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An Expedient and Multikilogram Synthesis of a Naphthalenoid H_3 Antagonist

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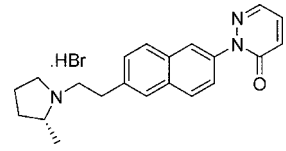
Abstract:

A facile and scaleable synthesis of potent and selective histamine H_3 receptor antagonist 1 is described, starting from commercially available 6-bromo-naphthalene-2-carboxylic acid methyl ester 3a. The key intermediate, 2-(6-bromonaphthalen-2-yl)ethanol 5 was prepared in good yield (78%) and purity (99%) via a one-carbon homologation of 3a. The coupling of 5 with pyridazinone 12 was accomplished effectively by a copper-catalyzed cross-coupling reaction. Activation of the hydroxyl group of 4, followed by displacement reaction with 2(*R*)-methylpyrrolidine 13, afforded the free base of 1, which was subsequently converted to its corresponding salt. The new process consisted of eight chemical steps and one salt formation step and required no chromatographic purification throughout the synthesis. It has been successfully implemented on pilot plant scale to prepare over 10 kg quantities of the target compound 1 in 43% overall yield in high purity (99%) and with the desired physical properties.

Introduction

The histamine H_3 receptor (H_3R), discovered in the early 1980s,[1] is a presynaptic G protein-coupled receptor that regulates the release of a variety of neurotransmitters.[2] Antagonists of this receptor are suggested to have potential utility for the therapeutic treatment of a variety of CNS disorders, such as memory and cognitive disorders,[3] and attention-deficit hyperactivity disorder (ADHD).[4] Despite intense interest in the field,[5] as yet no H_3R antagonist has gone through clinical trials and been approved for human use. Imidazole-based H_3R antagonists were among the earliest structures investigated, and their synthesis and pharmacological profiles have been reviewed.[6] However, this class of compounds has the potential to give rise to drug–drug interactions by inhibiting hepatic CYP (cytochrome P_{450}) enzymes and has been described as having relatively poor CNS penetration. For these reasons, most interest in the field has turned to non-imidazole H_3R antagonists. A recent example of such a compound is ABT-239, **2**,



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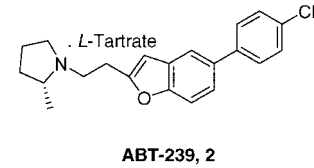

ABT-239, 2

which was found to be potent and effective in animal models for cognition and attention-deficit hyperactivity disorder (ADHD).[8] Efficient large-scale syntheses of ABT-239 have been reported.[9] Compound **1** is a member of a new series of naphthalene-based compounds that have shown potent H_3 antagonism and have been recently described.[10] The original synthesis of **1** was adequate to provide a small quantities for initial *in vitro* and *in vivo* biological tests, but the synthesis was judged not suitable for scale-up, as it involved several chromatographic purifications and also required the use of toxic solvents and reagents in large quantities. We therefore sought a facile synthetic route capable of preparing **1** on multikilogram scale. Herein, we report our studies achieving this goal.

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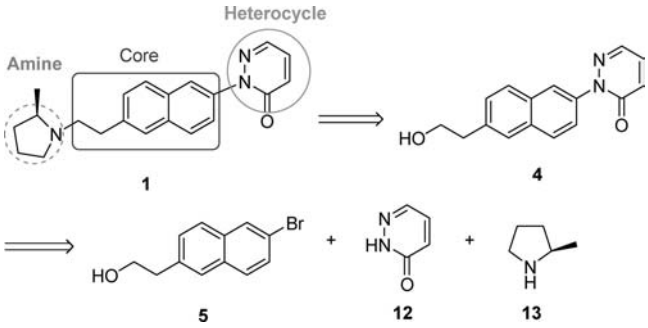
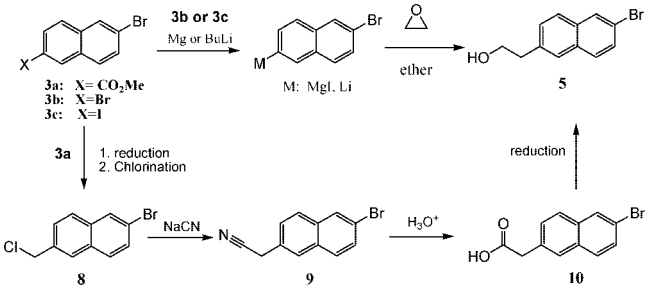
Results and Discussion

