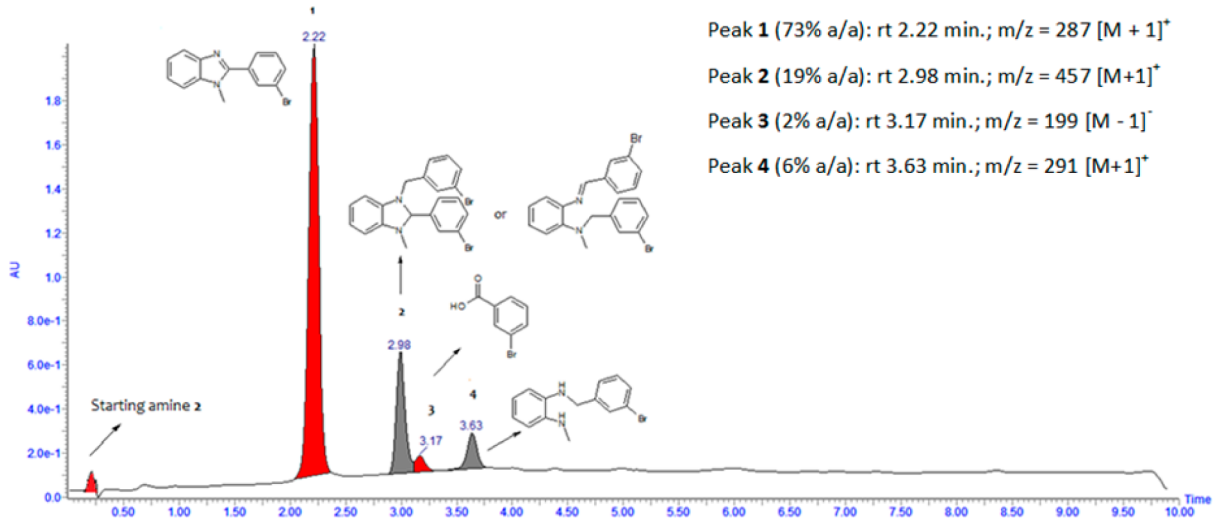

Figure 3. HPLC–MS check at the end of reaction (Method A).

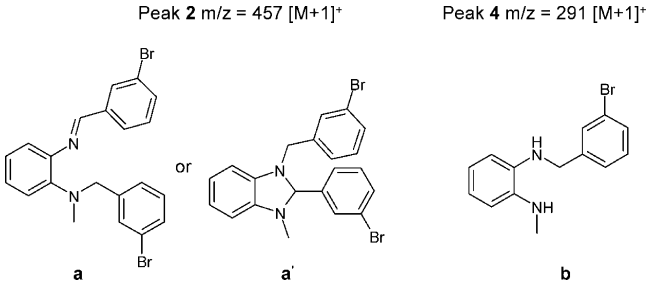

Figure 4. Hypothesized structures **a**, **a**′ and **b** for the major HPLC impurities peaks of Method A.

the increased % a/a of the corresponding signal with respect to Figure 3. We found in literature that in the absence or with a substoichiometric amount of the oxidizing agent (we employed 0.5 equiv), the reaction may lead either to 2-substituted benzimidazole or to "aldehydine" **d** by the *o*-phenylenediimine **c** rearrangement (Scheme 4).[16] Peaks 3 and 4 in Figure 6 actually confirmed this side reaction; since they had the same *m*/*z* value, we carried out a further reaction between *o*-phenylenediamine **4** and aldehyde **3** (without sodium bisulfite) in EtOH in order to distinguish *o*-diimine **c** from aldehydine **d**.

Stirring **4** and **3** in ethanol at room temperature we only observed (by HPLC–MS) the condensation reaction to obtain the diimine intermediate **c** (retention time and $[M + 1]^+$ identical with peak 4 in Figure 6), which rearranged to give **d** (retention time and $[M + 1]^+$ identical with peak 3 in Figure 6) under heating at 60 °C.

Scaling the method B procedure to 250 g of starting material **4**, we recovered after filtration the desired product **5** in 95% HPLC purity and 37% yield. The *N*-methylation of the benzimidazole ring was afforded with NaH (1.3 equiv) in THF (3 vol) at 25 °C in order to isolate **6** in 61% yield and excellent purity (99.1% by HPLC).

We concluded that the two-step procedure (Method B), despite the lower yield, had important advantages with respect to direct formation of **6** (Method A): the use of the cheaper and more stable starting phenylenediamine **4**; the easier workup procedure which avoided the active charcoal treatment; the higher purity of the isolated product which improved the rate of conversion and the general profile of the subsequent Buchwald coupling (see Stage 3 - Buchwald Coupling).

500 g Campaign. At the beginning of the second campaign, we focused our attention on the first two steps of Method B which had 23% overall yield and needed a further optimization. Adjusting the order of addition of the reactants, we confirmed that the water insoluble bisulfite–aldehyde complex **14** could be quantitatively formed by addition of the ionic nucleophile HSO_3^- as reported in Scheme 5.[6a,14]

After the addition of ethanol as cosolvent (5.5 vol) to the aqueous suspension, the adduct **14** seemed to react (on 5 g scale) with 1,2-phenylenediamine (1.1 equiv) in a cleaner way compared to the free aldehyde **3**. After heating at 70 °C for 2 h, the cyclization reaction was complete by HPLC analysis with 11% a/a of the aldehydine **d**.

