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Abstract: A short, efficient, and high-yielding synthesis of 4-aryl-2-aminopyridine derivatives has been developed. The route employs two palladium-catalyzed processes, the Suzuki reaction and the Buchwald–Hartwig amination, as the key steps. The same approach has been used for preparation of the corresponding quinoline derivatives. In addition, a brief study of biological properties showed the anticancer potential of these compounds.

Keywords: Aminopyridines, aminoquinolines, palladium catalysis, synthesis

INTRODUCTION

Aminopyridines constitute an important class of organic compounds. As pharmacophores, they are present in many biologically active derivatives or themselves show a range of physiological activities.[1] They are particularly interesting as modulators of the activity of various kinases.[1] The planarity and hydrogen-bonding ability of the 2-aminopyridine moiety resemble the related properties of the adenosinetriphosphate (ATP) 6-aminopurine fragment, making this class of compounds a good candidate for developing the ATP-competitive kinase inhibitors. In

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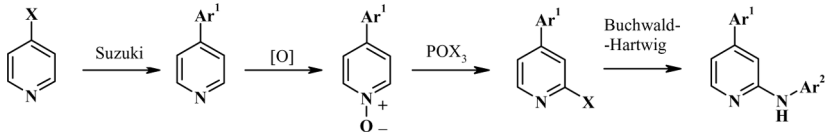


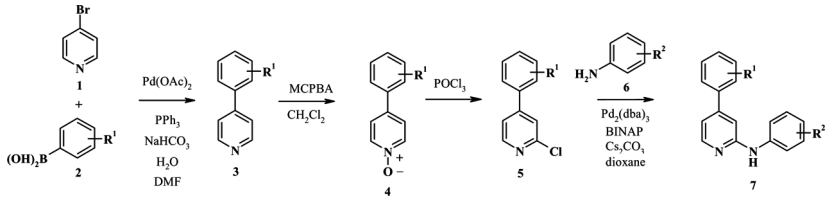
Scheme 1. Proposed synthesis of aminopyridine derivatives.

addition, these compounds, because of their chelating ability, have been commonly used as ligands for various transition metals.[2]

In our ongoing study of different aspects of amino-substituted pyridine derivatives and related compounds, we aimed to develop a synthetic route for an efficient preparation of these compounds, with potential to access a range of possible isomers. In addition, the method had been envisaged to allow for effective application using combinatorial/parallel synthesis methodologies. Our synthetic strategy for the preparation of the 2-aminopyridine derivatives was based on the palladium (Pd)–catalysed processes as outlined in Scheme 1. 4-Halopyridines are commercially available precursors and can be arylated using the Suzuki reaction.[3] The following steps, oxidation and subsequent chlorination of the N-oxide, were expected to afford a substrate ideally suited for the Buchwald–Hartwig amination procedure.[4] Obviously, the only issue with this synthetic strategy is regiochemistry of the chlorination step, which may result in a mixture of products when nonsymmetrical arylpyridine-N-oxides are used.

RESULTS AND DISCUSSION

Initial results are summarized in Scheme 2 and Table 1. The Suzuki reaction was carried out with 4-bromopyridine **1** and either *p*-methyl or *m*-trifluoromethylphenylboronic acid **2** in degassed dimethylformamide (DMF)/H_2O using $Pd(OAc)_2/PPh_3$ as the catalytic system and afforded



Scheme 2. Synthesis of 2-arylamino-4-arylpyridine derivatives.

Table 1. Synthesis of 2-arylamino-4-arylpyridine derivatives[a]

Entry	R^1	R^2	Yield (%) of **3**	Yield (%) of **4**	Yield (%) of **5**	Yield (%) of **7**
a	*p*-Me		80			
b	*p*-Me			97		
c	*p*-Me				69	
d	*p*-Me	*p*-MeO				60
e	*p*-Me	2-Naphthyl[b]				54
f	*m*-CF_3		68			
g	*m*-CF_3			97		
h	*m*-CF_3				84	
i	*m*-CF_3	*m*-MeO				70
j	*m*-CF_3	*p*-Et				66
k	*m*-CF_3	*p*-MeO				54
l	*m*-CF_3	2-Naphthyl[b]				63

