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Integrated Cross-Coupling Strategy for an α-Carboline-Based Aurora B Kinase Inhibitor

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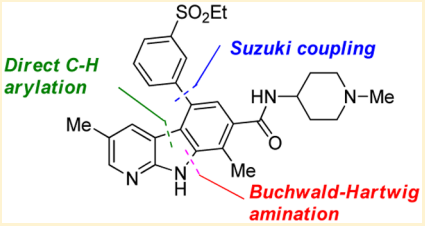
Supporting Information

ABSTRACT: An efficient and practical synthetic process for an α-carboline-based Aurora B kinase inhibitor was achieved using an integrated Pd-catalyzed cross-coupling strategy. The process features a mild and efficient method for construction of the α-carboline core by employing a Pd-catalyzed sequence of Buchwald–Hartwig amination and intramolecular direct C–H arylation at the ortho position of an unsubstituted aniline moiety, which is a key functionality for further derivatization with a Suzuki coupling via Sandmeyer iodination. The process has eliminated expensive starting materials and column chromatography purifications and enabled considerable enhancement of the total yield from 11% to 48%.



INTRODUCTION

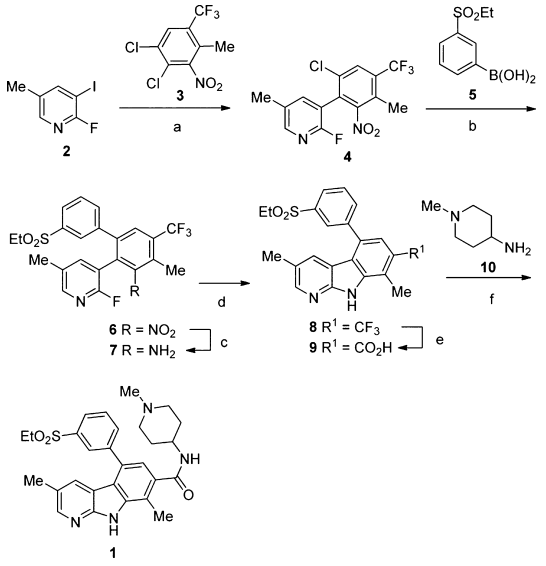
Species in the Aurora kinase family (A–C) are homologous serine-threonine protein kinases, which play important roles in the formation and distribution of chromosomes and cytokinesis.[1] Aurora B kinase is the catalytic component of the chromosomal passenger complex and is thought to have a critical role in cell division during the metaphase to anaphase stages. Hence, inhibition of Aurora B kinase activity has been considered as an attractive target for pharmacological intervention in the oncology drug field.[2]

During the course of our medicinal chemistry team's investigations into small-molecule Aurora B kinase inhibitors for antineoplastic activity, **1** was selected as a potent drug candidate in this area with a suitable profile for further clinical studies (Scheme 1).[3] The synthetic challenges associated with the chemical structure were identified as efficient synthesis of the α-carboline (pyrido[2,3-*b*]indole) core and regioselective installation of several substituents. While an early medicinal chemistry synthesis of **1** on the laboratory scale enabled successful preparation of the material for early toxicological and preclinical studies, the synthesis of **1** for further clinical evaluation was hampered by the limited scalability. In this context, a practical and scalable synthesis of **1** was required. Herein, we describe an efficient synthesis of **1** employing integrated cross-coupling reactions.

RESULTS AND DISCUSSION

The initial synthesis for preparing small quantities of **1** is outlined in Scheme 1.[4] The assembly of the α-carboline core was achieved by a sequence of Ullmann coupling of 2-fluoro-3-iodo-5-methylpyridine (**2**) with 2,3-dichloro-5-trifluoromethyl-6-methylnitrobenzene (**3**), followed by reduction of the nitro group and the final intramolecular cyclization with a S_NAr reaction between the fluorine and aromatic amine. However, the approach had several drawbacks from the viewpoint of

Scheme 1. Initial Synthetic Strategy for 1[a]



[a]Reagents and conditions: (a) Cu, NMP, 190 °C, 43%; (b) $Pd_2(dba)_3$, PCy_3, Cs_2CO_3, dioxane, reflux, 61%; (c) Fe, AcOH, 80 °C. 96%; (d) AcOH, reflux, 87%; (e) H_2SO_4, 120 °C, 96%; (f) HATU, TEA, DMF, 25 °C, 58%.