Repeating the experiment on 50 g scale, we adjusted the reaction conditions in sight of a 500 g scale up. The volumes of

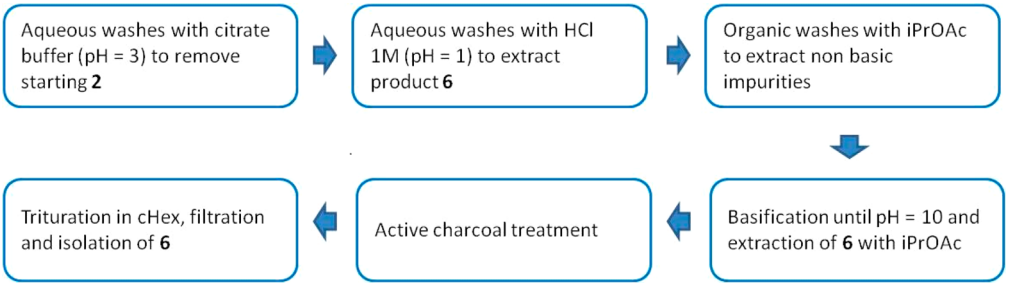

Figure 5. Sequence of washes used to isolate **6** on 20-g scale experiment.

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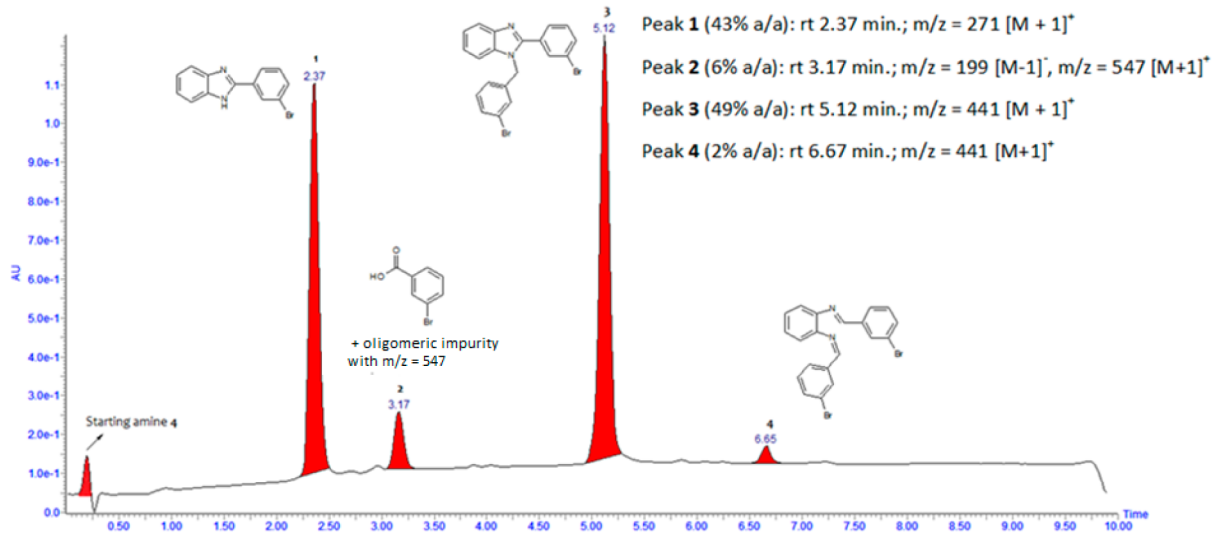
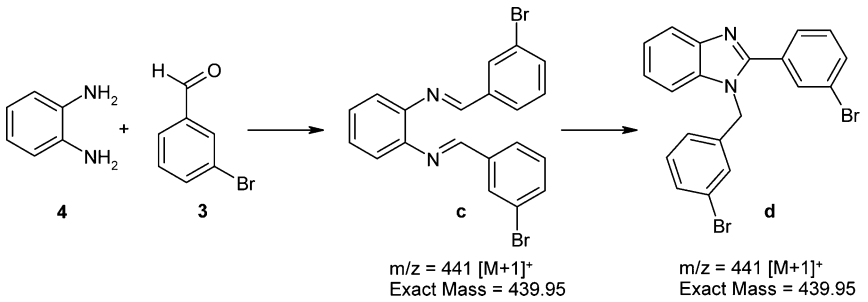
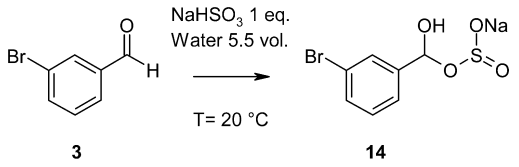


Figure 6. HPLC–MS check at the end of reaction (6 h at 60 °C; Method B).

Scheme 4. Aldehydine formation in the absence of $NaHSO_3$



Scheme 5. *In situ* formation of bisulfite–aldehyde complex 14



solvent (H_2O/EtOH = 1/1) were reduced from 11 to 7; a stoichiometric amount of **4** was used and its rate of addition was regulated in order to maintain the internal temperature of the system below 30 °C. The HPLC–MS check at the end of reaction confirmed a clean reaction profile with major impurities (**c** and **d**) lower than 2% a/a. On 500 g scale, we finally obtained the desired benzimidazole **5** in 82% yield and 98% HPLC purity.