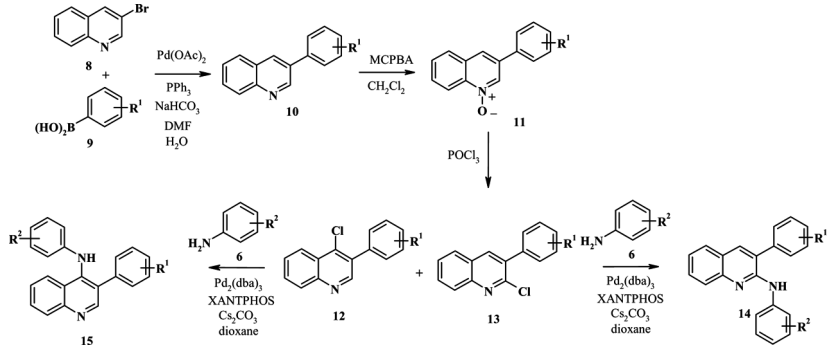
[a]Yields after dry-flash chromatography.
[b]Naphthyl amine used for the amination step.

the expected product **3** in good yield (entries a, f, Table 1). Comparable results were obtained using 4-chloro- or 4-iodopyridine derivatives.

The following step, oxidation of compound **3** to produce N-oxide **4**, employed *m*-chloroperoxibenzoic acid (MCPBA). The product was isolated in almost quantitative yields (entries b, g, Table 1) and then, without further purification, was submitted to the chlorination conditions using $POCl_3$ as reagent/solvent to afford chloride **5** in 50–60% yield over two steps.[5] Because the position 4(C) of the arylpyridine **4** was blocked by the substituent, the reaction afforded a single product. Finally, the amination of compound **5** using various amines performed with $Pd_2(dba)_3$, 2,2-bis(diphenylphosphino)-1,1-binaphtyl (BINAP) as a ligand, and Cs_2CO_3 as a base, produced final product **7** in moderate to good yields (entries d, e, i–l, Table 1).

The described synthetic route is straightforward and high-yielding, and it potentially may have wide application in the preparation of various arylaminopyridines. The use of halopyridines isomeric to compound **1** as starting materials would provide an access to various isomeric products of type **7**.

The same approach has been applied for preparation of the related quinoline derivatives, as outlined in Scheme 3 and Table 2. 3-Bromoquinoline was coupled effectively with various boronic acids under conditions previously described. Subsequent oxidation, carried out with MCPBA in CH_2Cl_2, was as efficient as in the case of the pyridine



Scheme 3. Synthesis of aminoquinoline derivatives.

derivatives affording N-oxide **11**. The chlorination step of the 3-aryl-N-oxide derivative **11** produced, as expected, two products (**12** and **13**), with **13** being the major one. The amination of chloro derivative **13** afforded 2-amino quinoline derivative **14** in good yields (entries d, f, n, Table 2). The 4-chloro isomer **12** underwent amination under the same conditions, with comparable results, to produce **15** (entries e, j, Table 2).

We also briefly studied the biological potential of the synthesized pyridine and quinoline derivatives. These compounds showed antiproliferative

Table 2. Synthesis of aminoquinoline derivatives[a]

Entry	R^1	R^2	Yield (%) of **10**	Yield (%) of **11**	Yield (%)[b] of **13**/**12**	Yield (%) of **14**	Yield (%) of **15**
a	H		76				
b	H			98			
c	H				65 (2:1)		
d	H	*m*-MeO				67	
e	H	*m*-MeO					60
f	H	*p*-Et				63	
g	*p*-MeO		55				
h	*p*-MeO			87			
i	*p*-MeO				63 (1:1)		
j	*p*-MeO	*p*-MeO					63
k	*p*-Me		79				
l	*p*-Me			92			
m	*p*-Me				73 (1.5:1)		
n	*p*-Me	*p*-MeO				56	

[a]Yields after dry-flash chromatography.
[b]Ratio of the products is in parentheses.

activity against several cancer cell lines such as HeLa, Fem-X, and K562, and this is now under detailed investigation.

