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A Convergent Process for the Preparation of Adamantane 11-β-HSD-1 Inhibitors

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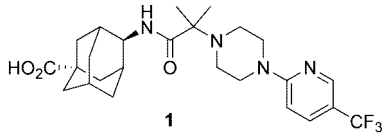
Abstract:

A convergent, scalable process was developed for the synthesis of adamantane 11-β-hydroxysteroid dehydrogenase-1 inhibitors *E*-4-(2-methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)propionylamino)adamantane-1-carboxylic acid (1) and *E*-4-(2-methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)propionylamino)-adamantane-1-carboxamide (2) to rapidly deliver material for development. The process was high yielding and provided 1 in 52% overall yield over six total steps with a five-step longest linear sequence and 2 in 45% overall yield over seven total steps with a six-step longest linear sequence. A process to prepare active pharmaceutical ingredient (API) of >99% purity at the kilogram scale has been developed under tight delivery timelines.

Introduction

Elevated circulating glucocorticoid levels have been associated with several metabolic comorbidities including obesity, diabetes, dyslipidemia and atherosclerosis, and 11-β-hydroxysteroid dehydrogenase-1 (11-β-HSD-1) has been found to catalyze the reduction of the inactive glucocorticoid cortisone to active glucocorticoid cortisol. Therefore, inhibition of 11-β-HSD-1 is under investigation as a potential therapy for the aforementioned metabolic comorbidities. Our drug discovery group has identified potent 11-β-HSD-1 inhibitors, including **2** and its penultimate intermediate (**1**),[1] and several hundred grams were needed to support development activities.



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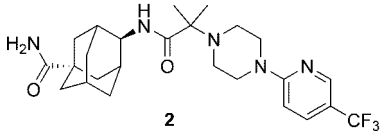

2

Results and Discussion

The synthesis of **2** is a high yielding, scalable, and convergent seven-step process. Compounds **3** and **4** were identified as starting materials for our route to the amide **2** employing the carboxylic acid **1** as the penultimate intermediate (Scheme 1) since both the carboxylic acid **1** and the amide **2** had been identified as targets for development.

Our synthesis began with the preparation of pyridylpiperazine **3** by a substitution reaction of 2-bromo-2-methylpropionic acid (**6**) with 1-(5-(trifluoromethyl)pyridine-2-yl)piperazine (**7**), both commercially available. Reaction in THF in the presence of triethylamine afforded **3** in a modest 60% yield. The reaction progressed presumably through the α-lactone and the main impurities, **8** and **9** (15−20%), in this process arose from multiple additions of the 2-bromo-isobutyric acid lactone (Scheme 2). Additionally, 5−10% unreacted starting material was observed. These impurities were completely removed upon precipitation with heptane, yielding highly pure **3** (99%) in a one pot procedure from readily available starting materials. Varying stoichiometry of **6**, **7**, and triethylamine did not significantly improve the reaction yield. Alternate syntheses were considered; however, each would require multiple steps. For example, reaction of the amine with ethyl 2-bromo-2-methylpropanoate or ethyl 2-bromopropanoate followed by saponification or saponification and methylation are two and three steps, respectively. Thus, the modest yield was deemed acceptable when considering the simplicity of the unit operations.

Amino ester **4** was prepared over three steps beginning with commercially available 5-hydroxy-2-adamantanone (**10**) (Scheme 3). Koch−Haaf carbonylation[2] of **10** was conducted by slowly charging a solution of **10** in formic acid into 30% oleum at 60 °C over 4−5 h.[3] An optional second charge of formic acid was performed based on the HPLC results of the in-process sampling of the reaction. An aqueous quench of the reaction mixture followed by extractive workup provided 4-oxoadamantane-1-carboxylic acid (**11**) in 88% yield. Even with a second charge of formic acid the reaction always contained approximately 5−10% starting material, most likely due to lowering the acid strength of the reaction mixture from the decomposition of formic acid. In fact, for each equivalent of formic acid charged, 1 equivt of water was produced in addition to the desired carbon monoxide. Similar yields to those above were obtained using concentrated sulfuric acid (96% w/w) if the temperature was elevated to 100 °C. However, the use of food grade sulfuric acid (93% w/w) under the same conditions only provided a 30% yield. The highly exothermic reaction of formic acid and 30% oleum generated carbon monoxide, which trapped the carbocation generated from protonation and solvolysis of

