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Development of Two Complementary Syntheses for a Privileged CGRP Receptor Antagonist Substructure

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ABSTRACT: 1-(Piperidin-4-yl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**1**) is a privileged substructure found in >1000 unique CGRP receptor antagonists. Two practical and efficient syntheses of **1** are described from complementary starting materials. One route features a chemoselective reductive amination, while the second route utilizes a Pd-catalyzed amination using an ammonia surrogate to overcome an issue of poor selectivity.

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide associated with the pathophysiology of migraines.[1] Inhibition of the CGRP receptor with a small molecule has the potential to be an effective and safe treatment for people who suffer from such afflictions.[2] The current standard of care for migraines is the triptan class of drugs, which are vascular constrictors and suffer from mechanism-based cardiovascular risks.[3] In contrast, a CGRP antagonist should prevent vasodilation, thereby circumventing cardiovascular risks.[4]

Pharmacophore modeling among the known CGRP receptor antagonists has revealed a highly conserved 'right-hand side' fragment that incorporates key hydrogen-bonding functionality into the molecule.[5] 1-(Piperidin-4-yl)-1*H*-imidazo[4,5-*b*]-pyridin-2(3*H*)-one (**1**) is one such privileged structure (Figure 1), having appeared in >1000 unique CGRP receptor

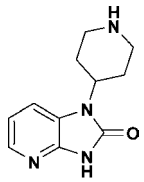

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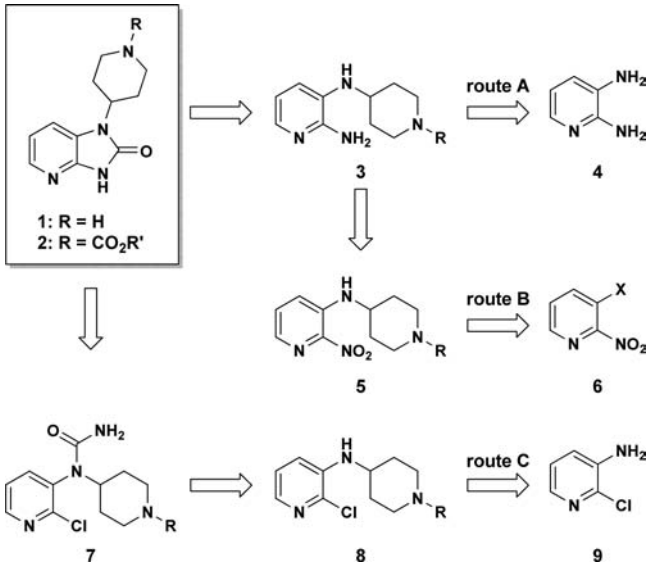
Figure 1. Conserved RHS fragment **1**.

antagonists,[6] including Merck's phase III clinical candidate telcagepant.[7]

While at least three distinct approaches to compound **1** exist in the literature, most suffer from deficiencies with starting material cost and reaction efficiency.[8] We envisioned that a complementary approach which addresses these challenges may provide more synthetic flexibility and find utility for many CGRP programs. Herein, we describe two such approaches to **1**, featuring a selective reductive amination and a palladium-catalyzed amination, respectively.

Scheme 1 depicts the three established approaches for the synthesis of **1**. In the most widely utilized approach (route A),[8a] the protected cyclic urea **2** is formed via the cyclization of

Scheme 1. Known routes for the preparation of 1



compound **3** using a phosgene equivalent. Compound **3** is prepared from the chemoselective reductive amination of 2,3-diaminopyridine (**4**) and a protected piperidin-4-one analogue. While route A is clearly the most direct of the available routes, published examples of it suffer from the key drawback of a poor-yielding reductive amination step. While the reductive amination reaction is indeed chemoselective for the C-3 nitrogen, isolated yields are typically ≤50%. The low yield can be attributed to competing direct reduction of the ketone due to the poor nucleophilicity of the electron-deficient arylamine. The low overall efficiency of route A most likely prompted previous researchers to examine alternative approaches. Compound **3** can also be obtained by reduction of nitropyridine **5**, which in turn is prepared via S_NAr addition of a protected 4-aminopiperidine to 3-halo-2-nitropyridine **6** (route