In conclusion, a short and efficient syntheses of 4-aryl-2-aminopyridine derivatives has been developed, and the same strategy has been applied for preparation of the corresponding quinoline derivatives. Further study of this process and its application in synthesis of a diverse set of compounds using the combinatorial/parallel synthesis is under way. An additional brief study of a biological profile of these compounds showed that they possess anticancer activity, and this is now under detailed investigation.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Varian Gemini 2000 instrument at 200 MHz and 50 MHz respectively. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) as the internal standard. Unless otherwise specified, deuterochloroform was used as a solvent. Mass spectral (MS) data were recorded using an Agilent MSD TOF spectrometer coupled with Agilent 1200 HPLC and Agilent Tecnology 6890 instruments with MSD 5975C. High-performance liquid chromatography (HPLC) employed an HP 1100 instrument with ultraviolet (UV) detector and reversed-phase Zorbax Extend-C18 column. Flash chromatography employed silica gel 60 (230–400 mesh), and thin-layer chromatography (TLC) was carried out using alumina plates with 0.25-mm silica layer (Kieselgel 60 F_{254}, Merck).

General Procedure for Suzuki Reaction

Boronic acid (4.28 mmol) was added to a solution of 4-bromopyridine hydrochloride (3.94 mmol) in degassed dimethylformamide (DMF) (56 mL), followed by $NaHCO_3$ (13.85 mmol) dissolved in degassed H_2O (11.2 mL), $Pd(OAc)_2$ (0.394 mmol), and PPh_3 (0.788 mmol). The mixture was then heated and stirred at 90–95°C (oil-bath temperature) under nitrogen atmosphere for 18 h. After being cooled to room temperature, the mixture was diluted with Et_2O (120 mL), washed with H_2O (3×40 mL), and dried (Na_2SO_4). The solvent was then evaporated under reduced pressure, and the residue was purified by flash or dry-flash chromatography to afford pyridine derivative.

4-*p*-Tolyl-pyridine (**3a**)

Flash chromatography (SiO_2, 1:1,v/v petroleum ether–diethyl ether) afforded the product (80%) as white solid, mp = 89–90°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 7.26–7.32 (m, 2 H), 7.48–7.57 (m, 4 H), 8.65–8.65 (m, 2 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.18, 121.39, 126.82, 129.39, 135.21, 139.20, 148.24, 150.21. $m/z = 169$ (M^+), 154, 141, 127, 115, 103, 91, 77, 63. $C_{12}H_{11}N$ required $m/z + 1 = 170.0964$; found: $m/z + 1 = 170.0961$.

4-(3-Trifluoromethyl-Phenyl)-pyridine (**3f**)

Flash chromatography (SiO_2, 7:3,v/v chloroform-diethyl ether) afforded the product (68%) as colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51–7.54 (m, 2 H), 7.59–7.74 (m, 2 H), 7.84–7.88 (m, 2 H), 8.70–8.73 (m, 2 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 121.66, 123.88, 125.78, 129.71, 130.33, 132.12, 139.20, 146.92, 150.56. $m/z = 223$ (M^+), 204, 183, 154, 127, 111, 95,75. $C_{12}H_8F_3N$ required $m/z + 1 = 224.0682$; found: $m/z + 1 = 224.0689$.

3-Phenylquinoline (**10a**)

Dry-flash chromatography (SiO_2, 65:35,v/v petroleum ether–ethyl acetate) afforded the product (76%) as white solid, mp = 50–51°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.78 (m, 7 H, arom.), 7.9 (d, 1 H), 8.17 (d, 1 H), 8.33 (d, 1 H), 9.20 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 127.1, 127.5, 128.0, 128.2, 129.1, 129.2, 129.5, 133.4, 147.1, 149.7. $m/z = 205$ (M^+), 176, 151, 102. $C_{15}H_{11}N$ required $m/z + 1 =$ 206.0964; found $m/z + 1 = 206.0971$.

