A Facile and Green Synthesis of a Naphthyridine Derivative: A Novel Hedgehog Pathway Modulator

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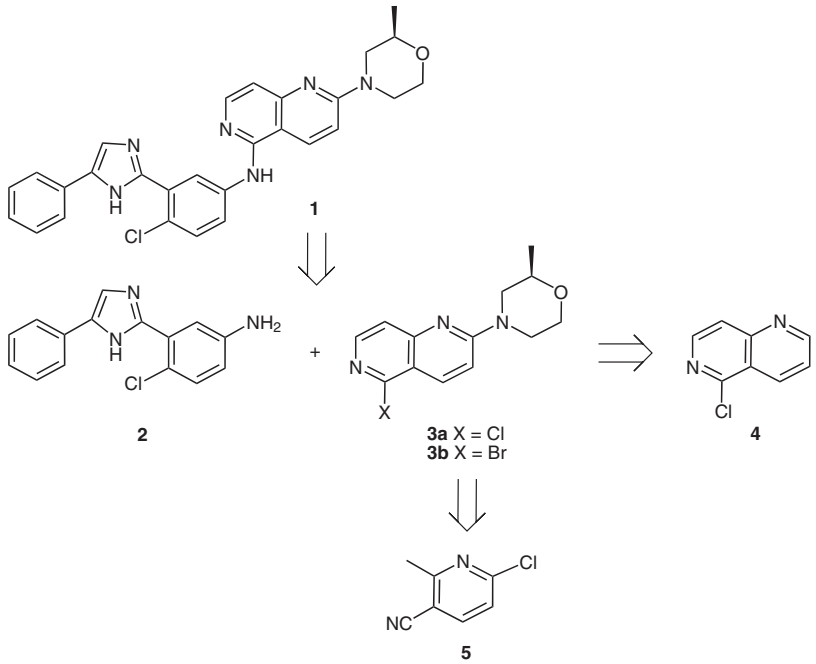
Abstract: A green and highly efficient synthesis of a naphthyridine derivative, a novel hedgehog pathway modulator, in high yield and purity from inexpensive starting materials is described. The key step involves an acid-promoted aryl amination reaction of aniline with naphthyridine halides.

Key words: aryl amination, acid-promoted coupling, green chemistry, naphthyridine, pyridine cyclization

An elevated hedgehog signaling pathway is associated with several human cancers.[1] It was demonstrated that blocking a smoothened receptor by an antagonist suppresses hedgehog signaling, downregulates cancer cell invasiveness, and induces apoptosis.[2] Compound **1** was identified as a novel hedgehog pathway inhibitor.[3] To assess its efficacy and safety in man, we needed to develop a commercially viable synthetic route for the manufacture of this active pharmaceutical ingredient supporting clinical trials. The reported synthesis of **1** started with a commercially available material bearing the required naphthyridine scaffold, 5-chloro-1,6-naphthyridine (**4**),[3] which is expensive and available only in laboratory scale. Herein, we disclose a synthesis that is efficient, economical, green, and robust. Our strategy, as outlined in Scheme 1, involved an attempt to assemble the target molecule by coupling aniline **2**[3] with bromonaphthyridine derivative **3b**. The key naphthyridine fragment **3b** can be synthesized from inexpensive starting materials, such as pyridine **5**.

Our synthesis started with the preparation of pyridinone **8** (Scheme 2) from inexpensive enamine **6** ($ 170/kg) and prop-2-ynolate **7** according to a literature procedure,[4] affording **8** (HPLC >98%) as a tan-colored solid. Employing a modified procedure reported by Singh et al.,[4] we found that **8** can be converted to chloropyridine **5** cleanly utilizing only three equivalents (instead of 8.5 equiv) of $POCl_3$ at 105 °C for one hour. Reducing the amount of $POCl_3$ avoided the necessity to remove excess $POCl_3$ by distillation and simplified the isolation of **5** by direct precipitation and filtration after pH adjustment with aqueous