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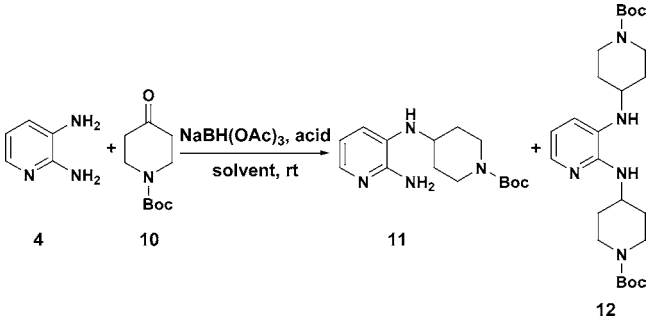
B).[8b] This route is disfavored due to the high temperatures required for the S_NAr reaction, the expense of both starting materials, and the likelihood of genotoxicity issues with the nitro-containing intermediates. The final established approach relies upon an intramolecular palladium-catalyzed cyclization of the primary urea **7** (route C).[8c,d] Compound **7** arises from the reaction of *N*-chlorosulfonyl isocyanate with compound **8**, which in turn is derived from a reductive amination of 2-chloro-3-aminopyridine **9** and a protected piperidin-4-one analogue. While route C is an efficient approach that makes use of inexpensive starting materials, we thought a complementary approach would provide manufacturing flexibility. We elected to consider a two-pronged approach in our strategy for an efficient preparation of **1**, opting to improve the reductive amination step in route A, while exploring a direct conversion of chloride **8** to amine **3**.

RESULTS AND DISCUSSION

Of the three approaches, route A is the shortest, requiring only three steps. However, the low-yielding reductive amination step of 2,3-diaminopyridine **4** with ketone **10** to afford the monoalkylated product **11** was a key concern (Scheme 2).

Scheme 2. Chemoselective reductive amination



Upon investigation of this reaction using sodium triacetoxyborane as the reducing agent, reductive amination yields remained low. Others have established that inefficient reactions for similar compounds are due to inefficient iminium ion formation.[9,10] Complicating the reaction was the undesired generation of impurity **12**, resulting from a second reductive amination at the C-2 nitrogen.

Selectivity for the desired monoalkylated product **11** was modest (4:1) irrespective of the solvent employed (Table 1, entries 1–2). Hence, the use of stoichiometric AcOH to enhance the amine/iminium equilibrium was examined but proved to be ineffective in improving the yield, although a modest increase in selectivity was realized (entries 3–4). We rationalized that a stronger acid should further aid in driving the iminium formation, and thus TFA was examined for this purpose.[11] Gratifyingly, complete conversion to the desired product **11** was achieved in 1 h using 2 equiv of TFA (entries 5–6). Importantly, formation of the dialkyated impurity **12** was minimized, presumably due to efficient iminium formation coupled with the enhanced rate of reduction.[12] After workup and crystallization from EtOAc/IPAc, an 86% yield of **11** was obtained with >94% purity. This improvement was expected to dramatically improve the overall efficiency of route A and render it a more viable preparative option.

Table 1. Effect of acid on reductive amination yield and selectivity (Scheme 2)

entry	acid	solvent	time (h)	yield (%)[a]	selectivity (**11**:**12**)[b]
1	–	DCE	24	51	4:1
2	–	EtOAc	24	43	4:1
3	AcOH	DCE	4	58	11:1
4	AcOH	EtOAc	4	53	10:1
5	TFA	DCE	1	95	63:1
6	TFA	EtOAc	1	90	56:1

[a]In-process solution yields. [b]ratio determined by HPLC on crude reaction mixture.