3-(4-Methoxyphenyl)quinoline (**10g**)

Dry-flash chromatography (SiO_2, 8:2,v/v petroleum ether–ethyl acetate) afforded the product (55%) as white solid, mp = 48–49°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 7.03–7.09 (m, 2 H, arom.), 7.52–7.74 (m, 4 H, arom.), 7.85 (d, 1 H), 8.12 (d, 1 H), 8.24 (d, 1 H), 9.16 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.3, 114.7, 126.9, 127.9, 128.1, 128.5, 129.1, 129.2, 130.3, 132.3, 147.1, 149.9, 159.8. $m/z = 235$ (M^+), 220, 192, 165, 139, 117. $C_{16}H_{13}NO$ required $m/z + 1 = 236.1070$; found $m/z + 1 = 236.1067$.

3-*p*-Tolylquinoline (**10k**)

Dry-flash chromatography (SiO_2, 7:3,v/v petroleum ether–ethyl acetate) afforded the product (79%) as white solid, mp = 47–48°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 7.26–7.36 (m, 2 H, arom.), 7.53–7.90 (m, 4 H, arom.), 7.87 (d, 1 H), 8.13 (d, 1 H), 8.28 (d, 1 H), 9.18 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.2, 127.0, 127.3, 128.0, 129.2, 129.9, 132.8, 133.8, 134.9, 138.1, 147.2, 149.9. $m/z = 219$ (M^+), 204, 189, 165, 108. $C_{16}H_{13}N$ required $m/z + 1 = 220.1121$; found $m/z + 1 = 220.1118$.

General Procedure for the Preparation of Pyridine/Quinoline-N-oxide Derivatives

MCPBA (3.54 mmol) was added to a solution of pyridine/quinoline derivative (2.72 mmol) in CH_2Cl_2 (30 mL). After being stirred for 48 h at room temperature, the mixture was extracted with 10% solution of $NaHCO_3$ (3×20 mL). The organic layer was then separated, and the water layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude pyridine-N-oxide was used in the next step without further purification.

General Procedure for the Preparation of Chloro Pyridine/Quinoline Derivatives

Pyridine/quinoline-N-oxide (1.9 mmol) was placed in a round-bottom flask, followed by $POCl_3$ (9 mL). The mixture was then stirred and heated at reflux for 18 h under an N_2 atmosphere. Toluene (20 mL) was then added, and the mixture was evaporated under reduced pressure. The residue was suspended in $NaHCO_3$ solution (10%, 20 mL) and then extracted with CH_2Cl_2(2×20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash or dry-flash chromatography to afford the product.

2-Chloro-4-p-tolyl-pyridine (**5c**)

Flash chromatography (SiO_2, dichloromethane) afforded the product (69%) as white solid, mp = 55–57°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 7.26–7.32 (m, 2 H), 7.40–7.43 (m, 1 H), 7.50–7.54 (m, 3 H), 8.40 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.21, 120.24, 121.74, 126.87, 129.98, 133.90, 139.98, 149.94, 151.49, 152.20. $m/z = 203$ (M^+), 188, 168, 139, 115, 91, 63. $C_{12}H_{10}ClN$ required $m/z + 1 = 204.0575$; found: $m/z + 1 = 204.0570$.

2-Chloro-4-(3-trifluoromethyl-phenyl)-pyridine (**5h**)

Dry-flash chromatography (SiO_2, 8:2,v/v dichloromethane–diethyl ether) afforded the product (84%) as a pale yellow solid, mp = 59–60°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.50 (m, 1 H); 7.56–7.86 (m, 5 H); 8.49 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 120.52, 122.21, 123.96, 126.34, 129.91, 130.38, 131.86, 137.79, 150.07, 150.34, 152.52; signal from CF_3 not detected. $m/z = 257$ (M^+), 238, 222, 175, 153, 126, 101, 75. $C_{12}H_7ClF_3N$ required $m/z + 1 = 258.0292$; found: $m/z + 1 = 258.0288$.