To further evaluate the safety profile of **1**, we were required to develop a scaleable process in a short time period. Oftentimes, the original synthetic route used by the medicinal chemistry team can serve as the starting point for the further improvement with the ultimate goal of developing a first enable route, albeit this usually requires significant modification. This happened to be the case with **1**. Retrosynthetically, **1** was comprised of three main pharmacophoric elements: an aromatic core, a heterocycle, and an amine (Scheme 1). Pyridazinone **12** was commercially available but not in bulk quantities, and it can be prepared by hydrogenolysis of 4,5-dicholoropyridazinone. Although (*R*)-2-methylpyrrolidine **13** was not commercially available at that time, it was easily obtained in the form of L-tartrate salt by a classical resolution of racemic 2-methylpyrrolidine with L-tartaric acid in a mixture of ethanol and methanol.[9] Thus, a facile and practical synthesis of core **5** was needed to provide an important precursor, *en route* to **1**, and ample opportunity to access a variety of structurally related compounds. The two obvious synthetic routes to **5** considered (Scheme 2) involved (1) the reaction of ethylene oxide with the appropriate mono-organometallic species, and (2) a one-carbon homologation of **3a** via a multistep process.

Scheme 1. **Retrosynthetic analysis of 1**



Scheme 2. **Synthetic routes targeted to preparation of key intermediate 5**



2,6-Dibromonaphthalene **3b** was a potentially useful starting material because of its commercial availability. Despite a rather conspicuous absence of literature describing regioselective reactions of **3b**, we decided to initially study the feasibility of generating mono-organometallic species of **3b** with magnesium (or isopropyl magnesium halide) or *n*-butyllithium under various conditions. We found, however, that we were unable to prepare the corresponding organometallic reagent cleanly. Instead, a mixture was produced, comprising starting material and mono- and di-organometallic species; overall, the results indicated that regioselective metalation was unlikely to be attained.[11] As an alternative approach to the mono-organometallic species, 2-bromo-6-iodo-naphthalene **3c**[12] was synthesized and found to convert to the corresponding Grignard species. Unfortunately, the reaction of the organometallic species with ethylene oxide proved to be very sluggish, despite investigation of various reaction conditions. Unable to make this shorter route viable in a timely fashion for the synthesis of **5**, we reassessed and refocused attention on improving the original synthetic route (Scheme 3). An additional motivation was that 6-bromo-naphthalene-2-carboxylic acid methyl ester **3a** was deemed an attractive starting material, as it was available from multiple sources in bulk quantities.

Initially, ester **3a** was reduced to alcohol **6** using $LiAlH_4$. However, this reagent induced substantial debromination, and 2-hydroxymethylnaphthalene was found to be a major by-product. This problem was magnified on scale-up, with up to 20% of the debrominated by-product generated. Although this by-product could be removed by crystallization, the isolated yield of **6** was substantially reduced. All attempts to minimize debromination by varying the amount of $LiAlH_4$ used, the addition rate, the reaction temperature and the solvent were not successful. Therefore other reducing reagents were examined, including DIBAL-H, $NaBH_4$, and $LiBH_4$. Of these, DIBAL-H proved to be the most effective and selective reagent for the reduction, producing less than 1% of the des-bromo by-product. This reaction was found to be much faster and cleaner in noncoordinating solvents such as toluene and CH_2Cl_2 than in coordinating solvents such as THF and DME. Investigations focused on toluene over CH_2Cl_2 as the solvent of choice, since it is more environmentally benign and also led to ease of workup and isolation. When the ester **3a** was subjected to the fully optimized reaction and isolation conditions, **6** was obtained in excellent yield (95%) and purity (99%) after crystallization from a mixture of toluene and heptane. The following reaction was the chlorination of alcohol **6**, which was carried out initially in 1,4-dioxane with $SOCl_2$ in the presence of $ZnCl_2$ as a catalyst. Although the reaction was found to be fast and clean, concern about the toxic nature of dioxane on scale prompted a search for an alternative and more environmentally friendly solvent. Among the solvents screened (THF, EtOAc, IPAC, DMF, DMA, NMP, DME, and toluene), dimethoxyethane (DME) gave superior overall results in the terms of isolated yield (95%) and purity (99%). Isolation of the product was also simplified by filtration after the solvent switch from DME to heptane. The next step required the displacement of chloride **7** with sodium cyanide. The reaction proceeded smoothly in aqueous CH_3CN to afford the desired nitrile **8** in excellent yield (95%) and good