In spite of the marked improvement made to route A, route C still had the important advantage of utilizing the least expensive starting materials of the available routes (Scheme 1). We opted to examine an alternative approach that would still make use of the inexpensive starting material 2-chloro-3-aminopyridine **9**. Hence, we hypothesized that 2-aminopyridine **3** could be derived from 2-chloropyridine **8** via a palladium-catalyzed amination reaction with ammonia or an ammonia surrogate (route D; Scheme 3). Such an approach would exploit the advantage of the inexpensive starting materials of route C while retaining the efficient ring formation of route A. Thus, the problem was distilled down to developing an efficient palladium-catalyzed amination reaction to convert the 2-chloropyridine **8** into 3-aminopyridine **3**.[13] Nonetheless, we expected that such a transformation would be challenging since either the C-3 amine or the newly formed C-2 amine may be competitive with the ammonia source for amination.[14]

The requisite starting material was prepared using a similar reductive amination procedure as described for the preparation of compound **11** (Scheme 2). Reductive amination of 2-chloro-3-aminopyridine **9** and ketone **10** proceeded smoothly, using $NaBH(OAc)_3$ and TFA which ensured complete conversion of **9** with minimal direct reduction of ketone **10** (Scheme 4).[15] The boc-protected 2-chloropyridine **13** was isolated in 95% yield with >98.8% purity by crystallization from EtOAc/heptane. With substrate **13** in hand, studies to examine the palladium-catalyzed amination commenced.

Initial screening for the palladium-catalyzed amination focused on determining the optimal ammonia source. A key design consideration was a simple removal of any protecting group introduced (or no protection) in order to maintain efficiency. As such, the following three ammonia sources were examined: lithium hexamethyldisilazane, ammonia, and benzophenone imine.

Initial attempts using LiHMDS as the ammonia source were met with poor conversion, leading only to trace amounts of the desired product **11** (Scheme 5).[16] As such, this avenue was not pursued further. Catalyst screening using a solution of ammonia in dioxane and a strong base (NaO*t*Bu) demonstrated modest conversions to compound **11**.[17] By charging ammonia gas instead to increasing the concentration of ammonia, better conversion was achieved. However, the reaction suffered from high levels of a dimeric impurity **15** resulting from an undesired amination of the product's C-2 or C-3 nitrogen.[18]

We hypothesized that benzophenone imine could be a useful ammonia surrogate to minimize formation of byproduct **15** by either directly blocking the C-2 reactive site or by increasing the steric congestion at C-3.[19] Preliminary screening identified $Pd(OAc)_2$ and Binap as a good catalyst/ligand combination to effect the desired transformation. A base screen instructed that strong bases still had the propensity to form impurity **15**,

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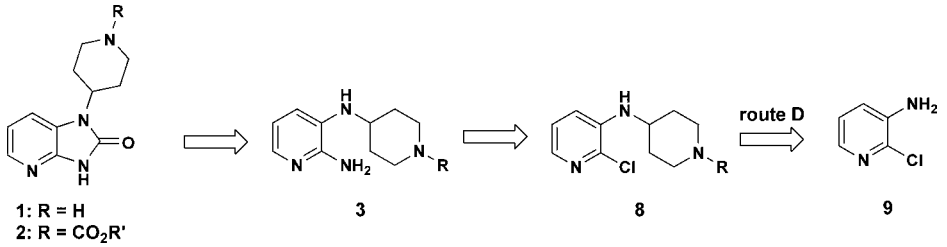
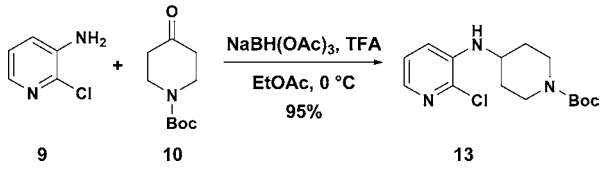
Scheme 3. Proposed Pd-catalyzed amination approach to 1, route D



Scheme 4. Preparation of Pd-catalyzed amination substrate 13



although encouraging yields of the desired imine product **14** were obtained using NaO*t*Bu (Table 2, entries 1−2).[20] Gratifyingly, the use of weak bases greatly reduced the levels of **15**. While yields of **14** were still poor using Na_2CO_3 and K_2CO_3, dramatic improvements were realized with K_3PO_4 and Cs_2CO_3 (entries 3−4 vs 5−6), leading us to choose the latter for further evaluation.