Scheme 1 Retrosynthetic analysis of **1**

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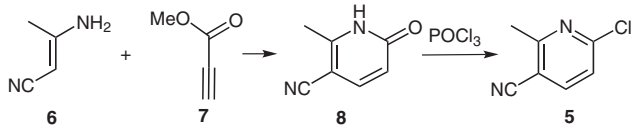
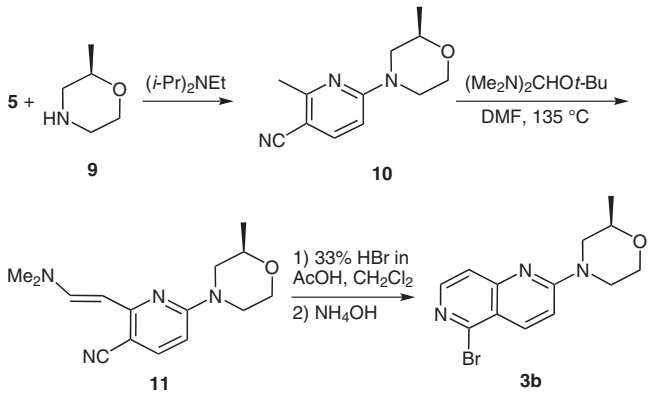


Scheme 2 Synthesis of trisubstituted pyridine **5**

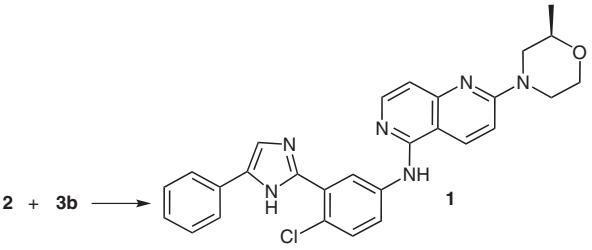
NH_4OH. Recrystallization of **5** from MTBE furnished pure **5** (HPLC >98%) in 84% yield.

Reaction of chloropyridine **5** with (*R*)-2-methylmorpholine (**9**) (Scheme 3) in the presence of DIPEA in MeCN at 80 °C generated 2-morpholinopyridine **10** as a solid in 95% yield (HPLC >98%). Solid **10** was obtained by direct precipitation from the reaction mixture upon addition of water. Chain elongation of **10** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent,[5] 3 equiv) in DMF at 135 °C afforded enamine **11** as a beige solid in 89% yield (HPLC >98%). Cyclization of pyridine **11** to naphthyridine **3b** with hydrogen bromide in CH_2Cl_2 was clean and fast (30 min) at 25 °C furnishing **3b** as the hydrobromide salt, that was easily isolated by filtration. Treatment of **3b**·HBr with aqueous NH_4OH provided **3b** as an off-white solid in 99% yield (based on **11**) with high purity (HPLC >98%).



Scheme 3 Synthesis of the naphthyridine fragment **3b**

To complete the synthesis, aniline **2** was prepared according to a reported procedure.[3] For the coupling of aniline **2** with bromonaphthyridine **3b** leading to the final target **1** (Scheme 4), two approaches have been probed. Employing Buchwald–Hartwig[6] aryl amination conditions (1.5 mol% $(dba)_3Pd_2$/6 mol% xantphos/K_3PO_4, 80 °C, 16 h), we observed the formation of **1** (92%) and an unknown impurity (8%), which can be separated by chromatography. To reduce the by-product formation for this final step, an alternative approach employing acid-promoted coupling of **2** with **3b** was investigated. After a brief screening of two acids (HCl, $MeSO_3H$) and three solvents (*n*-BuOH, EtOH, *i*-PrOH), we found that the $MeSO_3H$ and *i*-PrOH combination provided the best result. Employing 2.5 equivalents of $MeSO_3H$ and 1.1 equivalent of aniline **2**, a 97% conversion into **1** was achieved in four hours at 83 °C. Crystalline product **1** of high purity (HPLC 99%) was isolated in 75% yield without chromatographic purification. It is noteworthy that when HCl was used to promote the coupling of **2** with **3b**, transhalogenation of bromo-**3b** into chloro-**3a** was observed resulting in a significant slower rate of coupling.