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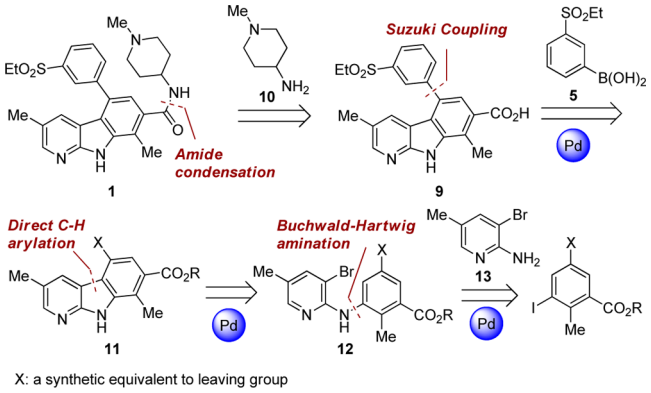
large-scale preparation to support further evaluation (e.g., clinical study), particularly in the Ullmann coupling step. For example, expensive and less commercially available **2** and **3** were used. Potentially explosive high-temperature cyclization (190 °C) of the nitro compound **3** was needed. In addition, this process was poorly reproducible in yield and quality; as the scale of the Ullmann reaction increased, the isolated yield of **4** and the amount of byproducts arising from poor regioselectivity and homocoupling were highly variable.

After considering these drawbacks of the previous synthesis, we sought to explore an alternative synthetic strategy for the α-carboline pharmacophore by employing a versatile Pd-catalyzed sequence of Buchwald–Hartwig amination[5] and direct C–H arylation,[6] which we investigated on the basis of Sakamoto and co-workers' precedent.[7] After our initial study on using this strategy, we reported the optimal catalyst systems: $Pd(OAc)_2$/XANTPHOS (4,5-bis(diphenylphosphino)-9,9′-dimethylxanthene)/Cs_2CO_3 for the amination and $Pd(OAc)_2$/DCHPB (2-dicyclohexylphosphino-2′-biphenyl)/DBU for the direct C–H arylation, respectively.[8] The outstanding feature of the synthetic sequence is that a combination of DCHPB and DBU plays a critical role in not only enhancing the reactivity but also suppressing the hydrodehalogenation for the direct C–H arylation,[9] and consequently the protocol enables a rapid and divergent synthesis of α-carbolines with various substituents, including base-sensitive ones such as ester groups. Using this protocol, an improved synthetic strategy has been proposed, as outlined retrosynthetically in Scheme 2. The key points of our

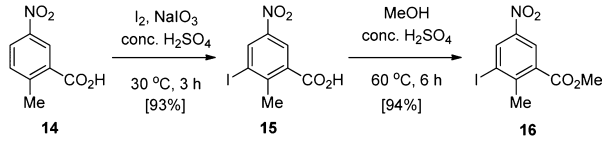
Scheme 2. Retrosynthetic Analysis of 1



synthetic strategy include achieving the Pd-catalyzed cyclization for α-carboline **11** with an ester group to be amidated with amine **10** and a substituent to be converted to a leaving group for the Suzuki coupling reaction with 3-ethylsulfonylphenylboronic acid (**5**).