Direct formation of the benzimidazole **6** by cyclization of *N*-methylphenylenediamine **2** with the aldehyde/bisulfite complex **14** was attempted. In the same conditions reported above, we observed complete HPLC conversion after 18 h at 70 °C. A tarry reaction mixture was obtained; after the workup, we recovered **6** as a pale-brown solid in 75% yield and 90% HPLC purity.

Moving to the methylation step, we initially employed MeI (1.2 equiv), potassium carbonate (2 equiv) and acetone (7 vol), but no reaction was observed while stirring them together with **5** at room temperature. Even if complete conversion was achieved upon heating at 35 °C (T_{int}) for 18 h, the formation of a large amount (25% a/a by HPLC) of the bis-methylated side product **f** (Figure 7) lowered the yield to 63%.

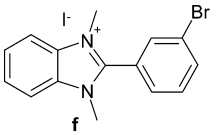


Figure 7. Chemical structure of the benzimidazolium iodide **f**.

We tried to contain the side reaction by adding MeI (1 equiv) to the suspension of benzimidazole **5** (1 equiv) and potassium carbonate (2 equiv) in acetone (7 vol) while heating at 45 °C (T_{int}). In this case the conversion was very low (40% a/a by HPLC after 1 h) and did not change after further addition of MeI (0.5 equiv).[15] Next, we decided to direct our attention to the employment of a stronger base for the benzimidazole deprotonation. The system KOH/DMSO (2.5 equiv in 2 vol) turned out to be optimal for our purpose: on 10 g scale the reaction worked at room temperature, and complete conversion was achieved within 20 min. A simple workup (water addition and filtration) gave the product **6** in 97% yield and 99% HPLC purity. Carrying out the experiment on 40 g scale the concentration was decreased using 3 volumes of solvent in order to minimize the formation of thick slurry throughout the reaction. We observed an exotherm during the deprotonation stage (ΔT = +7 °C, 2.5 equiv of KOH added all at once), the methyl iodide addition (ΔT = +8 °C, 1.0 equiv added over 20 min) and the quench with water (ΔT = +15 °C,

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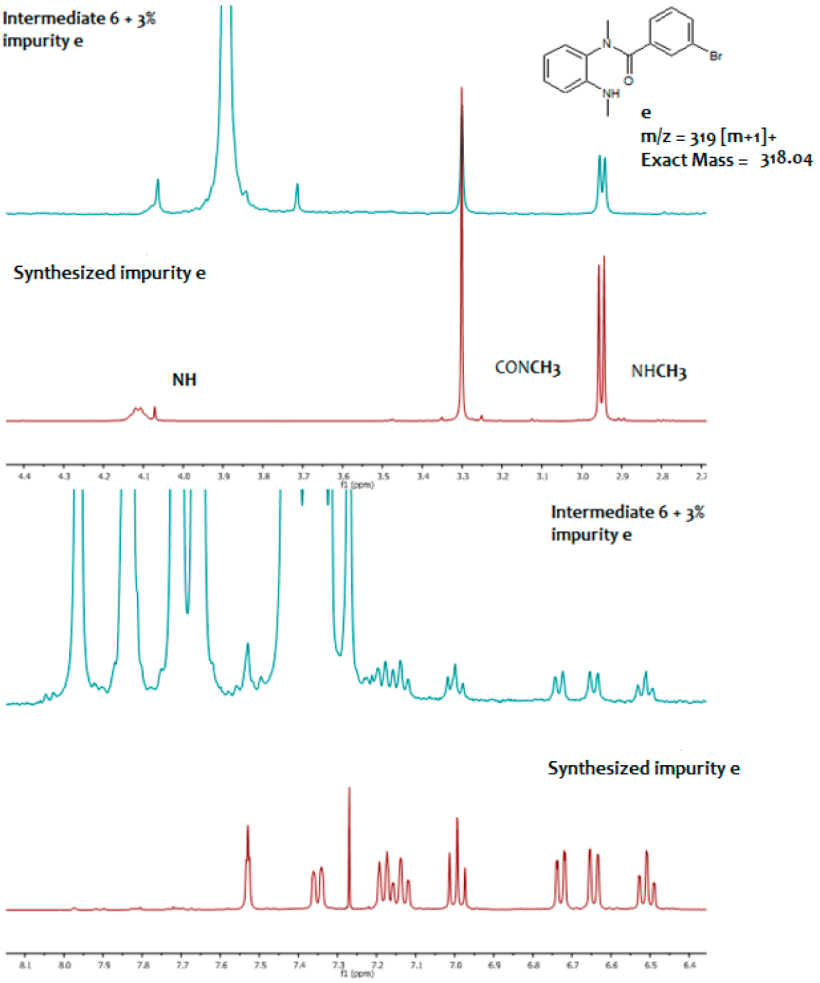

Figure 8. NMR spectra of contaminated **6** and the impurity **e**.

2 vol added over 45 min at 25 °C). Even if the product **6** was recovered in 86% yield and 97% HPLC purity, NMR analysis of the filtered compound showed free aniline peaks, confirming the presence of a partially ring-opened structure (3% mol by NMR spectrum, Figure 8) with m/z = 319 (by HPLC−MS). By the comparison between NMR spectra of contaminated compound **6** and the impurity 319 m/z (see Supporting Information for isolation of m/z 319), we clarified its structure which conforms to the "pseudo base" **e** originated from benzimidazolium iodide **f** by reaction with potassium hydroxide (Figure 8).[16] This was probably due to the excess of KOH employed that generated a strongly basic aqueous environment during the reaction quench.