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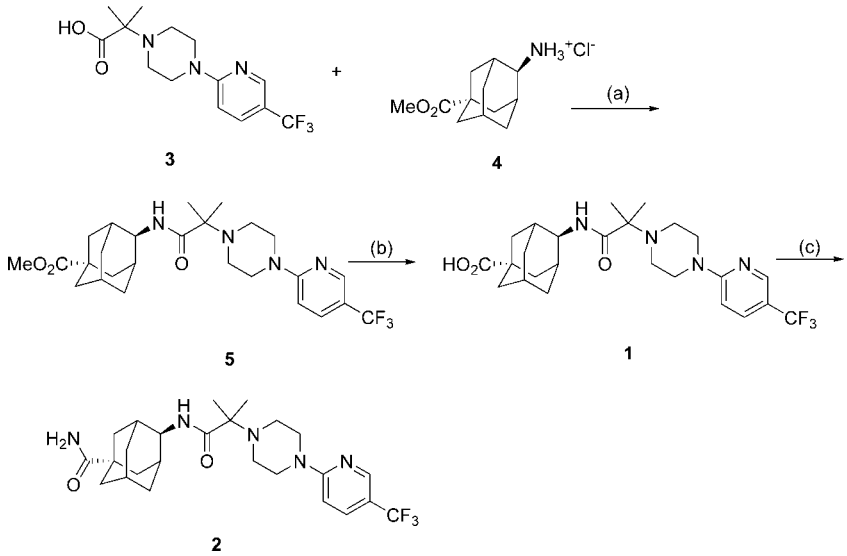
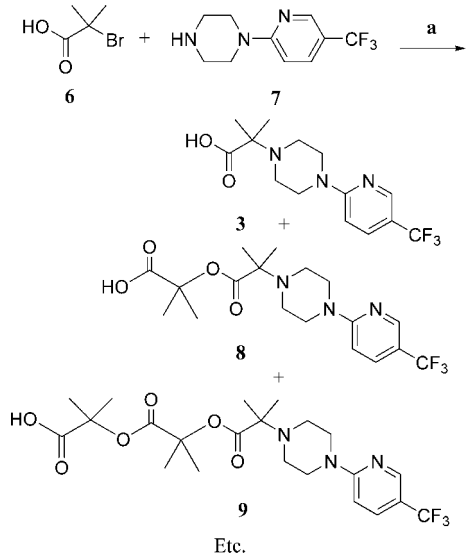
Scheme 1. **Synthesis of 1 and 2**[a]



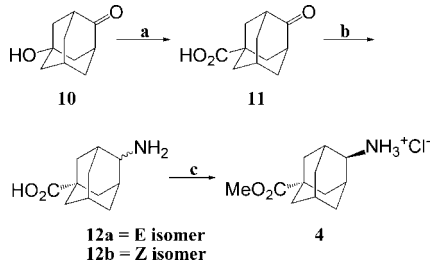
[a] Reagents and conditions: (a) EDAC·HCl, HOBt·H_2O, DIEA, DMF, water, 45 °C; (b) 1.25 N NaOH/IPA, 50 °C; (c) EDAC·HCl, HOBt·H_2O, DIEA, NH_4Cl, DMF, 45 °C.

Scheme 2. **Coupling of 2-bromo-2-methylpropionic acid (6) and 1-(5-(trifluoromethyl)pyridine-2-yl)piperazine (7)**[a]



[a] Reagents and conditions: (a) TEA, THF, 50 °C.