We noticed a curious dependence of the reaction's yield on the ligand to metal ratio. While nearly identical results were observed using a ratio of 1:1 and 2:1 (entries 6−7), a clear and significant local maximum was observed using a ligand to metal ratio of 1.5:1 (entry 8). While it is unclear why such a phenomenon was observed, the net result is an increase in solution yield of ∼15%. Hence, upon treatment of **13** with 1.1 equiv of benzophenone imine, 2.0 equiv of Cs_2CO_3, 2 mol % $Pd(OAc)_2$, and 3 mol % Binap in toluene, the pyridyl amine **14** was obtained in 85% solution yield with undetectable levels of impurity **15**.

With conditions in hand to selectively perform the Pd-catalyzed amination, we next focused on conversion of the benzophenone imine to the target amine without concurrent deprotection of the acid labile Boc group. Citric acid was found to be a sufficiently mild acid to effect the desired transformation, and a telescoped procedure was developed to avoid an additional isolation step.[21] Hence, upon subjection of **13** to the Pd-catalyzed amination conditions, followed by citric acid-mediated deprotection, amine **11** was obtained in 80% yield and ≥97.0% purity after crystallization from heptanes.

Table 2. Effect of base and ligand to metal on Pd-catalyzed amination (Scheme 5, R = N=CPh$_2$)

entry	base	$Pd(OAc)_2$:Binap	yield (%)[a]	selectivity (**14**:**15**)[b]
1	KO^{t}Bu	1:1	9	1:7
2	NaO^{t}Bu	1:1	66	4:1
3	Na_2CO_3	1:1	8	≥99:1
4	K_2CO_3	1:1	28	≥99:1
5	K_3PO_4	1:1	66	≥99:1
6	Cs_2CO_3	1:1	73	≥99:1
7	Cs_2CO_3	2:1	70	≥99:1
8	Cs_2CO_3	1.5:1	85	≥99:1

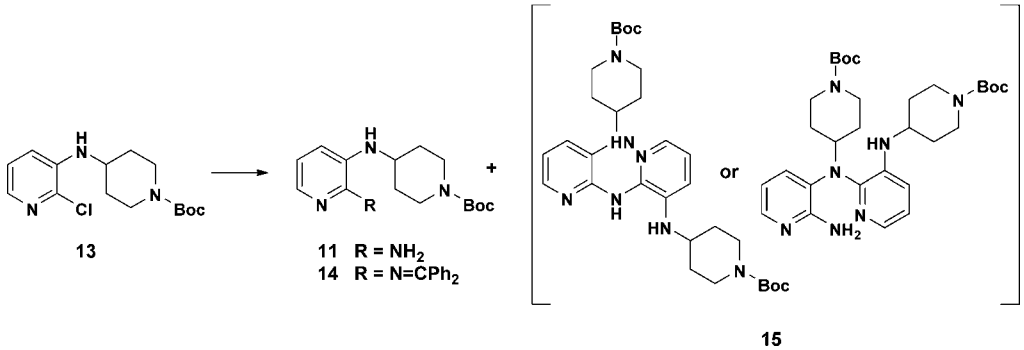
[a]In-process solution yields. [b]Ratio determined by HPLC on crude reaction mixture.

With two efficient, yet complementary approaches to **11** in hand, the synthesis of the CGRP substructure **1** was accomplished according to modified literature procedures (Scheme 6).[8a] Compound **11** was converted to the cyclized urea **16** upon treatment with CDI and TEA in 89% isolated yield and 98.5% purity. Finally, the Boc protecting group was removed using ethanolic HCl, and **1** was isolated as its bis-HCl salt in 94% yield and 99.9% purity. The 'selective reductive amination' route to **1** proceeds in only three steps with 72% overall yield from 2,3-diaminopyridine **4**. Alternatively, the 'Pd-catalyzed amination' route proceeds in five steps, with only four isolations, with 64% overall yield from the less expensive 2-chloro-3-aminopyridine **9**.