4-Chloro-3-phenylquinoline (**12c**)

Dry-flash chromatography (SiO_2, 8:2,v/v petroleum ether–ethyl acetate) afforded the product (22%) as colorless, thick oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.58 (m, 5 H, arom.), 7.66–7.84 (m, 2 H, arom.), 8.17 (m, 1 H), 8.37 (m, 1 H), 8.86 (s, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 124.7, 126.4, 128.0, 128.4, 129.6, 129.9, 130.1, 133.3, 136.3, 139.9, 147.9; 151.4. $m/z = 240$ ($M^+ + 1$), 231, 214, 148. $C_{15}H_{10}ClN$ required $m/z + 1 = 240.0575$; found $m/z + 1 = 240.0582$.

4-Chloro-3-(4-methoxyphenyl)quinoline (**12i**)

Dry-flash chromatography (SiO_2, 7:3,v/v petroleum ether–ethyl acetate) afforded the product (30%) as colorless, thick oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 7.06 (m, 2 H), 7.50 (m, 2 H), 7.68–7.79 (m, 2 H, arom), 8.15 (m, 1 H), 8.35 (m, 1 H), 8.86 (s, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.3, 113.9, 124.6, 126.5, 127.9, 128.5, 129.6, 129.9, 132.8, 139.7, 147.7, 151.7, 159.7. $m/z = 270$ ($M^+ + 1$), 231, 214, 148. $C_{16}H_{12}ClNO$ required $m/z + 1 = 270.0680$; found $m/z + 1 = 270.0690$.

4-Chloro-3-*p*-tolylquinoline (**12m**)

Dry-flash chromatography (SiO_2, 8:2,v/v petroleum ether–ethyl acetate) afforded the product (24%) as white solid, mp = 67–68°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 7.26–7.48 (m, 4 H, arom.), 7.64–7.81 (m, 3 H, arom.), 8.13 (d, 2 H), 8.34 (d, 1 H), 8.85 (s, 2 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.3, 124.7, 126.4, 127.9, 129.2, 129.7, 129.8, 129.9, 133.2, 133.4, 138.3, 139.7, 147.9, 151.6. $m/z = 254$ ($M^+ + 1$), 217, 203, 189, 108. $C_{16}H_{12}ClN$ required $m/z + 1 = 254.0731$; found $m/z + 1 = 254.0726$.

2-Chloro-3-phenylquinoline (**13c**)

Dry-flash chromatography (SiO_2, 8:2 v/v petroleum ether–ethyl acetate) afforded the product (40%) as white solid, mp = 51–52°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.59 (m, 6 H, arom.), 7.68–7.83 (m, 3 H, arom.), 8.08 (s, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 127.2, 127.3, 127.5, 128.3, 129.6, 130.4, 134.7, 138.8, 146.8, 149.5. $m/z = 239$ (M^+) 204, 176, 151, 102. $C_{15}H_{10}ClN$ required $m/z + 1 = 240.0575$; found $m/z + 1 = 240.0569$.

2-Chloro-3-(4-methoxyphenyl)quinoline (**13i**)

Dry-flash chromatography (SiO_2, 7:3 v/v petroleum ether–ethyl acetate) afforded the product (33%) as white solid, mp = 74–75°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 7.02 (m, 2 H), 7.47 (m, 2 H), 7.59 (m, 1 H), 7.69–7.85 (m, 3 H, arom), 8.08 (s, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.3, 113.7, 127.2, 127.4, 128.3, 130.0, 130.2, 130.9, 134.5, 138.6, 146.7, 159.7. $m/z = 270$ ($M^+ + 1$), 231, 214, 148. $C_{16}H_{12}ClNO$ required $m/z + 1 = 270.0680$; found $m/z + 1 = 270.0691$.