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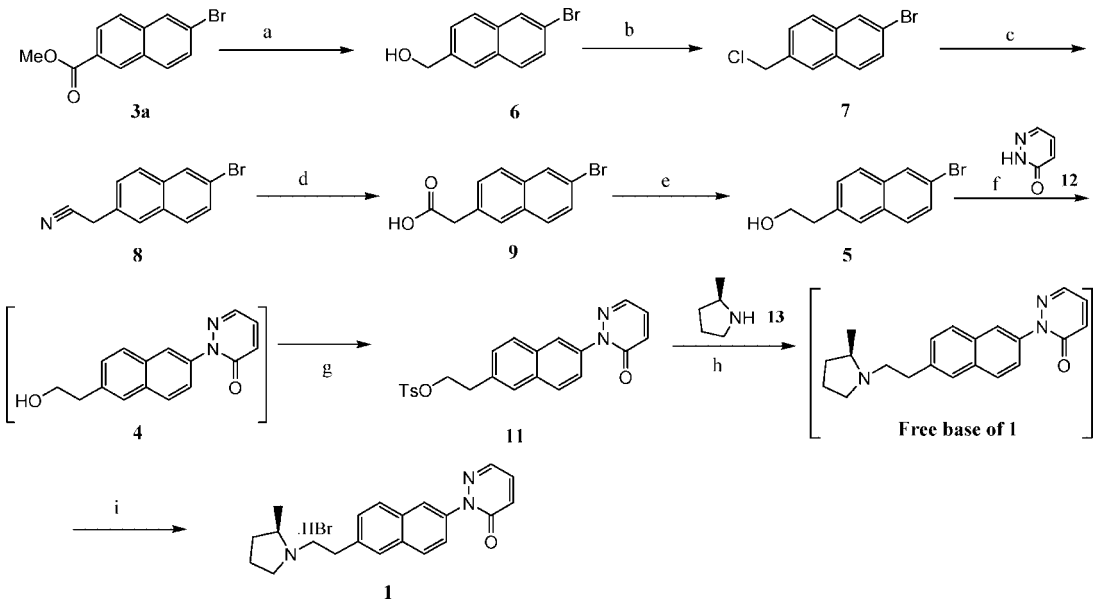
(12) According to the literature (Mulholland, K. G.; Zheng, Q.-H. *Synth. Commun.* **2001**, *31*, 3059), **3c** was prepared in 70% yield from regioselectively iodination of 2-bromo-naphthalene with I_2 in the presence of Ag(OTf). However, when 2-bromonaphthalene was subjected to the reaction conditions, 7-bromo-1-iodo-naphthalene rather than 2-bromo-6-iodo-naphthalene (**3c**) was isolated as the major product and confirmed by 2D NMR. The desired isomer **3c** was obtained from 6-bromo-naphthalen-2-ol through the Bucherer reaction and the following diazotization–iodide displacement reaction.

Scheme 3. **Large-scale synthesis of 1**[a]



[a] Reagents and conditions: (a) DIBAL-H, THF–toluene, 0 to 25 °C, 95%. (b) $SOCl_2$, $ZnCl_2$, DME, 5 °C, 96%. (c) NaCN, aq CH_3CN, reflux, 96%. (d) H_2SO_4, H_2O, CH_3CO_2H, reflux, 99%. (e) BH_3–THF complex, THF–toluene, 5 to 25 °C, 90%. (f) CuCl, 8-hyroxyquinoline, K_2CO_3, DMF, 140 °C, 85%. (g) TsCl, DMAP, Et_3N, CH_3CN, 25 °C, 88%. (h) K_2CO_3, CH_3CN, 65 °C, 85%. (i) 48% HBr, EtOH, 65 to –5 °C, 86%.

purity (97%). Several less polar and unknown impurities (total 2–3%) formed in this reaction can be readily removed in a subsequent step by crystallization. Therefore, without further process the isolated nitrile **8** was taken into aqueous HOAc–H_2SO_4 and hydrolyzed at 100 °C to afford the acid **9** in near quantitative yield and good purity. Several stable borane–amine complexes were initially screened for the reduction of acid **9** to alcohol **5**; however, these complexes were found to be ineffective. As expected, reduction of acid **9** to alcohol **5** with the more reactive borane–THF complex proceeded cleanly and rapidly at room temperature in excellent yield (90% isolated) and purity (99%).[13] The reaction worked well in many organic solvents such as THF, Toluene, MTBE, EtOAc, and IPAC. Toluene was judged best among the solvents studied due to its ease of workup and isolation. As an additional benefit, several unidentified impurities that had been carried along in the synthesis from the nitrile **8** formation step were efficiently removed by the crystallization of **5** from a mixture of toluene and heptane with the minimal loss of **5** in the process.