CONCLUSION

In conclusion, we have developed two efficient and scalable approaches to the 'CGRP privileged structure' 1-(piperidin-4-yl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (**1**). The more direct 'selective reductive amination' route was made practical by using a strong acid (TFA) to enhance the yield and selectivity of the key reductive amination step. The slightly longer 'Pd-catalyzed amination' route, which uses less expensive starting

Scheme 5. Pd-catalyzed amination



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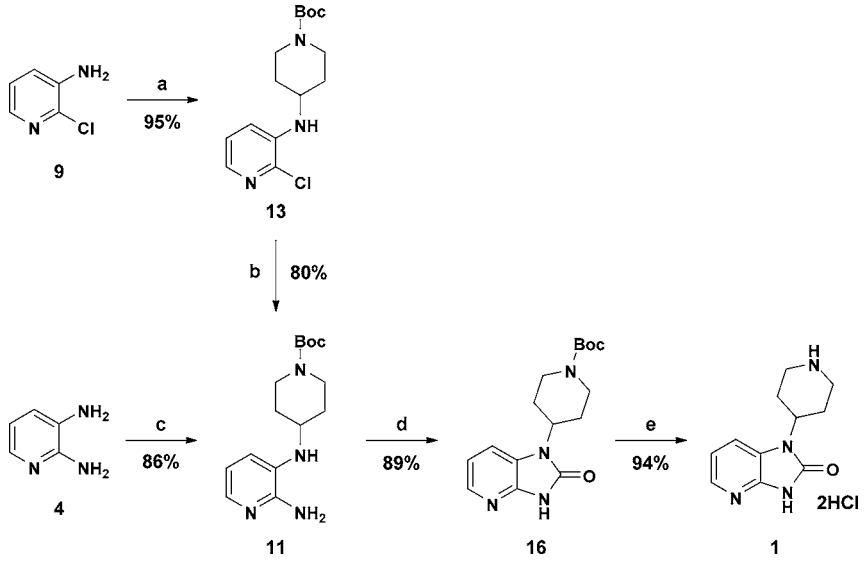
Scheme 6. Two complementary synthetic routes to 1[a]



[a]Reagents and conditions: (a) **10**, $NaBH(OAc)_3$, TFA, EtOAc, 0 °C. (b) i. Benzophenone imine, Cs_2CO_3, $Pd(OAc)_2$, *rac*-BINAP, toluene, 100 °C, ii. citric acid, EtOH, 60 °C (c) **10**, $NaBH(OAc)_3$, TFA, EtOAc, 0 °C. (d) CDI, Et_3N, MeCN, 10 °C. (e) HCl, EtOH, 40 °C.

materials, was made possible by the development of a selective and efficient Pd-catalyzed amination with benzophenone imine. Both of these approaches are expected to find broad utility in the synthesis of a wide range of CGRP antagonists.

EXPERIMENTAL SECTION

General Methods. HPLC analyses for compounds **13**, **11**, and **16** were collected on an Agilent 1200 liquid chromatograph using a DAD UV−vis detector. HPLC analyses for compound **1** were collected on a Waters Alliance 2695 liquid chromatograph using a PDA UV−vis detector. All results are reported as area percent (area %).