2-Chloro-3-*p*-tolylquinoline (**13m**)

Dry-flash chromatography (SiO_2, 8:2 v/v petroleum ether–ethyl acetate) afforded the product (49%) as colourless, thick oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 7.27 (m, 2 H), 7.42 (m, 2 H), 7.55 (m, 1 H), 7.69–7.84 (m, 2 H, arom.), 8.06 (d, 2 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.2, 127.2, 127.3, 127.5, 128.3, 129.0, 129.5, 130.3, 134.7, 134.8, 138.2, 138.7, 146.8. $m/z = 254$ ($M^+ + 1$), 231, 214, 154, 148. $C_{16}H_{12}ClN$ required $m/z + 1 = 254.0731$; found $m/z + 1 = 254.0742$.

General Procedure for the Preparation of Amino Pyridine/Quinoline Derivatives

Chloropyridine/quinoline derivative (0.155 mmol), dry dioxane (3.3 mL), 4-ethylaniline (0.170 mmol), and Cs_2CO_3 (0.202 mmol) were placed in a

round-bottom flask, followed by BINAP for pyridine derivatives or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS), for quinoline derivatives (0.0155 mmol), and $Pd_2(dba)_3$ (0.0155 mmol). The mixture was then stirred and heated at reflux (~110°C oil bath temperature) for 20 h. After being cooled to room temperature, the solvent was evaporated, Et_2O (30 mL) was added, and the solution washed with H_2O (3 × 15 mL). The organic layer was dried (Na_2SO4), and the solvent was then evaporated under reduced pressure. The residue was purified by flash or dry-flash chromatography to afford the product.

(4-Methoxy-phenyl)-(4-p-tolyl-pyridin-2-yl)-amine (**7d**)

Dry-flash chromatography (SiO_2, 9:1 v/v dichloromethane–diethyl ether) afforded the product (60%) as a pale yellow solid, mp = 144–146°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 3.82 (s, 3 H), 6.88–6.95 (m, 4 H), δ 7.14 (s, NH), 7.21–7.30 (m, 4 H), 7.41–7.46 (m, 2 H), 8.12 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.18, 55.52, 104.97, 112.65, 114.74, 124.67, 126.82, 129.67, 132.42, 135.54, 139.30, 146.61, 151.16, 156.71, 157.15. $m/z = 290$ (M^+), 275, 247, 220, 199, 178, 153, 115, 91, 63. $C_{19}H_{18}N_2O$, required $m/z + 1 = 291.14919$; found: $m/z + 1 = 291.15033$.

Naphthalen-2-yl-(4-p-tolyl-pyridin-2-yl)-amine (**7e**)

Dry-flash chromatography (SiO_2, 8:2 v/v petroleum ether–diethyl ether) afforded the product (54%) as pale yellow solid in 54% yield, mp = 157–158°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 6.98–7.05 (m, 2 H), 7.16 (s, 1 H), 7.23–7.27 (m, 3 H), 7.32–7.52 (m, 5 H), 7.73 (s, NH), 7.73–7.87 (m, 4 H), 8.28 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.18, 106.06, 113.83, 115.69, 121.41, 124.34, 126.47, 126.80, 127.07, 127.65, 129.15, 129.69, 130.04, 134.39, 135.81, 138.16, 139.01, 148.77, 150.32, 156.51. $m/z = 309$ ($M^+ - 1$), 290, 267, 247, 226, 202, 182, 155, 115, 96, 77. $C_{22}H_{18}N_2$ required $m/z + 1 = 311.1543$; found: $m/z + 1 = 311.1553$.

3-Methoxyphenyl-[4-(3-trifluoromethyl-phenyl)-pyridin-2-yl]-amine (**7i**)

Dry-flash chromatography (SiO_2, dichloromethane) afforded the product (70%) as a pale yellow solid, mp = 133–134.5°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.60–6.66 (m, 1 H), 6.92–7.09 (m, 2 H), 7.15 (s, NH), 7.26 (t, 1 H), 7.56–7.81 (m, 4 H), 8.29 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.24, 106.28, 106.33, 108.37, 112.78, 113.51, 123.93,

129.42, 130.11, 130.26, 131.38, 131.74, 139.74, 141.62, 148.88, 149.10, 156.70, 160.61. $m/z = 343$ ($M^+ - 1$), 328, 300, 249, 202, 172, 142, 115, 77. $C_{19}H_{15}F_3N_2O$, required $m/z + 1 = 345.12092$; found: $m/z + 1 = 345.12147$.