Scheme 3. **Preparation of aminoester (4)**[a]



[a] Reagents and conditions: (a) HCOOH, 30% oleum, 60 °C; (b) 7 N NH_3/MeOH, 5% Pd/C, H_2; (c) AcCl, MeOH, 0 °C−45 °C.

5-hydroxy-2-adamantanone. Before scale up, reaction calorimetry was performed for this step. It was determined that the adiabatic temperature rise associated with the rapid addition of the 5-hydroxy-2-adamantanone/formic acid solution charge to the oleum was 176 °C. In addition to the exotherm, the generation of a large volume of toxic and flammable carbon monoxide necessitated that several safety recommendations be implemented including adequate venting and controlled addition of the formic acid solution to maintain temperature at 60 °C and to minimize foaming.

Reductions of 5-substituted 2-adamantanones and 2-imino-5-substituted-adamantanes have been previously shown to exhibit π-facial stereoselectivity.[4] In our process, conversion of 4-oxoadamantane-1-carboxylic acid (**11**) to 2-amino-5-carboxyadamantane (**12**) was no exception. Reductive amination of 4-oxoadamantane-1-carboxylic acid (**11**) was carried out in 7N NH_3/MeOH and after incubation of the ketone in 7N NH_3/MeOH for 16 h, the resulting imine was hydrogenated in the presence of 5% Pd/C for sixteen hours at 40 psi. Upon completion of the reduction, water was added to dissolve precipitated product that formed during the course of the reaction. Unfortunately, the product, **12**, does not contain a suitable UV chromophore for determination of the geometric isomer ratio by UV/HPLC; however, a corona detector/HPLC system[5] was well suited for this application. In corona detection, a nebulized analyte stream attains a positive charge as it contacts a charged nitrogen stream, and the analyte charge is detected by an electrometer, generating a signal in direct proportion to the quantity of analyte present. With this detection method, it was determined that the *E*- and *Z*-isomers of **12** are indeed separable by HPLC and that the reaction provided a 3.3:1 *E*:*Z* (**12a**:**12b**) product ratio. Methanol and ammonia were distilled from the reaction mixture, resulting in an aqueous slurry of **12a**:

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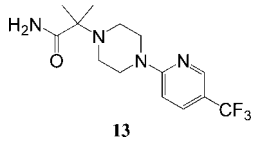
12b. Acetonitrile was added until an approximately 2:1 acetonitrile:water ratio was obtained to further crystallize product and enrich the desired *E*-isomer. Solubility studies in 2:1 acetonitrile:water indicated the *Z*-isomer was 3.5 times more soluble than the *E*-isomer (*Z*-isomer 3.02 mg/mL, *E*-isomer 0.85 mg/mL). Isolated product from the slurry provided product with a typical yield for **12** of 84% with an *E*:*Z* ratio of approximately 7:1. From the filtrate a solid enriched in *Z*-isomer **12b** was obtained. This material was used to prepare the *Z*-isomers of **1** and **2** for use as reference material.

Esterification of **12** was carried out in a methanol/HCl solution prepared by slowly charging acetyl chloride to methanol at 0 °C followed by warming to 25 °C. The methanol/HCl solution was charged to a reactor containing **12** resulting in a solution, which was heated to 45 °C to complete the esterification. After cooling to 25 °C, acetonitrile was charged to the reactor providing a slurry of **4**, followed by distillation while adding acetonitrile to remove methanol and HCl. The solids were reslurried in acetonitrile and isolated. Corona detection HPLC indicated no *Z*-isomer remained in the isolated solid. Indeed, solubility studies in acetonitrile demonstrated the *Z*-isomer was 9 times more soluble than the *E*-isomer (*Z*-isomer 0.98 mg/mL, *E*-isomer 0.11 mg/mL). On the basis of the solubility difference of the *E* and *Z* isomers of **4**, this step was chosen as the control point for removal of the undesired *Z*-isomer.