***tert*-Butyl-4 (2-chloropyridin-3-ylamino)piperidine-1-carboxylate (13).** 2-Chloropyridin-3-amine **9** (500 g, 3.89 mol), *tert*-butyl-4-oxopiperidine-1-carboxylate **10** (930 g, 4.67 mol), and ethyl acetate (7.5 L) at 0−5 °C were treated with trifluoroacetic acid (887 g, 7.78 mol) followed by sodium triacetoxyborohydride (1240 g, 5.83 mol) at ≤10 °C. The reaction was warmed to ambient temperature, stirred for 2 h, and quenched with water (1.5 L). The pH was adjusted to 10−11 with 20% sodium hydroxide solution, and the phases were separated. The product-rich organic layer was washed with water (3 × 5 L) and then concentrated under vacuum to ∼1.5 L. *n*-Heptane (5.0 L) was added to the solution at 40 °C, and the resulting slurry was cooled to 0−5 °C and aged for 1 h. The slurry was filtered, and the cake was washed with *n*-heptane (1.5 L) and dried at 50 °C under vacuum for 12 h to afford 1170 g of **13** as an off-white solid (98.8% HPLC area purity, 95% yield). Mp = 117.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (t, J = 2.8 Hz, 1H), 7.19 (multiple peaks, 2H), 5.16 (d, J = 8.4 Hz, 1H), 3.93 (d, J = 12.4 Hz, 2H), 3.48−3.57 (m, 1H), 2.76−3.01 (m, 2H), 1.85 (d, J = 11.2 Hz, 2H), 1.34−1.41 (multiple peaks, 11 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.3, 140.3, 136.4, 135.8, 124.3, 118.9, 79.1, 49.3, 43.1, 31.5, 28.6; IR (KBr) 3395, 2948, 1910, 1685, 1584, 1493, 1429, 1394, 1246, 1146; HRMS Calcd for $C_{15}H_{23}O_2N_3Cl$: 312.1479; HRMS found $[M + H]^+$: 312.1474.

***tert*-Butyl-4-(2-aminopyridin-3-ylamino)piperidine-1-carboxylate (11).** *tert*-Butyl-4-(2-chloropyridin-3-ylamino)-piperidine-1-carboxylate **13** (100 g, 0.32 mol), benzophenone imine (64 g, 0.35 mol), and toluene (1.4 L) were degassed with nitrogen for 30 min. Cesium carbonate (209 g, 0.641 mol), palladium acetate (1.40 g, 0.006 mol), and *rac*-BINAP (6.00 g, 0.009 mol) were added at ambient temperature. The reaction mixture was heated to 95−100 °C and stirred for 20 h. The reaction mixture was cooled to ambient temperature, water (1 L) was added, and the layers were separated. Charcoal (20 g) was added to the organic layer and stirred at 45 °C for 30 min; the mixture was then filtered through Celite. The solvent was evaporated under vacuum to afford a thick oily residue. This residue was dissolved in ethanol (1500 mL); citric acid (185 g, 0.959 mol) and water (11.5 g, 0.641 mol) were added. The reaction mixture was heated to 55−60 °C for 15 h. The solvent was evaporated under vacuum to afford a thick oily residue, and water (400 mL) was added. The pH was adjusted to 8−9 with 10% NaOH, the product was extracted with DCM (2 × 1 L), and washed with water (2 × 0.5 L). Charcoal (20.0 g) was added and the mixture was stirred for 30 min then filtered through Celite. The solvent was evaporated under vacuum and *n*-heptane (200 mL) was added at 35−40 °C. The resulting slurry was cooled to ambient temperature and aged for 30 min. The slurry was filtered, and the cake was washed with *n*-heptane (200 mL) and dried at 50 °C under vacuum for 12 h to afford 74.5 g of **11** as a pale-yellow solid (97.0 HPLC area purity, 80% yield). Mp = 158.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (dd, J = 4.8 Hz, 1.6 Hz,1H), 6.67 (dd, A of ABX, J_{AB} = 6.8 Hz, J_{AX} = 1.2 Hz, 1H), 6.44 (dd, B of ABX, J_{AB} = 7.6 Hz, J_{BX} = 5.2 Hz, 1H), 5.44 (s, 2H), 4.49 (d, J = 7.2 Hz, 1H), 3.89 (d, J = 13.2 Hz, 2H), 3.28−3.42 (m,1H), 2.83−3.00 (m, 2H), 1.91 (dd, J = 12.8 Hz, 2.8 Hz, 2H), 1.41 (s, 9 H), 1.21−1.30 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.4, 149.2, 134.7, 129.6, 114.8, 113.5, 79.0, 49.1, 42.9, 31.9, 28.6; IR (KBr) 3433, 3386, 2927, 1678, 1577, 1510, 1474, 1457, 1433; HRMS Calcd for $C_{15}H_{25}O_2N_4$: 293.1978; HRMS found $[M + H]^+$: 293.1972.