Scheme 4 Final steps of the synthesis

In conclusion, we have reported herein a practical synthesis of a naththyridine derivative **1**, an active pharmaceutical ingredient designed to be used as a cancer agent. Some notable features of our synthesis are: (1) economical (inexpensive starting materials used); (2) green (direct precipitation of the product by adding water to the reaction mixture, when applicable); (3) efficient (an overall yield of 63% from a known compound **5**); (4) simple (required no chromatography purification yet achieved >98% purity); and (5) practical (aryl amination reactions for morpholine **9** with pyridine chloride **5** or aniline **2** with naphthyridine **3b** do not require an expensive palladium–ligand complex).[7]

All reactions were conducted under an atmosphere of nitrogen. Solvents and common reagents were purchased from commercial source and used without further purification. Unless otherwise indicated, all solvent ratios are given as v/v. Concentration in vacuo refers to removal of the solvent at a reduced pressure. HPLC analyses were performed on a Waters HPLC System connected to a PDA UV detector over 210–400 nm. Solvent systems: A = MeCN; B = 0.05 M phosphate buffer pH 2.5. NMR spectra were recorded on a Bruker spectrometer (400 or 500 MHz). Chemical shifts are reported in ppm downfield from TMS. Mass spectra were carried out on Waters LCT Premier XE and Acquity UPLC. Elemental analyses were obtained by Robertson Microlit, Madison, NJ, USA. All new compounds are fully characterized.

6-Chloro-2-methylnicotinonitrile (5)

A 2-L, four-necked, round-bottomed flask was charged with 2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (**8**; 268.9 g, 2.0 mol) and $POCl_3$ (923 g, 6.0 mol). The slurry was allowed to heat to 90 °C and stirred for an additional 20 min (***Caution!*** vigorous gas evolution was observed). The solution was then heated to 105 °C and stirred for an additional 1 h. The mixture was cooled to 70 °C and slowly added to a precooled (–20 °C) solution containing concd NH_4OH (3.2 L) and H_2O (2 L), maintaining the temperature below 25 °C. After the quench, the resulting slurry was stirred at 20 °C for 20 min. The brown solid was collected by filtration and air-dried. A 5-L, four-necked, round-bottomed flask was charged with the crude brown solid (309 g) and MTBE (3.6 L). A slurry of activated carbon (73 g) in MTBE (400 mL) was added. The mixture was heated to 50 °C and stirred for an additional 10 min. The slurry (50 °C) was filtered through Celite. The filtrate was concentrated in vacuo at 45 °C until a final volume of 1 L was reached. The resulting slurry was cooled to –5 °C and stirred for an additional 1 h. The solid was collected by filtration, rinsed with the filtrate, and dried in vacuo at

25 °C for 2 h to give **5** as a white solid; yield: 258.2 g (84%); mp 106–110 °C.

HPLC Assay: >98% [Prodigy ODS-2 C_{18}, 5 μm, 150 mm × 4.6 mm, flow rate = 1 mL/min, 40 °C, isocratic, A–B (35:65)]; **8** t_R = 1.9 min, **5** t_R = 6.7 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2 Hz, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 154.4, 142.3, 121.9, 116.1, 107.9, 23.5.

Anal. Calcd for $C_7H_5ClN_2$: C, 55.10; H, 3.30; Cl, 23.24; N, 18.36. Found: C, 55.04; H, 3.31; Cl, 23.05; N, 18.31.

2-Methyl-6-(2-methylmorpholin-4-yl)nicotinonitrile (10)

A 12-L, four-necked, round-bottomed flask was charged with 6-chloro-2-methylnicotinonitrile (**5**; 152.6 g, 1.0 mol), (*R*)-(+)-2-methylmorpholine (**9**) as its hydrochloride (165.1 g, 1.2 mol), MeCN (2 L), and DIPEA (387.6 g, 3.0 mol). The mixture was heated to 80 °C and stirred for an additional 11 h. The reaction was monitored by HPLC until the conversion was completed. The mixture was cooled to 25 °C and aq 0.5 N HCl (1.4 L) was added. H_2O (5 L) was added slowly at 25 °C. The resulting slurry was cooled to 0 °C and stirred for an additional 1 h. The solid was collected by filtration, rinsed with H_2O (5 L), and dried in vacuo at 35 °C for 24 h to give **10** as a white solid; yield: 206 g (95%); mp 89–92 °C.

HPLC Assay: >98% [Prodigy ODS-2 C_{18}, 5 μm, 150 × 4.6 mm, flow rate = 1 mL/min, 40 °C, isocratic, A–B (50:50)]; **5** t_R = 3.87 min, **10** t_R = 5.15 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.8 Hz, 1 H), 6.41 (d, *J* = 8.8 Hz, 1 H), 4.23 (d, *J* = 12.9 Hz, 1 H), 4.15 (d, *J* = 13.1 Hz, 1 H), 3.99 (dd, *J* = 11.6, 3.5 Hz, 1 H), 3.55–3.67 (m, 2 H), 3.01 (dt, *J* = 12.6, 3.5 Hz, 1 H), 2.66 (dd, *J* = 13.1, 10.6 Hz, 1 H), 2.54 (s, 3 H), 1.24 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 158.7, 140.7, 118.8, 103.0, 95.6, 71.5, 66.2, 50.3, 43.9, 23.6, 18.8.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.92; H, 7.26; N, 19.49.