Aryl Iodide Preparation. Our initial efforts centered on the preparation of the adequate aryl iodide for the Pd-catalyzed amination.[10] Among a number of aromatic precursor candidates, readily available 2-methyl-5-nitrobenzoic acid derivatives were selected for the iodination, as we envisaged that the nitro group would contribute to the regioselective iodination and would be converted to a halogen through a reduction of the nitro group followed by a Sandmeyer reaction. After an intensive screening of aromatic precursors and iodination methods, 2-methyl-5-nitrobenzoic acid (**14**) was successfully iodinated by an effective iodination system (I_2/$NaIO_3$/concentrated H_2SO_4)[11] to afford the corresponding aryl iodide **15** in 93% yield with high regioselectivity (Scheme 3).[12]

Scheme 3. Preparation of Aryl Iodide 16



As the downstream Pd-catalyzed cross-coupling reactions were inhibited by the carboxylic acid moiety and our preliminary study showed that ester groups are tolerated under the sequence of Pd-catalyzed reaction conditions,[8] methyl esterification of **15** was carried out using Fisher esterification conditions to provide **16** in 94% yield (Scheme 3).[13]

α-Carboline Construction. With the desired aryl iodide **16** in hand, our subsequent efforts were turned to the construction of the α-carboline core. First, Pd-catalyzed Buchwald–Hartwig amination with our previously established catalyst system ($Pd(OAc)_2$/XANTPHOS/Cs_2CO_3) was conducted. The catalyst system was successfully applied to the coupling of **16** with 2-amino-3-bromo-5-methylpyridine (**13**). The reaction was completed within 5 h, and the coupling product **17** was obtained in 99% yield (Scheme 4).

Subsequently, Pd-catalyzed direct C–H arylation of **17** was addressed. However, the initial attempt to use the optimized catalyst system ($Pd(OAc)_2$/DCHPB/DBU) provided the undesired product **18**, arising from ester hydrolysis of **17**, as the main product rather than the desired α-carboline **19**. On considering the unexpected result that is inconsistent with our preliminary data that the ester group is tolerated under the reaction conditions,[8] we assumed that the hydrolysis could be attributed to the strong electron-withdrawing property of the nitro group on the aromatic ring. Therefore, we expected that increasing the electron density on the aromatic ring by reduction of the nitro group to an amino group prior to direct C–H arylation would suppress the ester hydrolysis of **17**. In addition, we considered that the increased electron density at the ortho position of the amino aromatic would promote electrophilic C–H insertion of Pd(II), similar to the promotion of an intramolecular direct arylation at the ortho position of a phenol.[14] Thus, we refocused our attention on the alternative route, by way of reducing the nitro group of **17** (Scheme 4).

Among the various precedent reduction methods for an aromatic nitro group, selective reduction of an aromatic nitro function over an aromatic bromide was required for the synthesis. Some reduction systems with metals in aqueous acidic solution were initially investigated. Although early studies using Fe- or Zn-based reduction systems suffered from side reactions such as hydrodehalogenation and incomplete conversion, the Sn-based reduction system ($SnCl_2$/HCl) gave satisfactory results, with **20** being exclusively obtained in 85% yield (Scheme 4).

With **20** in hand, the optimal catalyst system ($Pd(OAc)_2$/DCHPB/DBU) was again applied to intramolecular cyclization of **20**, and a full conversion was gratifyingly achieved with less than 3% of hydrolyzed product **22**. Undesired **22** was effectively removed through the crystallization workup, and crystalline **21** was finally isolated in 91% yield (Scheme 4). Importantly, the reaction was selective for intramolecular direct C–H arylation, and no coupling by-product arising from the intra- and intermolecular C–N coupling of aryl bromide with the N-unsubstituted aniline group was observed.