This issue was solved by adding MeI over 40 min (in order to minimize the formation of **f**), lowering the amount of base employed (2.0 equiv instead of 2.5 equiv) and quenching the reaction at 10−15 °C (T_{int}). In the second campaign experiment (600 g scale), 1.1 equiv of MeI (instead of 1.0 equiv) was necessary to complete the conversion.[17] The efficient heat exchange of the 10 L jacketed reactor allowed an improved control of the exotherms, while the preliminary calorimetric study of the reaction mixture by DSC analysis confirmed a low thermal risk. After crystallization from iPrOAc (2.5 vol), *N*-methylbenzimidazole **6** was isolated in 92% yield, 98% HPLC purity and clean NMR profile.

Stage 3 - Buchwald Coupling: Reproducibility at Larger Scales. Optimization of the coupling reaction was carried out by varying one at time the following parameters: solvent, batch of benzimidazole **6**, temperature, catalyst/ligand loading, cesium carbonate and ethyl isonipecotate equivalents.

Solvent. Toluene and 1,4-dioxane gave the same HPLC reaction profile in preliminary trials. Toluene was preferred since it was a suitable solvent for the crystallization of the desired product **7**.

*Batch of Benzimidazole **6**.* In the experimental trials we observed that rate of conversion was lower when employing the aryl bromide **6** obtained from Method A (94% HPLC purity) with respect to Method B (99% HPLC purity).

Temperature. Employing 5% mol of catalyst/ligand, 5 equiv of Cs_2CO_3 (Alfa Aesar batch, *vide infra*) and 2 equiv of ethyl isonipecotate at 85 °C (T_{int}) in toluene (10 vol) the conversion was partial (92% a/a by HPLC) in 18 h; in the same lapse of time at 100 °C (T_{int}), a complete conversion by HPLC analysis was observed employing the same batch of **6**.

Ethyl isonipecotate. In order to reduce costs and facilitate workup, 1.1 equiv (instead of 2) of ethyl isonipecotate were used without negative effect on the rate of conversion.

Cesium Carbonate. We employed 5 or 3 equiv of base and an identical rate of conversion was observed at 100 °C (T_{int}) in both experiments. Literature precedent indicates a strong influence of the Cs_2CO_3 particle size on the reaction rate of Pd-catalyzed N-alkylations.[18] In fact, we observed that when using a batch of Cs_2CO_3 with a smaller particle size, the coupling reaction was fast and complete conversion was achieved in less

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than 18 h. We qualitatively confirmed by microscope (Figure 9) that the Cabot high-purity grade Cs_2CO_3 (Aldrich product no. 562572) had a smaller particle size than the initially used Cs_2CO_3 (Alfa Aesar product no. 12887). We milled some of the poorly performing Cs_2CO_3 with pestle and mortar, and tested this material in a Buchwald reaction with a similar substrate where it performed equally well compared to the Aldrich Cs_2CO_3. For convenience, however we purchased and used only the Aldrich material from thereon.

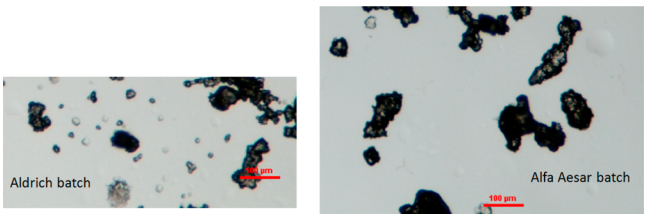

Figure 9. Comparison between the particle sizes of different batches of Cs_2CO_3.

By replacing cesium carbonate with NaO^{t}Bu, the *tert*-butyl ester **g** (Figure 10) was observed as side product (5% a/a by HPLC–MS).

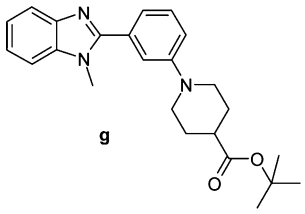

Figure 10. Side-product **g** observed by replacing Cs_2CO_3 with NaO^{t}Bu.

Mechanical Stirring. We also observed that on a smaller scale (10–50 g) mechanical stirring improved the reaction rate, as opposed to magnetic stirring, underlining the importance of efficient agitation when using cesium carbonate in heterogeneous reaction systems.

Catalyst/Ligand. Even if during the preliminary trials the reaction worked well both with $Pd_2(dba)_3$/Xphos in dioxane or $Pd(OAc)_2$/BINAP in toluene, we chose the latter reagents due to their lower cost. Maintaining the temperature at 100 °C, we carried out preliminary experiments with different catalyst loadings (Table 1).

Using 2% mol of catalyst a complete conversion by HPLC was achieved after 18 h; in this case we observed the formation of the dehalogenated starting benzimidazole (5% a/a by HPLC), however removable by trituration in cyclohexane.[19] We decided to employ these conditions for the scale up during the 250 g campaign, with a considerable cost saving and making the purification easier because of the employment of less BINAP. We isolated the desired product **7** in 53% yield and 98% HPLC purity. During the next 500 g scale campaign the catalyst loading was further optimized by premixing in toluene 3.5% mol of $Pd(OAc)_2$ and 5% mol of phosphine in order to favor the Pd(II) precatalyst reduction and improve the reaction rate. Using cesium carbonate with a smaller particle size, we achieved complete conversion in 3 h. Although the trituration was determined to be potentially useful in the purging of impurities, it was found that concentration of the toluene filtrate to an optimal volume (3 vol) produced a precipitated product with the desired impurity profile. So the desired ester **7** was isolated after crystallization from toluene in 77% yield (instead of 70% as in the MedChem procedure, Scheme 1) and 98% HPLC purity.