However, the product **4** contained residual ammonium chloride carried in from the reductive amination. If the ammonium chloride was not removed it would have amidated **3** to form the amide **13** in the next step.



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The amide **13** was difficult to remove in subsequent steps; therefore, removal of ammonium chloride was critical. Thus, **4** was desalted by dissolving the solids in methanol, and the solution was treated with diisopropylethylamine (DIEA) until the pH was basic to pH paper. This converted the ammonium chloride into ammonia. The solvent was evaporated under reduced pressure to remove the liberated ammonia, and the HCl salt was reformed by again treating with MeOH/HCl followed by evaporation to dryness under reduced pressure. DIEA hydrochloride was removed by recrystallization of the solids from ethyl acetate/isopropyl alcohol (IPA). Desalted **4** was filtered, washed with ethyl acetate, and dried to provide a typical yield from **12** of ~74%.

The alternative process of forming the methyl ester of **11** followed by reductive amination was also investigated. However, it was found that reductive amination of the methyl ester of **11** was not stereoselective, providing an approximately 1:1 *E*:*Z* ratio and thus a lower overall yield.

Initially, synthesis of **5** employed DEPBT (3-(diethoxyphosphoryloxy)-3H-benzo[*d*][1,2,3] triazin-4-one) as the coupling agent; however, as racemization was not an issue,[6] the cost of the reagent was high, and commercial lots were impure, an alternative coupling was desired. Thus, we used the more conventional *N*-hydroxybenzotriazole hydrate/1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (HOBt·H_2O/EDAC·HCl) mediated coupling of **3** and **4** in DMF/water in the presence of DIEA at 45 °C to prepare methyl ester **5**. A slurry remained throughout the reaction, as **5** exhibited limited solubility in the reaction mixture. In-process samples of the slurry were dissolved and UV/HPLC was used to monitor the reaction for disappearance of **3**, and upon completion, water was added to the reaction mixture to complete crystallization of the product. The slurry was cooled to ambient temperature, and the product was isolated by filtration to provide a typical yield of ~96% for the dried product.

The hydrolysis reaction to prepare **1** was also modified from the first-generation route to simplify processing. Initially, the reaction was carried out under anhydrous conditions in THF using potassium trimethylsilanolate (KOTMS) for conversion to the carboxylic acid **1**. The typical yield was high at 94%, but a new saponification route was necessary as KOTMS was difficult to source and product isolation involved a high-volume extractive workup.

Instead, saponification of **5** was performed in a 2:1 mixture of 1.25 N NaOH:IPA at 50 °C. Without IPA as a cosolvent, the solubility of **5** was limited and the hydrolysis required several hours. Within 3 h at 50 °C the initial slurry became a clear solution indicating the hydrolysis was complete, as confirmed by in-process testing by UV/HPLC. The pH was adjusted to 4−5 with 4 N HCl to induce crystallization of the product, and after isolation, the typical yield of **1** was ~97%.

Previously, **2** was prepared by dissolving **1** into methylene chloride and charging HOBt·H_2O and EDAC·HCl to form the active HOBt ester. After this preactivation, 80 equiv of NH_4OH were added, and the biphasic mixture stirred for several hours until the amidation was complete. An extractive workup was required for this biphasic reaction along with copious brine washes to remove the water-soluble EDAC urea byproduct. The organic layer was dried, and the solvent was evaporated to dryness under reduced pressure to provide the API in typical yields of ~90%.