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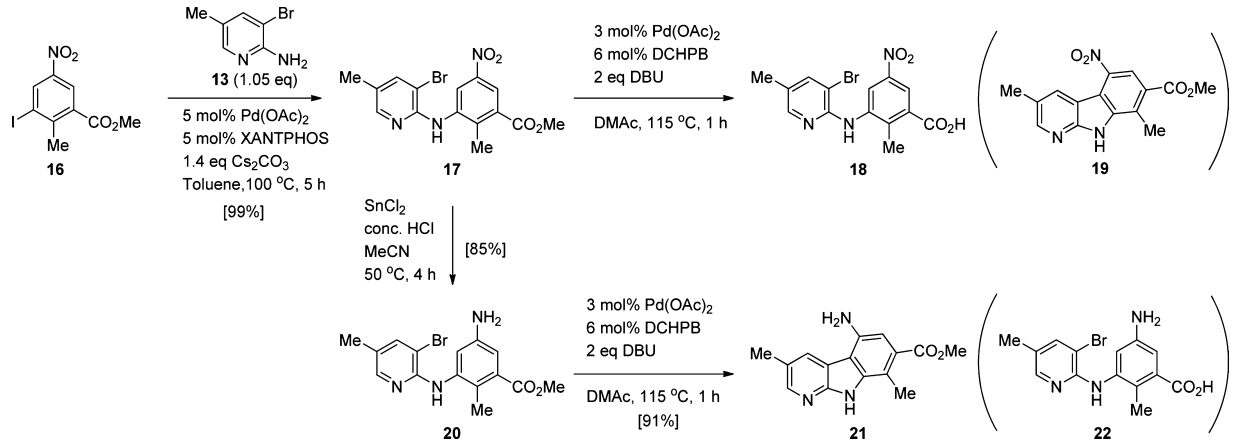
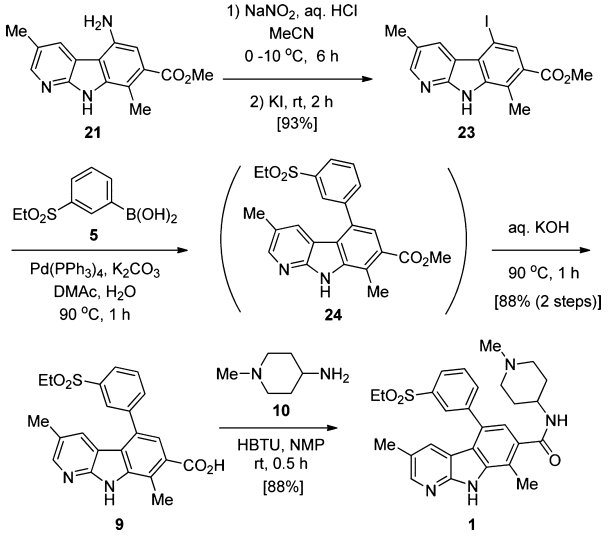
Scheme 4. Synthesis of α-Carboline 21



Functional Group Introduction on the α-Carboline. With the preparation of α-carboline **21** established, our subsequent efforts were focused on functionalization of the α-carboline. To accomplish the synthesis of **1**, halogenation and arylation at the 5-position and amide formation at the 7-position are required. First, a Sandmeyer reaction to halogenate the amino group was examined. Although the initial examination for bromination suffered from some side reactions, including dediazonation, the diazonation of **21** using $NaNO_2$/concentrated HCl/acetonitrile followed by addition of aqueous KI solution afforded **23** in 93% yield (Scheme 5). Subsequently,

Scheme 5. Synthesis of 1



Pd-catalyzed Suzuki coupling was studied, and the coupling of **23** with boronic acid **5** was achieved using $Pd(PPh_3)_4$ and K_2CO_3 to give **24** in 79% isolated yield, along with 8% of **9** arising from hydrolysis of **24**. To further simplify the sequential process, we attempted to combine the Suzuki coupling with the ester hydrolysis in one pot. In fact, after completion of the Suzuki coupling, hydrolysis with 10% KOH successfully provided **9** in 88% yield from **23**. Finally, amide formation of carboxylic acid **9** with 1-methylpiperidin-4-amine (**10**) was carried out in the presence of HBTU in NMP to afford **1** in 88% yield.