Table 1. Preliminary screening[a] of different catalyst/phosphine loadings (1:1 molar ratio)

entry	$Pd(OAc)_2$/BINAP loading (% mol)	conversion percentage[b]/time at 100 °C (T_{int})
1	2%	55% - 4 h
		62% - 5 h
		74% - 7 h
		100% - 18 h
2	5%	61% - 2 h
		79% - 4 h
		95% - 7 h
		100% - 18 h
3	8%	85% - 5 h
		100% - 8 h
4	10%	100% - 3.5 h

[a]Poorly performing Cs_2CO_3 was employed during this preliminary screening. [b]% a/a by HPLC analysis of a sample of the reaction mixture.

Stage 4 - Ester Hydrolysis. The synthesis of intermediate **8** was achieved, without further optimization, employing basic hydrolysis conditions (NaOH 15 wt %; 1.8 equiv) in dioxane (10 vol) while heating at 70 °C (T_{int}) for 2 h in both campaigns. After the workup, the desired product **8** was isolated by filtration at pH = 5 in more than 90% yield and more than 98% HPLC purity.

Stage 5 - Amidation and Salt Formation. Initially, for the synthesis of the amide **1** the direct aminolysis of the starting ester was considered. A literature survey showed that a catalytic amount (0.3 equiv) of triazabicyclodecane (TBD) promotes aminolysis.[20] On gram scale the reaction was performed in a pressure tube, heating at 95 °C overnight. Purification by silica column gave the product in 92% yield. However, the scalability of this promising approach was not investigated further because of time limitations.

The synthesis of the final intermediate **1** was achieved by employing CDI as coupling agent (1.2 equiv) in acetonitrile (8.5 vol) at 55 °C, without using TEA as in the MedChem procedure (Scheme 1). The presence of residual water in acid **8** (KF = 1–1.5 wt %) required an overcharge of the coupling agent to achieve full conversion to intermediate imidazolide. In these conditions the reaction profile was clean (by HPLC) and the conversion complete in 2 h. The main issue of this step was the final purification of the amorphous free base **1**. The formation of a filterable salt was then examined in order to enable the purification of the API by crystallization and ensure a suitable and stable physical form. A preliminary screen of four acids (fumaric, sulfuric, hydrochloric and hydrobromic acid) showed that the fumarate and the hydrobromide salt precipitated from an ethanol solution of the free base. While the fumarate appeared to be hygroscopic, the hydrobromide formation was carried out in the 250 g campaign to investigate its purity and recovery. The crude free base isolated after the campaign run contained imidazole (10% mol by NMR) as impurity. It was dissolved in EtOH (4 vol) and treated with 48 wt % aqHBr at 45 °C, followed by seeding the solution and cooling first to 25 °C then to 5 °C. This gave the salt in 90%

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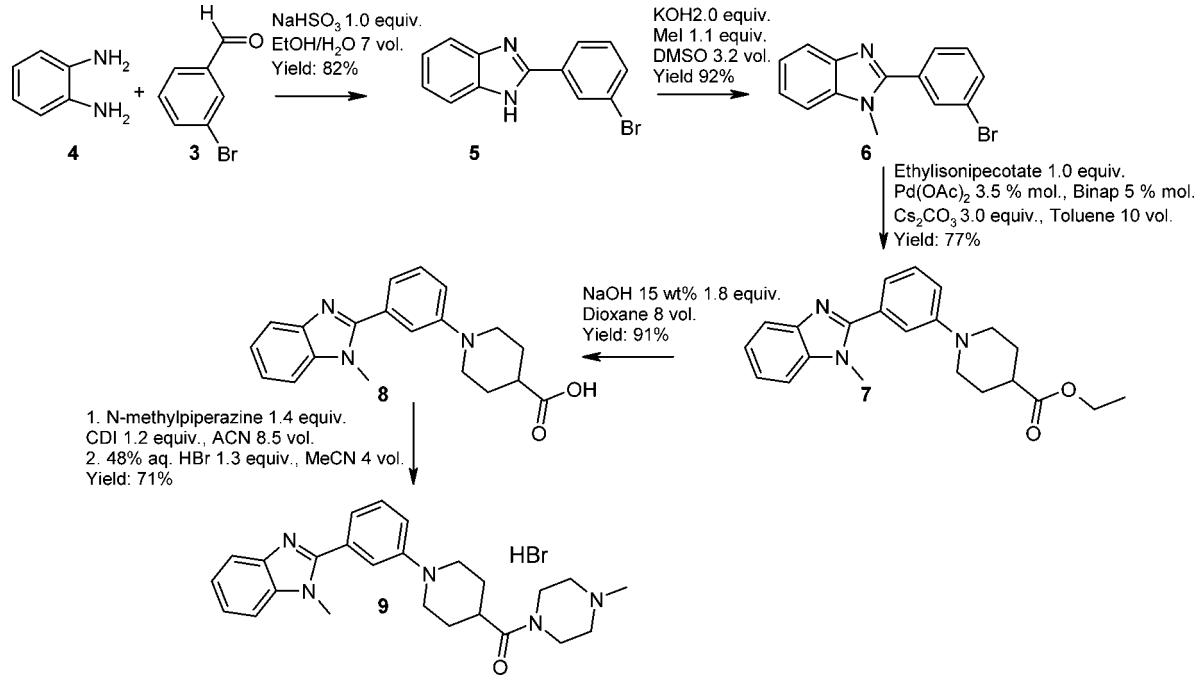
Scheme 6. 500 g campaign final synthetic route