2-(2-Dimethylaminovinyl)-6-(2-methylmorpholin-4-yl)nicotinonitrile (11)

A 3-L, three-necked, round bottomed flask was charged with **10** (169.6 g, 0.78 mol) and anhyd DMF (1.7 L). The mixture was heated to 150 °C. *tert*-Butoxybis(dimethylamino)methane (Bredereck's reagent, 449 g, 2.58 mol) was added in one portion. The mixture was allowed to heat to 135 °C and stirred for an additional 1.5 h. The reaction was monitored by HPLC until the conversion was completed. The mixture was cooled to 25 °C and evaporated at 70 °C/18 mmHg to obtain an oily residue (275 g), which solidified upon cooling. A solution of MTBE–heptane (1:1, 1.1 L) was added to give a slurry, which was cooled to –20 °C and stirred for an additional 30 min. The solid was collected by filtration, rinsed with a precooled (–20 °C) solution of MTBE–heptane (1:1, 800 mL), and dried in vacuo at 25 °C for 16 h to afford **11** as a beige solid; yield: 199.3 g (89%); mp 130–133 °C.

HPLC Assay: >98% [Prodigy ODS-2 C_{18}, 5 μm, 150 × 4.6 mm, flow rate = 1 mL/min, 40 °C, isocratic, A–B (50:50)]; **10** t_R = 5.15 min, **11** t_R = 3.33 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 12.4 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 6.12 (d, *J* = 8.8 Hz, 1 H), 5.36 (d, *J* = 12.6 Hz, 1 H), 4.13 (t, *J* = 15.7 Hz, 2 H), 3.97 (dd, *J* = 11.6, 2.5 Hz, 1 H), 3.54–3.67 (m, 2 H), 2.98 (dd, *J* = 12.9, 3.5 Hz, 1 H), 2.93 (s, 6 H), 2.63 (dd, *J* = 12.6, 10.4, Hz, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 158.3, 146.6, 141.0, 120.0, 100.0, 92.3, 90.0, 71.4, 66.3, 50.5, 43.8, 40.6, 18.8.

Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 65.93; H, 7.66; N, 20.64.

5-Bromo-2-(2-methylmorpholin-4-yl)[1,6]naphthyridine (3b)

A 12-L, four-necked, round-bottomed flask was charged with CH_2Cl_2 (3.7 L) and HBr (33 wt% solution in glacial AcOH, 1.24 kg, 5.05 mol). The solution was cooled to 0 °C. A solution of **11** (241 g, 0.84 mol) in CH_2Cl_2 (1 L) was added, causing an exotherm from 0 to 25 °C. The mixture was stirred at 25 °C for an additional 30 min to give a slurry. The reaction was monitored by HPLC until conversion was completed. The solid was collected by filtration, rinsed with CH_2Cl_2 (2 L), and air-dried for 16 h. The dried solid was dissolved in a mixture of MeOH–H_2O (1:6, 7 L) and filtered. To the filtrate was added slowly aq sat. NH_4OH (28%, 360 g) at 25 °C until pH ~9.0 was reached. The resulting slurry was cooled to 0 °C and stirred for an additional 30 min. The solid was collected by filtration, rinsed with H_2O (2 L), and dried in vacuo at 50 °C for 16 h to obtain **3b** as an off-white solid; yield: 256 g (99%); mp 139–142 °C.