With large quantities of alcohol **5** now in hand, we examined the coupling of **5** with pyridazinone **12**. This coupling reaction was originally achieved by employing copper powder (2 equiv) in refluxing pyridine. The yield for this transformation on small scale routinely exceeded 60% after column chromatographic purification, but on scaling up to the multigram scale the reaction was plagued with problems, such as poor reproducibility and reduced yields. Consequently, a chromatographic purification of **4** was required. Therefore, an alternative procedure suitable for scale-up was deemed necessary. Since palladium-catalyzed coupling reactions have become increasingly powerful and widely used methods to induce aromatic carbon–heteroatom bond formation, we assessed the Pd-catalyzed N-arylation reaction of pyridazinone **12**. In the course of the investigation, many reaction variables were examined, including ligand (DPPF, Xantphos, X-phos, BINAP), palladium source ($PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$), appropriate base (K_2CO_3, Cs_2CO_3, K_3PO_4, NaO*t*Bu, KO*t*Bu), and solvent (THF, DME, dioxane, toluene).[14] Unfortunately, none of these efforts were successful. No desired product was detected, and most of starting materials were recovered and unchanged. The low reactivity of pyridazinone in the Pd-catalyzed cross-coupling reaction might be rationalized by the fact that the decreased nucleophility of the pyridazinone ($pK_a = 10.5$) anion reduces coordination to the catalyst or, more likely, diminishes the tendency of the formed intermediate aryl–Pd–pyridazone complex to undergo reductive elimination to the product.[15] On the other hand, significant progress has been made in recent years in copper-catalyzed cross-coupling reaction with more efficient ligands, better copper sources and appropriate bases and solvents. As a result, a number of novel applications of these new methods have been reported.[16–18] The above disappointing results prompted us to reconsider the copper-mediated cross-coupling reaction as a viable method. We began the optimization of this step by varying copper and ligand sources. From these studies, copper(I) chloride was found to be the best copper

(13) Although borane–THF complex is fairly stable at 0 °C and can be safely used in the pilot plant, appropriately storing and handling of it is required. See Burkhart, E. R.; Matos, K. *Chem. Rev.* **2006**, *106*, 2617 for more information.

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catalyst, and 8-hydroxyquinoline was the best ligand.[19] Other reaction conditions were also examined, including base, solvent, and reaction temperature. In the end, the coupling of **5** with **12** proceeded remarkably well at 130–140 °C, using a catalytic amount of CuCl and 8-hydroxyquinoline (5 mol %) in NMP with K_2CO_3 as a base. These conditions were ultimately used to prepare **4** from **5** in ~85% assayed yield on large scale (>10 kg) without any detectable O-arylation by product. It was worthwhile to point out that most copper catalyst used in this step was effectively removed by washing the organic phase with aqueous ammonia solution and Na_2EDTA solution, respectively, during the workup. However, compound **4** was found to be difficult to isolate without incurring a significant loss of product to the mother liquors due to its high solubility in many organic solvents. For this reason, several reactive sulfonates of **4** including tosylate, mesylate and triflate were synthesized, and their physical properties evaluated. From these studies, the tosylate **11** was found to be best, as it was a highly crystalline solid with limited solubility in many solvents. This benefited the synthetic efficiency because the crude alcohol **4** did not need to be isolated but could be directly converted *in situ* to the tosylate **11** upon treatment with TsCl and TEA in acetonitrile in the presence of a catalytic amount of DMAP. The product was isolated by a simple purification and isolation procedure, which involved direct addition of ethanol to the reaction mixture to crystallize **11**. This procedure removed all impurities present in the reaction mixture, thereby fortuitously eliminating the need for any extractive aqueous workup. The tosylate **11** was thereby obtained in excellent purity (99% by HPLC) and good yield (88%) with copper level <10 ppm from **4**. *In situ* generation of 2(*R*)-methylpyrrolidine **13** from its L-tartrate was greatly accelerated in acetonitrile with milled K_2CO_3.[9a] Treatment of tosylate **11** with **13** afforded the desired free base of **1** in 85–90 % assayed yield. Since many of the unwanted by-products in the reaction mixture were neutral, an acid–base extractive workup should be able to remove all impurities without chromatographic purification. This proved to be the case: when the crude free base of **1** in toluene was treated with a mixture of 10% KH_2PO_4 aqueous solution/*N*-methylpyrrolidinone (90:10 by volume) only the free base of **1** was extracted into the acidic aqueous solution, leaving all the neutral impurities in the organic phase. The acidic aqueous solution was basified to pH 12, and the free base of **1** then extracted back into the organic phase with isopropyl acetate with the excellent recovery (>95%) and purity (99%). The hydrobromide salt was prepared by mixing the free base of **1** in ethanol with 48% aqueous HBr. After seeding and slowly cooling to –5 °C, the salt was isolated in 86% isolated yield.

In summary, a scaleable process was developed that is suitable for the synthesis of a new class of naphthalenoid H_3 antagonist exemplified by **1**. This process addressed several issues and concerns related to the original route by refining reaction conditions (reagents, solvents, temperature, etc.) as well as isolation and purification procedures, resulting in a chromatographic-free synthesis. The synthesis of **5** was achieved in a good yield (78%) and purity (99%) from **3a**. The key step, the coupling reaction of **5** with pyridazinone **12**, was found to be much more effective under a modified Ullmann–Goldberg reaction condition. This synthetic route was surprisingly efficient and practical as demonstrated in the preparation of 11 kg of **1** with the good overall yield (43%) and excellent purity (>99%) with copper level <1 ppm.

(19) For more detailed results, see Pu, Y.; Ku, Y.; Grieme, T.; Bhatia, A. V. *Tetrahedron Lett.* **2006**, *47*, 149.