CONCLUSION

An efficient and practical synthesis for Aurora B kinase inhibitor **1** has been established using an integrated Pd-catalyzed cross-coupling strategy. The synthesis features an efficient α-carboline assembly, employing a Pd-catalyzed sequence of a Buchwald−Hartwig amination and an intramolecular direct C−H arylation at the ortho position of an unsubstituted aniline moiety, which is then further derivatized by Sandmeyer iodination and Suzuki coupling. The present strategy is more practical than the former synthesis from the viewpoint of process robustness, the availability of starting compounds, and the versatility of the synthetic approach. While the former process relied on the Ullmann coupling reaction that is poorly reproducible on scaleup and is largely restricted to less commercially available and highly functionalized starting compounds, the current process consists of an effective Pd-catalyzed sequence from readily available starting compounds (2-amino-3-bromopyridine and nitrobenzene derivatives), and the strategy should be applicable to other derivatives. Furthermore, the process eliminates complicated column chromatography purifications, and all intermediates could be isolated as crystals following simple workup. Overall, the new process contributed to a considerable enhancement of the total yield, from 11% to 48%.

EXPERIMENTAL SECTION

General Considerations. All chemicals were obtained from commercial suppliers and were used without further purification. Degassing of solvents was conducted by repeating an evacuation/nitrogen refilling cycle. ^1H NMR and ^{13}C NMR spectra were recorded on 500 MHz spectrometers with tetramethylsilane as an internal standard. Chemical shifts are shown in ppm.

3-Iodo-2-methyl-5-nitrobenzoic Acid (15). To a mixture of 2-methyl-5-nitrobenzoic acid (**14**; 10.0 g, 55.2 mmol), iodine (5.6 g, 22.1 mmol, 0.4 equiv), and concentrated sulfuric acid (40 mL) was added sodium iodate (4.4 g, 22.1 mmol, 0.4 equiv) at 10−30 °C. The reaction mixture was stirred at 25−30 °C for 3 h. To a mixture of sodium sulfite (17.4 g, 138.0 mmol, 2.5 equiv), water (100 mL), and methanol (40 mL) was added the reaction mixture at 5−30 °C. After the mixture was stirred at 20−30 °C for 2 h, the resulting precipitates were filtered and washed with methanol/water (1/2, 20 mL × 2), and dried at 50 °C in vacuo to give 15.8 g (93% yield) of the title compound as off-white crystals. Mp: 178.3 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 2.67 (s, 3H), 8.41 (d, J = 2.5 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.7, 104.6, 124.0, 135.1, 135.3, 145.8, 148.2, 167.6. HRMS (EI): m/z calcd for $[M]^+$ $C_8H_6INO_4$, 306.9342; found, 306.9333.

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Methyl 3-Iodo-2-methyl-5-nitrobenzoate (16). To a mixture of 3-iodo-2-methyl-5-nitrobenzoic acid (**15**; 15.0 g, 48.9 mmol) and methanol (75 mL) was added dropwise concentrated sulfuric acid (10.4 mL, 195.4 mmol, 4.0 equiv) below 50 °C. The mixture was stirred at 60 °C for 6 h. After the mixture was stirred at 50 °C for 30 min, a solution of sodium sulfite (1.2 g, 9.8 mmol, 0.2 equiv) and water (30 mL) was added. The pH of the mixture was adjusted to 8−9 with 5% aqueous NH_3 at 50 °C. After the mixture was cooled to room temperature, water (30 mL) was added. The mixture was stirred at 50 °C for 30 min and 5 °C for 1 h. The resulting precipitates were filtered, and washed with methanol/H_2O (1/2, 30 mL × 2), and dried at 50 °C in vacuo to give 14.8 g (94% yield) of the title compound as pale yellow crystals. Mp: 64.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.65 (s, 3H), 3.91 (s, 3H), 8.46 (d, J = 2.5 Hz, 1H), 8.72 (d, J = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.7, 53.5, 104.8, 124.4, 132.4, 136.2, 145.8, 148.6, 166.1. HRMS (EI): m/z calcd for $[M]^+C_9H_8INO_4$, 320.9498; found, 320.9492.