yield with 99% HPLC purity, but still containing 6% mol of imidazole by NMR analysis. Another crystallization from EtOH (3.5 vol) completely removed the coproduct. Then, in spite of drying in the vacuum oven (T_{oven} = 65 °C, p = 10 mbar, 4 d), the EtOH content was reduced only to 2.4 wt %. During drying the colour changed from off-white to yellow without affecting the HPLC purity and giving the desired compound in 80% yield. It is important to note that by using HBr in ethanol for the salt formation and drying the salt at 65 °C for prolonged periods, the formation of EtBr (a genotoxic impurity) was a potential issue. In the 500 g campaign, with the view to the difficulty to remove residual ethanol from the HBr salt in the first campaign, acetonitrile instead of EtOH was employed as solvent for the salt formation. The salt **9** started to precipitate already without adding a seed and was recovered in 71% yield, 99% HPLC purity and less than 1 wt % of residual solvent by NMR (Scheme 6). However, replacing EtOH with acetonitrile did not obviate the GTI issue, since acetamide can form hydrolytically in the presence of HBr and trace of moisture. These aspects have to be considered as forward-looking statements for manufacture of clinical material in the later stages of development.

CONCLUSIONS

Two synthesis campaigns of SEN826 as HBr salt were carried out to give 250 g in the first campaign and 500 g in the second campaign. In order to provide API material for preclinical work, a suitable synthetic route was developed. An alternative route was investigated initially, but was found to be inferior to the original route; however, some useful indications for the design of a new convergent approach were found. Thus, the original route was further optimized. Its main features are:

(1) Robust and high-yielding formation of the key intermediate **6** via the in situ bisulfite−aldehyde complex formation;
(2) Buchwald−Hartwig coupling with improved yield (77%), short reaction time (3 h), reasonably low catalyst loading (3.5% mol of precatalyst; 5% mol of ligand), reasons of poor reproducibility at larger scales elucidated;
(3) No chromatographic purification;
(4) Five-step synthesis with good overall yield (37%); the intermediates are all solids apart from the free base intermediate **1**;
(5) Generally low-cost (except Pd-catalyst) and nonhazardous/toxic (except for MeI and phenylenediamine) reagents.

EXPERIMENTAL SECTION

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 215 nm. HPLC method: Waters Symmetry C18 3.5 μm 4.6 mm × 75 mm column; flow rate 1.0 mL/min; mobile phase A: 10 mM aq K_2HPO_4 buffer or 0.1% aq formic acid; mobile phase B: acetonitrile or acetonitrile 0.1% formic acid; gradient (13 min): 95:5 A/B to 10:90 A/B over 10 min, 2 min at 10:90 A/B then 10:90 A/B to 95:5 A/B over 1 min.

UPLC−MS analyses were run using an Acquity Waters UPLC equipped with a Waters SQD (ES ionization) and Waters Acquity PDA detector. UPLC method: BEH C18 1.7 μm, 2.1 mm × 50 mm column; flow rate 0.6 mL/min; mobile phase A: 0.1% NH_4HCO_3 in H_2O 95%/MeCN 5%; mobile phase B: 100% MeCN; gradient (4 min): 95:5 A/B to 25:75 A/B over 2.1 min, 25:75 A/B to 15:85 A/B over 0.2 min then 1.0 min at 15:85 A/B, 15:85 A/B to 95:5 A/B over 0.2 min then 0.5 min at 95:5 A/B. Retention times were 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-(3-Bromo-phenyl)-1*H*-benzimidazole (5). Sodium bisulfite (281 g; 2.7 mol; 1.0 equiv) was charged to the 10 L jacketed reactor under nitrogen flow and water (1.8 L; 3.5 vol) was added. A clear solution formed after 5 min under stirring. Neat 3-Br-benzaldehyde **3** (500 g; 2.7 mol; 1.0 equiv) was added dropwise over 5 min. The heterogeneous

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mixture was stirred for 20 min while observing an exotherm (ΔT = +5 °C; from 20 to 25 °C) and a white precipitate formation. Ethanol (1.8 L; 3.5 vol) and 1,2-phenylenediamine **4** (307 g; 2.7 mol; 1.0 equiv) were respectively added. The resulting mixture was heated to 70 °C (T_{int}), and after 3 h HPLC analysis showed complete conversion. The reaction suspension was cooled to room temperature (T_{int} = 20 °C) and filtered on a Büchner funnel, washing with EtOH/H_2O = 1/1 (2 × 1.0 L) and water (1 × 1.0 L). The product was dried in an oven (T_{oven} = 40 °C; p = 10 mbar; 18 h) until constant weight. The intermediate **5** (605 g) was isolated in 82% yield as a white solid.

UPLC−MS: t_R = 1.44 min; m/z = 273 $[M + 1]^+$.

HRMS calcd for $C_{13}H_{10}BrN_2$ $[M + 1]^+$ 273.00274, found 273.00278.

HPLC: t_R = 5.04 min; 97.5% purity.

Water content (KF): 0.06 wt %.