Experimental Section

General Remarks. The NMR spectra were recorded on a Varian 400 MHz instrument at 400 MHz for ^1H and 100 MHz for ^{13}C. The electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained using a LC-MS spectrometer. All the reactions were performed under a positive pressure of nitrogen. All chemicals and reagents were purchased and used without further purification unless otherwise mentioned. All melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All reaction progress was monitored by HPLC with purities being determined by peak area % at 230 nm. All assayed yields were obtained by HPLC, using pure and characterized standards.

(6-Bromo-naphthalen-2-yl)-methanol, 6. A solution of DIBAL-H (1.5 M in toluene, $d = 0.846$, 88.0 kg, 156.0 mol) was slowly charged into a solution of 6-bromo-naphthalene-2-carboxylic acid methyl ester **3a** (19.6 kg, 73.9 mol) in anhydrous THF (115.6 kg) so that the internal temperature of the reaction mixture did not exceed 25 °C. The reaction mixture was agitated for 2 h or until **3a** was consumed as indicated by HPLC. The reaction mixture was quenched slowly by pouring into a cooled 4 N HCl aqueous solution (120.0 kg), maintaining the internal temperature <25 °C. The resulting mixture was agitated for 3 h, and the upper organic phase separated. The organic phase was washed with 4 N HCl aqueous solution (30.0 kg), 5% aqueous $NaHCO_3$ solution (150.0 kg), and 6% aqueous NaCl solution (150.0 kg), respectively. The resulting solution was distilled under reduced pressure with the continuous addition of heptane to maintain a total volume of ~120 L until the solvent ratio of heptane/toluene in the mixture reached greater than 8:1 (w/w) by GC. The resulting slurry was diluted with heptane (89.0 kg), adjusted to 0 °C, and mixed for 4 h. The product was collected by filtration and dried under vacuum at 45 °C for 12 h to afford 16.8 kg of **6** (96%, purity > 99% by HPLC) as a white solid. Mp: 152–153 °C. ^1H NMR [$CDCl_3$]: δ 1.83 (s, 1H), 4.84 (s, 2H), 7.42 (dd, $J = 8.5$, 1.7 Hz, 1H), 7.53 (dd, $J = 8.8$, 1.9 Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.76 (s, 1H), 7.78 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 65.3, 119.6, 125.0, 125.9, 127.1, 129.2, 129.3, 129.5, 131.5, 133.6, 138.5. CI-MS (NH_3): *m*/*z* 236 ($M + NH_4^+ - H_2O$).

2-Bromo-6-chloromethyl-naphthalene, 7. To a reaction vessel were charged (6-bromo-naphthalen-2-yl)-methanol **6** (16.8 kg, 70.9 mol), zinc chloride (242 g, 1.8 mol, 2.5 mol %), and 1,2-dimethoxyethane (DME, 147.0 kg). The reaction mixture was then cooled to ~5 °C, and thionyl chloride (16.9 kg, 142.0 mol) was added slowly at <25 °C. The mixture was agitated for 3 h or until **6** was consumed as shown by HPLC. The mixture was distilled under a reduced pressure with the continuous addition of heptane to maintain a total volume of ~120 L until the solvent ratio of heptane/DME in the mixture

reached greater than 95:1 (w/w) by GC. The resulting slurry was diluted with heptane (82.0 kg), cooled to −15 °C, and mixed for 6 h. The product was isolated by filtration, rinsed with heptane (54.7 kg), and dried in vacuo at 45 °C for 12 h to afford 17.4 kg (96%, purity > 99% by HPLC) of **7** as a white solid. Mp: 130–131 °C. ^{1}H NMR [$CDCl_3$]: δ 4.71 (s, 2H), 7.50 (dd, J = 8.5, 1.8 Hz, 1H), 7.54 (dd, J = 8.7, 2.0 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.76 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 46.4, 120.3, 127.0, 127.1, 127.5, 129.3, 129.5, 129.5, 131.2, 133.7, 135.0. CI-MS (NH_3): *m/z* 254 (M + NH_4^+ – 18). Anal. Calcd for $C_{11}H_8BrCl$: C, 51.70; H, 3.16; Br, 31.27; Cl, 13.87. Found: C, 52.11; H, 2.99; Br, 31.33 0.19; Cl, 13.60.