4-Ethylphenyl-[4-(3-trifluoromethyl-phenyl)-pyridin-2-yl]-amine (**7j**)

Dry-flash chromatography (SiO_2, 1:1 v/v petroleum ether–diethyl ether) afforded the product (66%) as a white solid, mp = 168–170°C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3 H), 2.65 (q, 2 H), 6.81 (s, NH), 6.92 (dd, 1 H), 7.00–7.06 (m, 1 H), 7.19–7.22 (m, 2 H), 7.26–7.29 (m, 2 H), 7.55–7.58 (m, 1 H), 7.66–7.67 (m, 1 H), 7.72–7.74 (m, 1 H), 7.80 (s, 1 H), 8.3 (d, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.62, 28.28, 105.59, 113.14, 121.45, 123.80 (q), 125.24, 128.82, 129.45, 130.30, 131.26, 137.51, 139.78, 149.78, 149.04, 157.07. $m/z = 341$ ($M^+ - 1$), 327, 313, 286, 242, 202, 163, 128, 103, 77. $C_{20}H_{17}F_3N_2$ required $m/z + 1 = 343.1417$; found: m/z + 1 = 343.1424.

4-Methoxyphenyl-[4-(3-trifluoromethyl-phenyl)-pyridin-2-yl]-amine (**7k**)

Dry-flash chromatography (SiO_2, 4:6 v/v petroleum ether–diethyl ether) afforded the product (54%) as pale yellow solid, mp = 141.5–142.5°C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 6.64 (s, NH), 6.84–6.97 (m, 4 H), 7.25–7.33 (m, 3 H), 7.51–7.78 (m, 4 H), 8.23 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.50, 104.89, 112.83, 114.74, 123.81 (q), 124.38, 125.40 (q), 129.42, 130.31, 132.88, 139.94, 149.12, 156.53, 158.02; signals from CF_3 and two quaternary C not detected. $m/z = 344$ (M^+), 329, 301, 202, 172, 142, 115, 77. $C_{19}H_{15}F_3N_2O$ required $m/z + 1 = 345.1209$; found: $m/z + 1 = 345.1210$.

Naphthalen-2-yl-[4-(3-trifluoromethyl-phenyl)-pyridin-2-yl]-amine (**7l**)

Dry-flash chromatography (SiO_2, dichloromethane) afforded the product (63%) as a pale yellow solid, mp = 164–165°C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, NH), 7.00 (m, 1 H), 7.13 (s, 1 H), 7.26–7.41 (m, 1 H), 7.45–7.47 (m, 2 H), 7.56–7.57(m, 1 H), 7.66–7.68 (m, 1 H), 7.75–7.84 (m, 5 H), 7.91 (d, 1 H), 8.45 (d, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 99.98, 106.34, 113.74, 116.06, 121.36, 123.79 (q), 123.93 (q), 125.48 (q), 126.55, 127.08, 127.66, 129.23, 129.51, 130.23 (q), 131.30, 131.56, 134.31, 137.76, 139.70, 148.93, 149.17, 156.67. $m/z = 363$ ($M^+ - 1$), 345, 322, 293, 266, 249, 219, 202, 181, 164, 146, 115, 95, 77. $C_{22}H_{15}F_3N_2$ required $m/z + 1 = 365.12601$; found: $m/z + 1 = 365.12676$.

N-(3-Methoxyphenyl)-3-phenylquinolin-2-amine (**14d**)

Dry-flash chromatography (SiO_2, 7:3 v/v dichloromethane–ethyl acetate) afforded the product (76%) as dark-yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.71 (s, 3 H), 5.28 (s, NH), 6.45 (m, 1 H), 6.73 (d, 1 H), 6.92–7.07 (m, 2 H), 7.25–7.40 (m, 3 H), 7.58–7.70 (m, 2 H), 7.94 (s, 1 H), 8.07 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.2, 106.9, 109.6, 113.7, 123.2, 123.4, 124.5, 126.8, 127.4, 128.2, 128.7, 128.8, 129.1, 131.0, 136.4, 140.0, 141.2, 150.7, 159.7. $m/z = 327$ ($M^+ + 1$), 231, 214, 148, 119. $C_{22}H_{18}N_2O$ required $m/z + 1 = 327.1492$; found $m/z + 1 = 327.1510$.