HPLC Assay: >98% [Prodigy ODS-2 C_{18}, 5 μm, 150 × 4.6 mm, flow rate = 1 mL/min, 40 °C, isocratic, A–B (50:50)]; **11** t_R = 3.33 min, **3b** t_R = 5.48 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 5.8 Hz, 1 H), 8.14 (d, *J* = 9.4 Hz, 1 H), 7.35 (d, *J* = 5.8 Hz, 1 H), 6.97 (d, *J* = 9.4 Hz, 1 H), 4.40 (d, *J* = 12.9 Hz, 1 H), 4.32 (d, *J* = 13.1 Hz, 1 H), 4.03 (dd, *J* = 11.6, 2.5 Hz, 1 H), 3.59–3.71 (m, 2 H), 3.14 (dt, *J* = 12.1, 2.9 Hz, 1 H), 2.79 (dd, *J* = 13.1, 10.2 Hz, 1 H), 1.28 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 152.6, 146.3, 143.6, 137.8, 120.3, 119.5, 111.0, 71.7, 66.3, 50.6, 44.2, 18.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}BrN_3O$: 308.0398; found: 308.0364.

[4-Chloro-3-(5-phenyl-1*H*-imidazol-2-yl)phenyl][2-(2-methylmorpholin-4-yl)[1,6]naphthyridin-5-yl]amine (1)

A 12-L, four-necked, round-bottomed flask was charged with **3b** (74.0 g, 0.24 mol), 4-chloro-3-(5-phenyl-1*H*-imidazol-2-yl)phenylamine (**2**;[3] 71.2 g, 0.264 mol), *i*-PrOH (2.4 L), and $MeSO_3H$ (57.7 g, 0.6 mol). The mixture was heated to 83 °C and stirred for an additional 6 h. The reaction was monitored by HPLC until the conversion was completed. The mixture was cooled to 40 °C. H_2O (2.8 L), EtOAc (1.6 L), and sat. aq $NaHCO_3$ (2.0 L) were added. The mixture was allowed to heat to 40 °C to give a solution. The organic phase was separated, washed with sat. aq $NaHCO_3$ (400 mL), and concentrated in vacuo to remove *i*-PrOH. The concentrated solution was diluted with EtOAc (2.2 L) and washed in sequence with sat. aq $NaHCO_3$ (500 mL) and brine (1 L). The organic layer was concentrated in vacuo until the final volume of 1.5 L was reached. The resulting solution was filtered and evaporated. The residue was dissolved into MeOH (4.8 L) at 64 °C and stirred for an additional 30 min to obtain a slurry, which was cooled to 20 °C and stirred for an additional 1 h. The solid was collected by filtration and dried in vacuo at 60 °C for 16 h to afford **1** as an off-white solid; yield: 87.3 g (75%); mp 167–170 °C.

HPLC Assay: 99% [Prodigy ODS-2 C_{18}, 5 μm, 150 × 4.6 mm, flow rate = 1 mL/min, 40 °C, isocratic, A–B (50:50)]; **3b** t_R = 5.48 min, **2** t_R = 2.14 min, **1** t_R = 2.85 min.

Chiral HPLC Assay: 99% ee [Chiralcel OJ-H, 5 μm, 150 × 4.6 mm, flow rate = 1.0 mL/min, 40 °C, isocratic, hexane–EtOH–MeOH = 70:15:15; UV: λ = 278 nm]; (*R*)-**1** t_R = 16.9 min, (*S*)-**1** t_R = 19.4 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 8.06 (d, *J* = 6.0 Hz, 1 H), 8.01 (d, *J* = 9.1 Hz, 1 H), 7.87 (s, 1 H), 7.74 (s, 1 H), 7.37–7.43 (m, 3 H), 7.22–7.31 (m, 2 H), 7.00 (d, *J* = 6.0 Hz, 1 H), 6.77 (d, *J* = 9.5 Hz, 1 H), 4.35 (d, *J* = 12.9 Hz, 1 H), 4.24 (d, *J* = 12.9 Hz, 1 H), 4.01 (d, *J* = 11.7 Hz, 1 H), 3.60–3.72 (m, 2 H), 3.09 (dt, *J* = 3.1, 12.6 Hz, 1 H), 2.74 (t, *J* = 10.7 Hz, 1 H), 1.28 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7, 152.5, 152.3, 144.8, 143.7, 140.6, 140.5, 134.6, 133.1, 129.8, 129.7, 128.5, 126.2, 124.4, 122.2, 122.0, 121.2, 114.5, 112.9, 108.8, 107.8, 71.2, 65.7, 50.2, 43.8, 18.7.

Anal. Calcd for $C_{28}H_{25}ClN_6O$: C, 67.67; H, 5.07; Cl, 7.13; N, 16.91. Found: C, 67.41; H, 4.99; Cl, 7.27; N, 16.87.

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