For the second-generation route, removal of halogenated solvents and a simplified workup were desired as well as elimination of the need for evaporation to dryness for product isolation. Thus, methylene chloride was replaced with DMF as the solvent, which also eliminated the biphasic reaction and the need for an extractive workup. Prior formation of the active ester was unnecessary if aqueous NH_4OH, which could have possibly quenched the EDAC·HCl in a homogeneous reaction, was avoided. On the basis of our previous experience in removing ammonium chloride from **4**, ammonium chloride/DIEA appeared to be an ideal source for the generation of ammonia in situ. Ammonium chloride in DMF in the presence of DIEA generated free ammonia,[7] which was then available to couple with the active ester of **1** formed from HOBt·H_2O/EDAC·HCl activation. After coupling for 4−5 h, the reaction

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was complete by HPLC and water was added to the reactor to crystallize the product. The product was filtered, washed with DMF/water, dried, and recrystallized from methanol/water. The isolated product was washed with methanol/water and dried to provide 1.3 kg **2** in ~ 85% yield.

Should larger quantities of **1** and **2** become needed, additional process optimization will be necessary. The dangerous addition of formic acid to oleum in the Koch−Haaf carbonylation needs to be avoided. Preliminary results indicate that formic acid can be replaced in the carbonylation with carbon monoxide gas under 100 psi pressure at 100 °C in concentrated sulfuric acid with a water quench to provide acid **11**. The potentially dangerous exothermic addition of formic acid would therefore be avoided, leading to a simplified and safer step. In addition, the yield was improved, the workup was simplified, and the amount of halogenated solvent was reduced because without water being formed during carbonylation, the reaction could be driven to completion. Therefore, a series of extractions was eliminated because basic extraction to sequester **11** in the aqueous layer for separation of residual starting material **10** was unnecessary. The early steps in which solvent was stripped to near dryness, while acceptable at the current scale, will need to be reconsidered at larger scale. Finally, ammonia gas should be investigated in place of in situ generation of ammonia for the amidation of **1** to prepare **2**.

Conclusions

Carboxylic acid **1** was prepared in 50−53% overall yield in six steps, and amide **2** was prepared in 43−45% overall yield in seven steps. Control of impurity formation, e.g. **13** and the *Z*-isomer of **4**, enabled preparation of **1** and **2** with purities >99% in each case.

Experimental Section

General. Commercially available reagents and solvents were used without further purification. All reactions were carried out under nitrogen unless otherwise indicated. NMR spectra were obtained on a Bruker DRX 400 NMR spectrometer. UV/HPLC data was collected on an Agilent 1100 series HPLC. Corona detection HPLC data was collected on an Agilent 1100 series HPLC fitted with an ESA Corona CAD HPLC detector.

2-Methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)propanoic Acid (3). A 100-L glass round-bottom flask was evacuated, purged with nitrogen, and charged with **7** (1.23 kg, 5.32 mol), **6** (0.98 kg, 5.85 mol,) and tetrahyrofuran (16 L). The contents were mixed to dissolve the solids. Triethylamine (1.36 kg, 13.44 mol) was charged to the reactor, and the contents were heated to 50 °C for 16 h. The reaction was cooled to 25 °C. Heptane (21 kg) was added to precipitate the product, and the resulting slurry was filtered and washed with heptane (21 kg). The solids were reslurried in IPA/water (32 kg IPA/1.85 kg water) at 80 °C for 1 h. After cooling to 0 °C and stirring for 1 h, the solids were filtered and washed with isopropyl alcohol (17 kg). The solids were dried at 50 °C until the loss by TGA was less than 1%. Yield: 1.01 kg (59.8% assay adjusted yield). ^{1}H NMR (400 MHz, D_2O) δ 1.09−1.16 (m, 6 H) 2.56−2.64 (m, 4 H) 3.38−3.45 (m, 4 H) 6.72 (d, J = 9.19 Hz, 1 H) 7.63 (dd, J = 9.19, 2.33 Hz, 1 H) 8.14 (s, 1 H).