^{1}H NMR (400 MHz DMSO-d_6): δ 8.36 (t, J = 1.5 Hz, 1H), 8.18 (dt, J = 7.8, 1.5 Hz, 1H), 7.65 (dm, J = 7.9 Hz, 1H), 7.61 (m, 2H), 7.48 (t, J = 7.9 Hz, 1H), 7.20 (m, 2H).

^{13}C NMR (100 MHz DMSO-d_6): δ 150.3, 150.2, 133.08, 131.83, 129.57, 126.06, 123.10, 122.94, 119.8 (broad), 111.3 (broad).

Synthesis of 2-(3-Bromo-phenyl)-1-methyl-benzimidazole (6). Potassium hydroxide (241 g in pellets; 4.3 mol; 2.0 equiv) was charged to the 10 L jacketed reactor under nitrogen flux and DMSO (0.5 L; 0.9 vol) was added. The resulting suspension was stirred for 15 min while observing an exotherm (ΔT = +5 °C; from 20 to 25 °C). Solid benzimidazole **5** (588 g; 2.2 mol; 1.0 equiv) was then added portion-wise (6 × ∼100 g) over 25 min; an exotherm was observed during the addition (ΔT = +10 °C; from 20 to 30 °C). A solution of MeI (335 g; 2.4 mol; 1.1 equiv) in DMSO (1.0 L) was added over 40 min (ΔT = +3 °C; from 20 to 23 °C), and a solid started to precipitate. After 2 h, HPLC analysis showed complete conversion. Ice (2.0 kg) was added portion-wise followed by water (1.0 L), maintaining the temperature at 15 °C (T_{int}). Next, the white suspension was stirred at 20 °C for 2 h and then filtered on a Büchner funnel, washing with water (2 × 0.5 L). The filtered product was crystallized from ^{i}PrOAc (2.5 vol) and dried in an oven (T_{oven} = 40 °C; p = 10 mbar; 12 h) until constant weight. The desired intermediate **6** was recovered as pale-yellow solid in 92% yield.

UPLC−MS: t_R = 1.60 min; m/z = 289 $[M + 1]^+$.

HRMS calcd for $C_{14}H_{12}BrN_2$ $[M + 1]^+$ 287.01839, found 287.01842.

HPLC: t_R = 4.10 min; 98.3% purity.

^{1}H NMR (400 MHz DMSO-d_6): δ 8.02 (t, J = 1.7 Hz, 1H), 7.85 (dt, J = 7.8, 1.7 Hz, 1H), 7.73 (dm, J = 7.8 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.30 (dt, J = 7.2, 1.2 Hz, 1H), 7.27 (dt, J = 7.2, 1.2 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz DMSO-d_6): δ 152.0, 151.9, 143.0, 137.3, 133.1, 132.4, 131.5, 128.9, 123.4, 122.8, 122.6, 119.8, 119.7, 111.4, 32.3.

Synthesis of Ethyl 1-[3-(1-Methyl-benzoimidazol-2-yl)-phenyl]-piperidine-4-carboxylate (7). $Pd(OAc)_2$ (15.7 g; 0.07 mol; 3.5% mol), BINAP (63.9 g; 0.1 mol; 5% mol) and toluene (5.0 L; 8.8 vol) were charged to the 10 L jacketed reactor under nitrogen atmosphere. The resulting suspension was stirred at 20 °C (T_{int}) for 30 min. A solution of ethyl isonipecotate (346 g; 2.2 mol; 1.1 equiv) in toluene (0.5 L) was added dropwise in 5 min. Next, 3-Br-benzimidazole **6** (570 g; 2.0 mol; 1.0 equiv) was added followed by Cs_2CO_3 (1.95 kg; 6.0 mol; 3.0 equiv) and toluene (0.2 L). The resulting suspension was heated to 100 °C (T_{int}) for 3 h and then checked by HPLC (conversion complete). The mixture was cooled to room temperature and filtered through a cellulose pad, washing with toluene (2 × 0.5 L). The mother liquors were concentrated under reduced pressure (T_{int} = 70 °C; p = 400 mbar; 5.0 L of solvent distilled) and cooled to −20 °C (T_{int}) for 1 h. The yellow suspension was filtered on a Büchner funnel and the cake was washed with toluene (2 × 0.15 L cooled at −20 °C). The solid was dried in an oven until constant weight (T_{oven} = 40 °C; p = 10 mbar, 4 h). The desired intermediate **7** (560 g) was isolated as a pale-yellow solid in 77% yield.

UPLC−MS: t_R = 1.76 min; m/z = 364 $[M + 1]^+$.

HRMS calcd for $C_{22}H_{26}N_3O_2$ $[M + 1]^+$ 364.20251, found 364.20248.

HPLC: t_R = 4.41 min; 98.1% purity.

^{1}H NMR (400 MHz DMSO-d_6): δ 7.66 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.32 (m, 1H), 7.28−7.16 (m, 3H), 7.09 (m, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.71 (m, 2H), 2.82 (m, 2H), 2.48 (m, 1H), 1.90 (m, 2H), 1.66 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz DMSO-d_6): δ 174.9, 154.3, 151.7, 143.13, 137.2, 131.5, 129.9, 122.9, 122.5, 120.0, 119.6, 117.7, 117.1, 111.1, 60.6, 48.5, 40.9, 32.3, 28.1, 14.8.