***tert*-Butyl-4-(2-aminopyridin-3-ylamino)piperidine-1-carboxylate (11).** 2,3-Diamino pyridine **4** (10.0 g, 91.6 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate **10** (21.9 g, 110

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mmol), and ethyl acetate (100 mL) were cooled to 0−5 °C. Trifluoroacetic acid (23.4 g, 205 mmol) followed by sodium triacetoxyborohydride (29.1 g, 137 mmol) were added at ≤10 °C. The reaction mixture was warmed to ambient temperature, stirred for 2 h, and then cooled to ≤10 °C. The reaction mixture was quenched with 10% sodium hydroxide solution (∼180 mL), and the pH was adjusted to 8.5−9.0 while maintaining the reaction temperature at ≤10 °C. The reaction mixture was diluted with ethyl acetate (200 mL), and the organic layer was separated and washed with water (100 mL). The solution was concentrated under vacuum to ∼30 mL, and isopropyl acetate (50 mL) was added at 40 °C. The resulting slurry was cooled to 10−15 °C and then aged for 1 h. The slurry was filtered, and the cake was washed with ice-cold water (25 mL) and then dried at 50 °C under vacuum for 12 h to afford 23.0 g of **11** as a pale-brown solid (94.4% HPLC area purity, 86% yield).

***tert*-Butyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-1-yl)piperidine-1-carboxylate (16).** *tert*-Butyl-4-(2-aminopyridin-3-ylamino)piperidine-1-carboxylate **11** (50.0 g, 0.171 mol), and acetonitrile (500 mL) were treated with *N*,*N*-diisopropylethylamine (48.9 g,0.378 mol) followed by 1,1′-carbonyldiimidazole (41.6 g, 0.256 mol) at ambient temperature. The mixture was stirred for 2 h. The reaction mixture was cooled to 0−5 °C and stirred for 30 min. The resulting slurry was filtered, and the cake was washed with acetonitrile (200 mL) and dried at 50 °C under vacuum for 12 h to afford 48.5 g of **16** as a white solid (98.5% HPLC area purity, 89% yield). Mp = 201.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 7.90 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.53 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 6.99 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 4.32−4.38 (m, 1H), 4.10 (d, J = 12.0 Hz, 2H), 2.78−2.84 (m, 2H), 2.13 (dq, J = 12.4 Hz, 4.4 Hz, 2H), 1.72 (d, J = 10.4 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.3, 153.5, 143.9, 140.1, 123.7, 116.9, 115.1, 79.3, 50.4, 43.2, 29.1, 28.6; IR (KBr) 3363, 2975, 2862, br 1692, 1617, 1455, 1430, 1366, 1240, 1136; HRMS Calcd for $C_{16}H_{23}O_3N_4$: 319.1770; HRMS found [M + H]$^+$: 319.1767.

1-(Piperidin-4-yl)-1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one dihydrochloride (1). *tert*-Butyl-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxylate **16** (50.0 g, 0.157 mol) and HCl (4.0 M in EtOH; 250 mL) were heated to 50−55 °C for 16 h. The reaction mixture was cooled to ambient temperature and the resulting slurry filtered. The cake was washed with ethanol (100 mL) and dried at 50 °C under vacuum for 12 h to afford 42.8 g of **1** as an off-white solid (99.9% HPLC area purity, 94% yield). Mp = 357.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (bs, 1H), 9.48 (bs, 1H), 9.14 (bs, 1H), 7.89−7.94 (multiple peaks, 3H), 7.05 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 4.60 (dt, J = 12.4 Hz, 3.6 Hz, 1H), 3.40 (d, J = 12.4 Hz, 2H), 3.09 (q, J = 12.0 Hz, 2H), 2.60−2.69 (m, 2H), 1.87 (d, J = 12.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.2, 143.4, 139.1, 123.6, 116.9, 116.2, 47.1, 43.1, 25.4; IR (KBr) 3294, 3114, 2914, 2812, 2708, 1736, 1667, 1563, 1381, 1227, 1136; HRMS Calcd for $C_{11}H_{15}ON_4$: 219.1246; HRMS found [M + H]$^+$: 219.1240.

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