Methyl 3-[(3-Bromo-5-methylpyridin-2-yl)amino]-2-methyl-5-nitrobenzoate (17). To a mixture of palladium acetate (349.1 mg, 1.6 mmol, 0.05 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS; 1.4 g, 2.3 mmol, 0.075 equiv) in degassed anisole (130 mL) were added methyl 3-iodo-2-methyl-5-nitrobenzoate (**16**; 10.0 g, 31.1 mmol, 1 equiv), 3-bromo-5-methylpyridin-2-ylamine (**13**; 6.1 g, 32.7 mmol, 1.05 equiv), and cesium carbonate (14.2 g, 43.5 mmol, 1.4 equiv) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h and then stirred at 125 °C for 5 h. After the reaction mixture was cooled to room temperature, water (65 mL) was added. The mixture was concentrated in vacuo. The resulting residue was suspended in methanol (100 mL) and acetone (20 mL). The pH of the mixture was adjusted to 6.5−7.5 with 6 mol/L aqueous HCl (ca. 10 mL). The mixture was refluxed for 1 h and stirred at room temperature for 1.5 h. The resulting precipitates were filtered and washed with methanol/acetone/water (10/2/1, 10 mL × 2) and dried at 60 °C in vacuo to give 11.7 g (99%) of the title compound as dark brown crystals. Mp: 187.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 7.89 (d, J = 1.6 Hz, 1H), 7.95 (d, J = 1.3 Hz, 1H), 8.16 (s, 1H), 8.29 (d, J = 2.5 Hz, 1H), 8.56 (d, J = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.3, 17.0, 53.2, 106.8, 119.6, 121.1, 126.9, 132.7, 140.8, 142.2, 142.5, 145.6, 146.5, 150.8, 166.8. HRMS (EI): m/z calcd for $[M]^+$ $C_{15}H_{14}BrN_3O_4$, 379.0168; found, 379.0159.

Methyl 5-Amino-3-[(3-bromo-5-methylpyridin-2-yl)amino]-2-methylbenzoate (20). To a solution of methyl 3-[(3-bromo-5-methylpyridin-2-yl)amino]-2-methyl-5-nitrobenzoate (**17**; 15.2 g, 40.0 mmol, 1 equiv) and tin(II) chloride dihydrate (28.0 g, 120.0 mmol, 3 equiv) in methanol (152 mL) was added concentrated HCl (36%) (15.2 mL). The mixture was stirred at 50 °C for 4 h. The mixture was diluted with tetrahydrofuran (228 mL). The pH of the mixture was adjusted to 7−9 with 25% ammonia solution (30.4 mL) with cooling in an ice bath, before 20% aqueous potassium sodium (+)-tartrate tetrahydrate solution (460 mL) was added to the mixture. After the mixture was stirred at room temperature for 1 h, ethyl acetate (228 mL) and NaCl (60.8 g) were added, and the mixture was stirred at room temperature for 1 h. The organic layer was separated, successively washed with 5% aqueous $NaHCO_3$ (228 mL) and 20% aqueous NaCl (228 mL), and concentrated in vacuo. The resulting residue was suspended in ethanol (80 mL) at room temperature for 0.5 h. The resulting precipitates were filtered and washed with ethanol (20 mL) and further dried at 50 °C in vacuo to give 11.9 g (85% yield) of the title compound as brown crystals. Mp: 122.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.11 (s, 3H), 2.16 (s, 3H), 3.79 (s, 3H), 5.12 (s, 2H), 6.83 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 7.51 (s, 1H), 7.76 (d, J = 1.0 Hz, 1H), 7.84 (d, J = 1.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.6, 16.9, 52.2, 105.7, 112.0, 115.2, 120.6, 124.7, 131.8, 141.0, 141.6, 146.5, 146.8, 151.9, 168.9. HRMS (EI): m/z calcd for $[M]^+$ $C_{15}H_{16}BrN_3O_2$, 349.0426; found, 349.0424.