(6-Bromo-naphthalen-2-yl)-acetonitrile, 8. To a reaction vessel were charged 2-bromo-6-chloromethyl-naphthalene (**7**) (17.4 kg, 68.1 mol), sodium cyanide (97%, 4.5 kg, 89.0 mol), acetonitrile (136.8 kg), and water (21.3 kg). The reaction mixture was heated to reflux (~80 °C), and agitated for 15 h or until **7** was consumed by HPLC. The reaction mixture was cooled to 30 °C and quenched with water (150.0 kg). The mixture was distilled under reduced pressure to approximately 150 L volume and diluted with water (200 kg). The resulting slurry was cooled to 0 °C and mixed for 5 h. The product was collected by filtration, rinsed with water (300 kg), and purged with nitrogen for 10 h to give 26.5 kg (loss on drying = 39.8%, 95% yield, purity = 97.6% by HPLC) wet cake of **8**. The wet cake was used directly in the next step. However, an analytical sample was obtained by drying the wet cake in vacuo at 45 °C for 20 h. Mp: 118–119 °C. ^{1}H NMR [$CDCl_3$]: δ 3.86 (s, 2H), 7.38 (dd, J = 8.5, 1.8 Hz, 1H), 7.57 (dd, J = 8.7, 1.9 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.98 (d, J = 1.8 Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 24.1, 117.3, 120.3, 126.2, 126.5, 127.4, 127.8, 129.0, 129.5, 129.9, 131.4, 133.4. CI-MS (NH_3): *m/z* 263 (M + NH_4^+). Anal. Calcd for $C_{12}H_8BrN$: C, 58.56; H, 3.28; Br, 32.47; N, 5.69. Found: C, 58.31; H, 3.24; Br, 32.19; N, 5.39.

(6-Bromo-naphthalen-2-yl)-acetic acid, 9. To a reaction vessel were charged (6-bromo-naphthalen-2-yl)-acetonitrile **8** (26.5 kg, 60.2% potency, 64.8 mol), water (380.0 kg), acetic acid (125.4 kg), and sulfuric acid (81.0 kg). The slurry was heated to reflux (~110 °C) and mixed for 20 h or until **8** was consumed by HPLC. The slurry was cooled to 25 °C, diluted with water (120.0 kg), and mixed for 4 h. The product was isolated by filtration, rinsed with water (180 kg), and dried in vacuo at 60 °C for 20 h to afford 17.1 kg (99%, purity = 96.4% by HPLC) of **9** as a tan solid. Mp: 178–180 °C. ^{1}H NMR [DMSO-d_6]: δ 3.75 (s, 2H), 7.48 (dd, J = 8.5, 1.7 Hz, 1H), 7.60 (dd, J = 8.5, 1.9 Hz, 1H), 7.80 (s, 1H), 7.83 (d, J = 6.1, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 1.9 Hz, 1H), 12.41(s, br, 1H). ^{13}C NMR [DMSO-d_6]: δ 40.7, 118.3, 126.4, 127.3, 128.5, 128.7, 128.9, 129.2, 130.9, 132.5, 133.0, 171.7. CI-MS (NH_3): *m/z* 282 (M + NH_4^+).

2-(6-Bromo-naphthalen-2-yl)-ethanol, 5. A borane–THF complex solution (1 M in THF, d = 0.90, 80.1 kg, 89.0 mol) was added slowly to slurry of (6-bromo-naphthalen-2-yl)-acetic acid (**9**) (17.1 kg, 64.5 mol) in toluene (285.5 kg) at <30 °C. The solution was mixed for 1 h or until **9** was consumed by HPLC. Citric acid 10% aqueous solution (290 kg) was added slowly while maintaining a nitrogen atmosphere, and the mixture was agitated for 0.5 h. The upper organic layer was separated and then washed with 5% aqueous $NaHCO_3$ (290 kg) and 25% aqueous NaCl (200 kg), respectively. The organic solution was distilled under reduced pressure to ~70 L volume, and heptane (150.5 kg) was charged into the slurry. The slurry was mixed at 25 °C for 6 h, then at −5 °C for 2 h. The product was isolated by filtration, rinsed with heptane (27.5 kg), and dried in vacuo at 60 °C for 20 h to afford 14.5 kg (90%, purity = 99.1% by HPLC) of **9** as a tan solid. Mp: 104–105 °C. ^{1}H NMR [$CDCl_3$]: δ 1.47 (s, 1H), 3.00 (t, J = 6.5 Hz, 2H), 3.93 (t, J = 6.5 Hz, 2H), 7.36 (dd, J = 8.5, 1.8 Hz, 1H), 7.51 (dd, J = 8.8, 1.9 Hz, 1H), 7.63 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 1.9 Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 39.4, 63.4, 119.0, 127.0, 127.1, 128.1, 128.8, 129.1, 129.3, 131.6, 133.0, 136.3. CI-MS (NH_3): *m/z* 268 (M + NH_4^+), 250 (M + NH_4^+ – H_2O). Anal. Calcd for $C_{12}H_{11}BrO$: C, 57.39; H, 4.42; Br, 31.82. Found: C, 57.27; H, 4.50; Br, 31.68.