4-Oxoadamantane-1-carboxylic Acid (11). A 25-L glass round-bottom flask was evacuated, purged with nitrogen, and charged with **10** (1.04 kg, 6.26 mol). To the flask was charged formic acid (98%) (8.40 kg, 178.84 mmol), and the contents were mixed to dissolve the solids. A separate 100-L glass round-bottom flask was evacuated, purged with nitrogen, and charged with 30% oleum (26.7 kg). The oleum was heated to 50 °C. To the oleum flask was charged the solution of **10** slowly over 4−5 h, maintaining the internal temperature at 70 °C. The solution was mixed an additional 1 h at 70 °C. An additional charge of formic acid (98%) (4.30 kg, 91.57 mol) was added slowly over 1−2 h to complete the carbonylation. The solution was mixed an additional 2 h at 70 °C. To a separate reactor was charged 10% NaCl (40 kg) and cooled to a 0 °C internal temperature. The reaction mixture was cooled to 10 °C and charged in portions to the cooled 10% NaCl solution, maintaining the internal temperature at no more than 70 °C. The quenched solution was cooled to 20−25 °C and extracted with methylene chloride (3 × 9.8 kg). The methylene chloride layer (top layer) was washed with 10% NaCl (2.2 kg). The product was extracted from the methylene chloride layer (bottom layer) into 10% sodium carbonate (3 × 8.1 kg). The combined sodium carbonate layers were acidified to pH 1−3 with concentrated HCl and extracted with methylene chloride (3 × 9.8 kg). The combined methylene chloride layers were washed with water (2.0 kg). The solvent was evaporated under reduced pressure, and the solids were distilled from EtOAc (3 × 1.9 kg). The residue was distilled from heptane (2 × 3.6 kg) and then slurried in heptane (3.6 kg) and heated to 50 °C for 1 h. The suspension was cooled to 25 ± 5 °C and filtered. The wet cake was washed with heptane (1.4 kg) and dried under vacuum at 50 °C until the loss by TGA was less than 1%. Yield: 1.07 kg (88.0% assay adjusted yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.09 (m, 4 H) 2.14 (d, J = 0.27 Hz, 1 H) 2.15 (s, 1 H) 2.22 (s, 5 H) 2.60 (s, 2 H).

2-Amino-5-carboxyadamantane (12). To an evacuated and purged reactor was charged **11** (1.07 kg, 5.51 mol), 7 N NH_3/MeOH (16.40 kg, 147.35 mol), and 5% Pd/C (107 g). The reaction mixture was stirred under nitrogen pressure for 16 h at 40 psi. The reactor was purged with hydrogen and mixed under hydrogen pressure for 16 h at 40 psi. Water (20 kg) was added to dissolve precipitated solids. The reaction mixture was filtered, and the catalyst cake was washed with water (2 kg). The solvent was distilled at 40 °C until approximately 20 L of a slurry remained. Acetonitrile (31 kg) was added to the slurry. The slurry was stirred at 25 °C for 12 h. The product was filtered and washed with cold (0 °C) acetonitrile (5.5 kg) and dried under vacuum at 50 °C until the loss by TGA was less than 3%. Yield: 0.90 kg (83.6% assay adjusted yield). ^{1}H NMR (400 MHz, D_2O) δ 1.47 (d, J = 12.62 Hz, 2 H) 1.63−1.73 (m, 3 H) 1.73−1.81 (m, 5 H) 1.85 (d, J = 4.25 Hz, 3 H) 3.08 (s, 1 H) 4.65 (s, 4 H).

***E*-2-Amino-5-carboxyadamantane Methyl Ester Hydrochloride Salt (4).** A 25-L glass round-bottom flask was evacuated, purged with nitrogen, charged with methanol (7.2 kg), and cooled to an internal temperature of 0 °C. Acetyl chloride (2.30 kg, 29.30 mol) was charged, maintaining the internal temperature at less than 30 °C. The solution was stirred at 25 °C for 30 min. In a separate evacuated and purged 50-L flask was charged **12** (0.90 kg, 4.61 mol). The previously prepared HCl/methanol solution was charged to the 50-L flask. The contents of the flask were heated to 45 °C

for 16 h. Reaction completion was monitored by corona detection HPLC.[5] The reaction was cooled to 30 °C. Acetonitrile (7.2 kg) was charged to the flask. The solution was distilled to approximately 25% of the original volume. Acetonitrile (7.2 kg) was charged to the flask, and the slurry was distilled to near dryness. Acetonitrile (7.2 kg) was charged to the flask, and the slurry was again distilled to near dryness. Acetonitrile (7.2 kg) was charged to the flask. The slurry was filtered, and the cake was washed with acetonitrile (7.2 kg). The solids were dried under vacuum at 50 °C for 12 h.