N-(4-Ethylphenyl)-3-phenylquinolin-2-amine (**14f**)

Dry-flash chromatography (SiO_2, 6:4 v/v dichloromethane–ethyl acetate) afforded the product (63%) as dark-yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (t, 3 H), 2.61 (q, 2 H), 6.94 (s, NH), 7.11–7.16 (m, 2 H), 7.27–7.48 (m, 1 H), 7.50–7.67 (m, 9 H), 7.77 (s, 1 H), 7.87 (d, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 15.7, 28.2, 119.5, 123.2, 124.0, 126.2, 126.7, 127.2, 128.1, 128.3, 128.5, 129.2, 129.4, 129.5, 137.0, 137.1, 137.8, 138.3, 146.7, 151.4. $m/z = 325$ ($M^+ + 1$), 231, 214, 148, 119. $C_{23}H_{20}N_2$ required $m/z + 1 = 325.1699$; found $m/z + 1 = 325.1710$.

N-(4-Methoxyphenyl)-3-p-tolylquinolin-2-amine (**14n**)

Dry-flash chromatography (SiO_2, 6:4 v/v dichloromethane–ethyl acetate) afforded the product (56%) as dark-yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3 H), 3.80 (s, 3 H), 6.70 (s, NH), 6.88 (m, 1 H), 7.26–7.80 (m, 12 H), ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.2, 55.5, 114.0, 121.1, 122.9, 124.1, 125.4, 126.1, 126.7, 127.2, 128.4, 129.0, 129.1, 129.3, 130.1, 130.5, 133.7, 134.2, 136.6, 138.4, 143.3, 146.9, 151.7, 155.1. $m/z = 340$ (M^+), 205, 191, 156, 131, 103. $C_{23}H_{20}N_2O$ required $m/z + 1 = 341.1648$; found $m/z + 1 = 341.1650$.

N-(4-Methoxyphenyl)-3-phenylquinolin-4-amine (**15e**)

Dry-flash chromatography (SiO_2, 7:3 v/v dichloromethane–ethyl acetate) afforded the product (60%) as dark-yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 6.07 (s, NH), 6.73–6.83 (m, 4 H), 7.26–7.44 (m, 3 H), 7.58–7.77 (m, 2 H), 8.08 (d, 1 H), 8.75 (s,

1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 55.5, 114.5, 121.1, 122.0, 124.5, 125.0, 125.3, 128.1, 129.3, 129.4, 129.8, 136.2, 138.2, 144.5, 149.1, 151.9, 155.5. $m/z = 327$ ($M^+ + 1$), 231, 214, 148, 119. $C_{22}H_{18}N_2O$ required $m/z + 1 = 327.1492$; found $m/z + 1 = 327.1490$.

N,3-*Bis*(4-methoxyphenyl)quinolin-4-amine (**15j**)

Dry-flash chromatography (SiO_2, 7:3 v/v dichloromethane–ethyl acetate) afforded the product (63%) as dark-yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 3 H), 3.84 (s, 3 H), 6.05 (s, NH), 6.79 (m, 4 H), 6.99 (m, 2 H), 7.26–7.38 (m, 3 H), 7.57–7.75 (m, 2 H), 8.07 (d, 1 H), 8.74 (s, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 29.6, 55.3, 55.5, 114.6, 114.8, 121.1, 121.9, 124.3, 125.0, 125.3, 128.1, 129.0, 129.5, 130.5, 138.2, 144.6, 148.7, 151.8, 155.5, 159.6. $m/z = 357$ ($M^+ + 1$), 231, 214, 148. $C_{23}H_{20}N_2O_2$ required $m/z + 1 = 357.1598$; found $m/z + 1 = 357.1598$.

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