Methyl 5-Amino-3,8-dimethyl-9*H*-pyrido[2,3-*b*]indole-7-carboxylate (21). To a mixture of palladium acetate (202.1 mg, 0.9 mmol, 0.03 equiv) and 2-(dicyclohexylphosphino)biphenyl (DCHPB; 630.9 mg, 1.8 mmol, 0.06 equiv) in degassed *N*,*N*-dimethylacetamide (DMAc) (20 mL) were added DBU (0.9 g, 60.0 mmol, 2.0 equiv) and methyl 5-amino-3-[(3-bromo-5-methylpyridin-2-yl)amino]-2-methylbenzoate (**20**; 10.5 g, 30.0 mmol, 1 equiv) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h and then stirred at 130 °C for 1 h. The reaction mixture was cooled to room temperature, and water (40 mL) was added to the mixture. The resulting slurry was stirred at room temperature for 0.5 h and in an ice bath for 0.5 h. The resulting precipitates were filtered, washed with water (10 mL × 2), and dried at 60 °C in vacuo to give 7.4 g (91% yield) of the title compound as light yellow crystals. Mp: 295.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.46 (s, 3H), 2.60 (s, 3H), 3.84 (s, 3H), 5.67 (s, 2H), 6.99 (s, 1H), 8.24 (d, J = 1.3 Hz, 1H), 8.49 (d, J = 1.0 Hz, 1H), 11.62 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.5, 18.6, 52.1, 106.6, 109.9, 110.3, 115.3, 123.9, 127.9, 130.3, 140.4, 142.3, 145.9, 151.2, 168.9. HRMS (EI): m/z calcd for $[M]^+$ $C_{15}H_{15}N_3O_2$, 269.1164; found, 269.1151.

Methyl 5-Iodo-3,8-dimethyl-9*H*-pyrido[2,3-*b*]indole-7-carboxylate (23). To a mixture of methyl 5-amino-3,8-dimethyl-9*H*-pyrido[2,3-*b*]indole-7-carboxylate (**21**); 2.7 g, 10.0 mmol) and 6 mol/L aqueous HCl (54 mL) was added dropwise sodium nitrite (724.5 mg, 10.5 mmol, 1.05 equiv) in water (54 mL) below 10 °C. The mixture was stirred at 0−10 °C for 30 min. Potassium iodide (5.0 g, 30.0 mmol, 3.0 equiv) in water (54 mL) was added dropwise to the mixture below 10 °C. The mixture was stirred at room temperature for 2 h. Methanol (16 mL) and aqueous 10% sodium sulfite solution (54 mL) were added to the reaction mixture. The pH of the reaction mixture was adjusted to 7−9 with 5 mol/L aqueous NaOH (55 mL) below 30 °C. The mixture was stirred at 5−10 °C. The resulting precipitates were filtered, washed with cold water (20 mL × 2), and dried at 60 °C in vacuo to give 3.5 g (93% yield) of the title compound as brown crystals. Mp: 270.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.51 (s, 3H), 2.74 (s, 3H), 3.88 (s, 3H), 8.06 (s, 1H), 8.47 (d, J = 1.0 Hz, 1H), 8.89 (s, 1H), 12.23 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.2, 18.7, 52.6, 84.4, 115.7, 123.7, 124.0, 124.2, 128.1, 129.5, 131.1, 140.0, 149.3, 151.7, 167.0. HRMS (EI): m/z calcd for $[M^+]$ $C_{15}H_{13}IN_2O_2$, 380.0022; found, 380.0027.