The product was desalted by charging the entire amount of product to an evacuated and purged 25-L reactor. Methanol (7.5 kg) and DIEA (0.9 kg, 6.97 mol) were charged to the reactor and the contents mixed for 2 h. The solution was distilled to near dryness to remove most of the ammonia. Methanol (7.5 kg) was charged to the reactor and mixed to dissolve the resulting solids. The solution was distilled to near dryness to remove residual ammonia. The methanol charge and distillation were repeated. Methanol (7.5 kg) was charged to a separate container and cooled to an internal temperature of 0 °C. Acetyl chloride (0.50 kg, 6.37 mol) was charged maintaining the internal temperature at less than 30 °C. The solution was stirred at 25 °C for 30 min. The HCl/methanol solution was charged to the 25-L flask and mix until the solids dissolved. The solution was distilled to near dryness. In a separate container ethyl acetate (32 kg) and isopropyl alcohol (3.4 kg) were charged and mixed. Approximately 1/3 of the ethyl acetate/IPA mixture was charged to the 25-L flask. The slurry was mixed for 30 min and filtered. The cake was washed in two portions with the remaining ethyl acetate/IPA mixture. The cake was washed with ethyl acetate and dried at 55 °C until the loss by TGA was less than 1%. Yield: 0.90 kg (74.2% assay adjusted yield). ^{1}H NMR (400 MHz, D_2O) δ 1.58 (d, J = 13.31 Hz, 2 H) 1.75−1.82 (m, 4 H) 1.83−1.90 (m, 2 H) 1.94 (s, 2 H) 1.97 (d, J = 2.33 Hz, 1 H) 2.06 (s, 2 H) 3.41 (s, 1 H) 3.57 (s, 3 H).

Methyl-*E*-4-(2-methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)propionylamino)adamantane-1-carboxylate (5). A 50-L glass round-bottom flask was evacuated and purged with nitrogen. To the flask was charged **3** (1.01 kg, 3.18 mol), **4** (0.82 kg, 3.34 mol), HOBt·H_2O(0.54 kg, 3.53 mol), and EDAC·HCl (0.67 kg, 3.50 mol). In a separate flask were charged DMF (9.8 kg), water (1.3 kg), and DIEA (0.87 kg, 6.73 mol, 2.12 equiv.). The resulting solution was charged to the solids in the flask. The contents of the flask were mixed at 45 °C for 3 h. Reaction completion was monitored by UV/HPLC. Water (8.4 kg) was slowly charged to the flask over no less than 30 min. The contents of the flask were mixed at 45 °C for 1 h and then cooled to ambient temperature. The slurry was filtered, and the wet cake was washed in three equal portions with a mixture of DMF (3.4 kg) and water (5.3 kg). The cake was washed three times with water (6.1 kg). The cake was dried at 55 °C until the loss by TGA was less than 2%. Yield: 1.56 kg (96.3% assay adjusted yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 6 H) 1.54 (d, J = 12.62 Hz, 2 H) 1.73 (d, J = 12.90 Hz, 2 H) 1.81 (d, J = 2.33 Hz, 2 H) 1.85−1.94 (m, 7 H) 2.47−2.56 (m, 4 H) 3.58 (s, 3 H) 3.65 (s, 4 H) 3.78 (d, J = 7.82 Hz, 1 H) 6.95 (d, J = 9.06 Hz, 1 H) 7.70 (d, J = 7.96 Hz, 1 H) 7.78 (dd, J = 9.13, 2.54 Hz, 1 H) 8.38−8.41 (m, 1 H).