Synthesis of 1-[3-(1-Methyl-benzoimidazol-2-yl)-phenyl]-piperidine-4-carboxylic acid (8). The starting ester **7** (550 g; 1.5 mol; 1.0 equiv) was charged to the 10 L jacketed reactor under nitrogen flux and dioxane (4.4 L) was added. The suspension was stirred at 20 °C for 10 min in order to obtain a clear homogeneous solution. A solution of NaOH (108 g; 2.7 mol; 1.8 equiv) in water (0.6 L) was added all at once; the biphasic mixture was heated to 70 °C (T_{int}) under mechanical stirring. After 2 h, HPLC analysis showed complete conversion. The solvent was concentrated under reduced pressure (T_{int} = 70 °C; p = 400 mbar; 4.0 L of solvent distilled). The residue was diluted with water (2.0 L) and acidified with HCl 1 N to pH = 4.7 (measured by digital pH-meter) while cooling at 20 °C (T_{int}). The white suspension was stirred at 20 °C for 3 h and then filtered on a Büchner funnel, washing with water (2 × 0.5 L). The solid was dried in an oven (T_{oven} = 40 °C; p = 10 mbar; 18 h) until constant weight (458 g). The desired product **8** was recovered as an off-white solid in 91% yield.

UPLC−MS: t_R = 0.82 min; m/z = 334 $[M + 1]^-$.

HRMS calcd for $C_{20}H_{22}N_3O_2$ $[M + 1]^+$ 336.17121, found 336.17124.

HPLC: t_R = 3.35 min; 98.7% purity.

Water content (KF): 0.9 wt %.

^{1}H NMR (400 MHz DMSO-d_6): δ 12.27 (broad, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.31 (t, J = 2.0 Hz, 1H), 7.27 (td, J = 7.3, 1.2 Hz, 1H), 7.22 (td, J = 7.3, 1.2 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.10 (dd, J = 7.9, 2.0 Hz, H), 3.84 (s, 3H), 3.71 (m, 2H), 2.82 (m, 2H), 2.41 (m, 1H), 1.90 (m, 2H), 1.65 (m, 2H).

^{13}C NMR (100 MHz DMSO-d_6): δ 176.6, 154.3, 151.7, 143.0, 137.2, 131.4, 129.9, 122.9, 122.6, 119.9, 119.6, 117.7, 117.1, 111.2, 48.6, 40.1, 32.3, 28.1.

Synthesis of {1-[3-(1-Methyl-benzoimidazol-2-yl)-phenyl]-piperidin-4-yl}-(4-methyl-piperazin-1-yl)-methanone Hydrobromide (9). The starting carboxylic acid **8** (450 g; 1.3 mol; 1.0 equiv) was charged to the 10 L jacketed reactor under nitrogen atmosphere and suspended in MeCN (2.7 L;

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6.0 vol) at 20 °C (T_{int}). CDI (253 g; 1.6 mol; 1.2 equiv) was added all at once and the resulting mixture was heated to 50 °C (T_{int}). After 1 h, the HPLC analysis of a sample (quenched with butyl amine) showed complete activation. A solution of *N*-methyl-piperazine (182 g; 1.8 mol; 1.4 equiv) in MeCN (1.1 L; 2.5 vol) was added dropwise in 15 min; next, the reaction mixture was heated to 55 °C (T_{int}) for 2 h (conversion complete by HPLC). The mixture was concentrated under reduced pressure (T_{int} = 40 °C; p = 350 mbar; 3.5 L of solvent distilled), the residue was diluted with DCM (2.5 L) and washed with water (2 × 1.5 L). The organic layer was concentrated under reduced pressure (T_{int} = 25 °C; p = 400 mbar; 2.0 L of solvent distilled) and the residue was diluted in MeCN (1.7 L; 4 vol). Aqueous HBr 48 wt % (285 g; 1.7 mol; 1.3 equiv) was added dropwise over 30 min at 20 °C, observing a slight exotherm (ΔT = +1 °C; from 20 to 21 °C). After the addition was complete, the suspension was stirred at 20 °C (T_{int}) for 3 h and then cooled to 5 °C (T_{int}) for 2 h. After filtration on a Büchner funnel and washing with MeCN (2 × 0.25 L), the recovered solid was dried in oven until constant weight (T_{oven} = 50 °C; p = 10 atm; 18 h) in order to obtain 460 g of **1** as hydrobromide salt. Yield: 71%.

UPLC–MS: t_R = 1.24 min; m/z = 418 $[M + 1]^+$.

HRMS calcd for $C_{25}H_{33}N_5O$ $[M + 1]^+$ 418.26069, found 418.26075.

HPLC: t_R = 5.99 min; purity 99.1%.

^{1}H NMR (400 MHz DMSO-d_6): δ 9.80 (broad, 1H), 7.89 (m, 1H), 7.77 (m, 1H), 7.55–7.45 (m, 3H), 7.38 (s, 1H), 7.24 (m, 2H), 4.48–4.15 (m, 2H), 3.96 (s, 3H), 3.86 (m, 2H), 3.55–3.15 (m, 3H), 3.10–2.82 (m, 6H), 2.81 (s, 3H), 1.76–1.57 (m, 4H).

^{13}C NMR (100 MHz DMSO-d_6): δ 173.5, 152.3, 151.5, 135.1, 135.0, 130.5, 126.2, 125.6, 125.3, 119.9, 119.1, 117.1, 116.5, 113.0, 53.2, 48.2, 42.7, 38.8, 37.4, 33.1, 28.2.

Water content (KF): 3.5 wt %.

Pd content (ICP-MS): 128 ppm.

Bromine content (ionic exchange LC): 20 wt % (1.2 equiv).

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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