5-[3-(Ethylsulfonyl)phenyl]-3,8-dimethyl-9*H*-pyrido[2,3-*b*]-indole-7-carboxylic Acid (9). To a solution of tetrakis-(triphenylphosphine)palladium ($Pd(PPh_3)_4$; 174.0 mg, 0.15 mmol, 0.05 equiv), methyl 5-iodo-3,8-dimethyl-9*H*-pyrido[2,3-*b*]-indole-7-carboxylate (**23**; 1.1 g, 3.0 mmol), and 3-(ethylsulfonyl)phenylboronic acid (**5**; 1.3 g, 6.0 mmol, 2 equiv) in degassed *N*,*N*-dimethylacetamide (DMAc; 25 mL) was added potassium carbonate (829.2 mg, 6.0 mmol, 2.0 equiv) in water (10 mL). The resulting mixture was stirred at room temperature for 0.5 h and heated at 90 °C for 1 h. A 2 mol/L aqueous NaOH solution (30 mL) was added to the reaction mixture below 95 °C, and this mixture was stirred at 90 °C for 1 h. After the mixture was cooled to room temperature, the pH was adjusted to 5−7 with 6 mol/L aqueous HCl (10 mL) below 30 °C. The mixture was stirred in an ice bath for 0.5 h, and the resulting precipitates were filtered, washed with cold water (10 mL × 2), and dried at 60 °C in vacuo to give 1.1 g (88% yield) of the title compound as gray crystals. Mp: 332.5−338.5 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.18 (t, J = 7.3 Hz, 3H), 2.27 (s, 3H), 2.85 (s, 3H), 3.43 (q, J = 7.5 Hz, 2H), 7.52 (s, 1H), 7.58 (s, 1H), 7.87−7.90 (m, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.12 (s, 1H), 8.35 (s, 1H), 12.13 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.7, 15.3, 18.4, 49.5, 114.3, 119.1, 122.8, 123.0, 124.1, 127.6, 128.2, 129.5, 130.0, 130.7, 132.6, 134.5, 139.5, 140.0, 141.3, 148.3, 151.9, 169.7. HRMS (FAB-double-focusing magnetic sector): m/z calcd for $[M - H]^-$ $C_{22}H_{20}N_2O_4S$, 407.1055; found, 407.1066.

5-[3-(Ethylsulfonyl)phenyl]-3,8-dimethyl-*N*-(1-methylpiperidin-4-yl)-9*H*-pyrido[2,3-*b*]indole-7-carboxamide (1). To *N*-methyl-2-pyrrolidinone (NMP; 94.7 mL) was added 5-[3-(ethylsulfonyl)phenyl]-3,8-dimethyl-9*H*-pyrido[2,3-*b*]indole-7-carboxylic acid (**9**; 33.9 g, 82.9 mmol). The mixture was stirred at 65−75 °C until the dissolution of **9**. After the mixture was cooled to 25−35 °C, *N*-methyl-4-aminopiperidine (**10**; 18.9 g, 165.8 mmol, 2.0 equiv) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU; 34.6 g, 91.2 mmol, 1.1 equiv) were added to the

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mixture. The mixture was stirred at 20−30 °C for 2 h, and water (24 mL) was added to the reaction mixture. A solution of KOH (8.4 g, 149.2 mmol, 1.8 equiv) dissolved in water (26 mL) was added dropwise to the mixture. Additional water (52 mL) was then added to the mixture. The mixture was stirred at room temperature. The resulting precipitates were filtered and washed with 25% aqueous NMP (28 mL × 2) and dried at 60 °C in vacuo to give 36.8 g (88% yield) of the title compound as brown crystals. Mp: 240.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.19 (t, J = 7.4 Hz, 3H), 1.51−1.60 (m, 2H), 1.83 (d, J = 10.1 Hz, 2H), 1.91−2.04 (m, 2H), 2.17 (s, 3H), 2.28 (s, 3H), 2.61 (s, 3H), 2.76 (d, J = 12.0 Hz, 2H), 3.42 (q, J = 7.3 Hz, 2H), 3.72−3.80 (m, 1H), 7.09 (s, 1H), 7.52 (s, 1H), 7.88−7.92 (m, 1H), 8.01−8.06 (m, 2H), 8.12 (t, J = 1.6 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.31 (s, 1H), 12.02 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 7.7, 14.6, 18.4, 31.9, 46.5, 46.8, 49.5, 54.8, 114.5, 117.5, 119.0, 120.4, 124.0, 127.6, 128.2, 129.7, 130.7, 132.7, 134.5, 135.8, 139.4, 139.7, 141.4, 147.7, 151.7, 168.7. HRMS (ESI-orbitrap): m/z calcd for $[M + H]^+$ $C_{28}H_{33}N_4O_3S$, 505.2260; found, 505.2268.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR and ^{13}C NMR data for all new compounds. 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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