2-[6-(2-Hydroxy-ethyl)-naphthalen-2-yl]-2*H*-pyridazin-3-one, 4. To a reaction vessel were charged 2-(6-bromo-naphthalen-2-yl)-ethanol **5** (14.5 kg, 57.7 mol), CuCl (286 g, 2.9 mol, 5 mol %), 8-hydroxyquinoline (420.0 g, 2.9 mol, 5 mol %), K_2CO_3 powder (12.0 kg, 87.0 mol), pyridazinone **12** (8.3 kg, 86.4 mol), and DMF (66.0 kg). The reaction vessel was evacuated and backfilled with nitrogen (repeated 3 times). The reaction vessel was then pressurized with nitrogen to 5 psi and isolated. The mixture was heated to 140 °C and maintained at that temperature for 18 h or until **5** was consumed by HPLC (Caution: the internal pressure will rise, so vent as needed). The reaction mixture was cooled to 20 °C, and ethyl acetate (270 kg), 30% aqueous NH_4OH (105 kg), and 4% Na_2EDTA/23% aqueous NaCl solution (140 kg) were added. The mixture was agitated for 0.5 h, filtered through a pad of filter aid, and then rinsed with ethyl acetate (20 kg). The lower aqueous solution was extracted with ethyl acetate (105 kg × 2). The combined organics were washed with 4% Na_2EDTA/23% aqueous NaCl solution (280 kg × 3). The organic solution was assayed to contain 13.2 kg (85% assayed yield, purity = 92.3%) of the product **4** and was used directly in the next step without further purification. However, an analytical sample was obtained by recrystallization from ethyl acetate/heptane. Mp: 139–140 °C. ^{1}H NMR [$CDCl_3$]: δ 1.9 (s, br, 1H), 3.00 (t, J = 6.4 Hz, 2H), 3.89 (t, J = 6.4 Hz, 2H), 7.03 (dd, J = 9.5, 1.7 Hz, 1H), 7.23 (dd, J = 9.5, 3.8 Hz, 1H), 7.36 (dd, J = 8.5, 1.7 Hz, 1H), 7.67 (s, br, 1H), 7.66 (dd, J = 8.5, 2.2 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.90 (dd, J = 3.8, 1.8 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H). ^{13}C NMR [DMSO-d_6]: 39.5, 63,4, 123.1, 123.5, 126.9, 127.8, 127.9, 128.3, 139.8, 130.9, 131.4, 132.5, 126.5, 136.9, 138.2, 159.8. CI-MS (NH_3): *m/z* 283 (M + NH_4^+), 267 (M + NH_4^+ – NH_3). Anal. Calcd for: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.76; H, 5.28; N, 10.46.

Toluene-4-sulfonic Acid 2-[6-(6-Oxo-6*H*-pyridazin-1-yl)-naphthalen-2-yl]-ethyl Ester, 11. The above organic solution of **4** in ethyl acetate was concentrated to ~75 L volume, and acetonitrile (280 kg) was added. The solution was distilled to ~75 L volume and diluted with acetonitrile (140 kg). The solution was added to a reaction vessel containing TsCl (19.8 kg, 103.9 mol) and DMAP (635 g, 5.2 mol) and was followed

by the addition of triethylamine (15.8 kg, 155.9 mol). The reaction mixture was agitated at 25 °C for 6 h or until **4** was consumed by HPLC. The reaction mixture was distilled down to ~90 L, and ethanol 3A (175 kg) was then added. The suspension was mixed at 25 °C for 1 h and 0 °C for 3 h. The product was isolated by filtration, washed with ethanol 3A (60 kg), and dried in vacuo at 45 °C for 12 h to afford 18.1 kg (88%, purity = 98.0% by HPLC) of **11** as an off-white solid. Mp: 142–143 °C. ^{1}H NMR [$CDCl_3$]: δ 2.34 (s, 3H), 3.10 (t, J = 6.7 Hz, 2H), 4.31 (t, J = 6.7 Hz, 2H), 7.07 (dd, J = 9.5, 1.8 Hz, 1H), 7.11 (d, J = 7.9 Hz, 2H), 7.23 (dd, J = 8.4, 1.7 Hz, 1H), 7.26 (dd, J = 9.5, 3.7 Hz, 1H), 7.52 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.68 (dd, J = 8.8, 2.1 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 3.8, 1.6 Hz, 1H), 8.07 (d, J = 1.9 Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 21.8, 35.6, 70.4, 123.2, 123.4, 126.9, 127.3, 127.5, 127.8, 128.3, 129.3, 130.8, 131.0, 131.6, 132.3, 132.3, 134.5, 136.5, 138.4, 144.2, 159.7. CI-MS (NH_3): m/z 438 (M + NH_4^+), 421 (M + NH_4^+ – NH_3). Anal. Calcd for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66. Found: C, 65.63; H, 4.69; N, 6.65.