***E*-4-(2-methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl) propionylamino)adamantane-1-carboxylic Acid (1).** A 25-L glass round-bottom flask was evacuated, purged with nitrogen, and charged with **5** (1.56 kg, 3.07 mol), 1.25 N NaOH (5.8 kg, 7.25 mol), and IPA (2.9 kg). The contents of the flask were mixed at 50 °C for no less than 3 h. Reaction completion was monitored by UV/HPLC. The internal temperature was adjusted to 20 °C. The pH of the solution was adjusted to 4−5 with 4 N HCl to crystallize the product. The slurry was mixed 1 h and filtered. The cake was washed with water (2.0 kg) and dried under vacuum at 70 °C until the loss by TGA was less than 0.5%. Yield: 1.49 kg (98.0% assay adjusted yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (s, 6 H) 1.55 (d, J = 12.49 Hz, 2 H) 1.71−1.81 (m, 4 H) 1.85−1.94 (m, 7 H) 2.48−2.57 (m, 4 H) 3.66 (s, 4 H) 3.79 (d, J = 7.96 Hz, 1 H) 6.96 (d, J = 9.06 Hz, 1 H) 7.71 (d, J = 7.96 Hz, 1 H) 7.78 (dd, J = 9.13, 2.54 Hz, 1 H) 8.40 (dd, J = 1.72, 0.75 Hz, 1 H) 12.08 (s, 1 H).

***E*-4-(2-Methyl-2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl) propionylamino)adamantane-1-carboxamide (2).** A 50-L glass round-bottom flask was evacuated, purged with nitrogen, and charged with **1** (1.49 kg, 3.01 mol), NH_4Cl (0.32 kg, 5.98 mol), HOBt·H_2O (0.69 kg, 4.51 mol), EDAC·HCl (0.87 kg, 4.54 mol), and DMF (11 kg) followed by DIEA (1.56 kg, 12.07 mol). The contents were heated to 35 °C and mixed 4 h. Reaction completion was monitored by UV/HPLC. The internal temperature was adjusted to 25 °C. Water (4.5 kg) was charged over 30 min, and the solution was mixed 30 min to crystallize the product. Additional water (10.0 kg) was charged over 30 min and the slurry mixed 1 h to complete crystallization. The slurry was filtered and washed with a mixture of DMF (13.5 kg) and water (20.0 kg) in three portions. The cake was washed with water (3 × 11.0 kg). The product was recrystallized from methanol/water to remove residual DMF. The filter cake was charged back to the flask, and methanol (9 kg) was charged. The internal temperature of the flask was adjusted to 60 °C to dissolve the solids. Water (6.8 kg) was charged to the flask, and the contents were mixed 30 min to begin crystallization. Additional water (6.8 kg) was charged over 30 min, and the slurry was mixed 1 h to complete crystallization. The slurry was filtered and washed with a mixture of water (1.2 kg) and methanol (0.8 kg). The cake was then washed with water (6.8 kg) and dried under vacuum at 70 °C until the loss by TGA was less than 1%. Yield: 1.29 kg (86.8% assay adjusted yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (s, 6 H) 1.53 (s, 2 H) 1.69−1.77 (m, 4 H) 1.80−1.92 (m, 7 H) 2.48−2.57 (m, 4 H) 3.65 (s, 4 H) 3.79 (d, J = 7.96 Hz, 1 H) 6.73 (s, 1 H) 6.95 (d, J = 9.06 Hz, 1 H) 7.00 (s, 1 H) 7.70 (d, J = 8.10 Hz, 1 H) 7.77 (dd, J = 9.19, 2.47 Hz, 1 H) 8.39 (dd, J = 1.72, 0.75 Hz, 1 H).

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