Free Base of 1. A suspension of (*R*)-2-methylpyrroldine L-tartrate (14.2 kg, 60.4 mol) and milled K_2CO_3 (12.1 kg, 87.5 mol) in acetonitrile (300 kg) was heated to 70 °C and mixed for 24 h. The suspension was cooled to 25 °C, and toluene-4-sulfonic acid 2-[6-(6-oxo-6*H*-pyridazin-1-yl)-naphthalen-2-yl]-ethyl ester **11** (17.5 kg, 41.6 mol) was added. The suspension was reheated back to 70 °C and mixed for an additional 24 h or until **11** was consumed by HPLC. The reaction mixture was cooled to 25 °C, filtered through a pad of filter agent to remove the salt by-products, and then rinsed with acetonitrile (95 kg). The filtrate was distilled under reduced pressure to ~70 L, and toluene (129 kg) was added. The mixture was concentrated to ~125 L volume and then washed with 25% aqueous NaCl (125 kg). The organic solution was extracted with a solution of 10% aqueous KH_2PO_4/NMP (90:10, v/v) (125 kg × 2). Isopropyl acetate (109 kg) was added to the combined aqueous product solution, and the pH of the mixture adjusted to 12 with 50% aqueous NaOH (~14 kg) at <25 °C. The contents were mixed for 0.5 h, and the upper organic layer was separated. The organic solution was washed first with 5% aqueous $NaHCO_3$/20% aqueous NaCl solution (125 kg), then with 25% aqueous NaCl solution (125 kg). The organic solution was distilled to ~75 L volume and diluted with isopropyl acetate (60 kg). The solution was distilled again to ~60 L, filtered to remove all inorganic salts, and rinsed with isopropyl acetate (20 kg). The filtrate was assayed to contain 11.9 kg (86%, Purity = 99.1% by HPLC) of the free base of **1** and used directly in the next step without further purification. However, an analytical sample was obtained by recrystallization from heptane. Mp: 56–58 °C. ^{1}H NMR [$CDCl_3$]: δ 1.14 (d, J = 6.1 Hz, 3H), 1.46 (m, 1H), 1.75 (m, 1H), 1.82 (m, 1H), 1.95 (m, 1H), 2.25 (q, J = 8.8 Hz, 1H), 2.40 (m, 2H), 3.00 (m, 2H), 3.13 (m, 1H), 3.30 (td, J = 8.5, 2.9 Hz, 1H), 7.07 (dd, J = 9.5, 1.8 Hz, 1H), 7.24 (dd, J = 9.5, 3.7 Hz, 1H), 7.39 (dd, J = 8.4, 1.7 Hz, 1H), 7.66 (dd, J = 8.9, 2.1 Hz, 1H), 7.68 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.91 (dd, J = 3.8, 1.6 Hz, 1H), 8.06 (d, J = 1.9 Hz, 1H). ^{13}C NMR [$CDCl_3$]: δ 19.1, 21.9, 32.8, 35.7, 54.1, 55.8, 60.2, 122.9, 123.5, 126.2, 127.8, 127.9, 128.1, 130.8, 131.0, 131.3, 132.6, 136.4, 138.0, 138.9, 159.8. ESI-MS: m/z 334 (M + 1).

Compound 1. The above freebase of **1** (11.9 kg, 35.6 mol) solution in IPAC was distilled to one-half volume, and ethanol 3A (100 kg) was added to the solution. The solution was distilled to ~100 L, and 48% aqueous HBr (6.44 kg, 38.7 mol) was added at 30 °C. The solution was heated to 55 °C, and seed crystals of **1** (260 g) were added. The solution was slowly cooled to −5 °C and then mixed for 4 h. The product was filtered and then dried in vacuo at 50 °C for 12 h to afford 13.1 kg (87%, purity > 99%) of **1** as an off-white solid. Mp: 221–222 °C. ^{1}H NMR [CD_3OD]: δ 1.48 (d, J = 6.2 Hz, 3H), 1.75 (m, 1H), 2.09 (m, 2H), 2.32 (m, 1H), 3.25 (m, 3H), 3.35 (m, 1H), 3.55 (m, 1H), 3.75 (m, 2H), 7.10 (dd, J = 9.5, 1.6 Hz, 1H), 7.49 (dd, J = 9.5, 3.9 Hz, 1H), 7.52 (dd, J = 8.4, 1.8 Hz, 1H), 7.65 (dd, J = 8.8, 2.0 Hz, 1H), 7.87 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 1.6 Hz, 1H), 8.07 (dd, J = 3.9, 1.7 Hz, 1H). ^{13}C NMR [CD_3OD]: δ 16.5, 22.7, 32.5, 33.1, 55.0, 55.2, 66.2, 124.7, 124.9, 128.0, 128.4, 128.9, 129.7, 131.2, 133.0, 133.5, 133.8, 136.0, 138.9, 139.9, 161.8. CI-MS (NH_3): m/z 334 (M + NH_4^+). Anal. Calcd for $C_{21}H_{24}BrN_3O$: C, 60.87; H, 5.84; Br, 19.28; N, 10.14. Found: C, 60.55; H, 5.68; Br, 19.42; N, 9.97.

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