Sequential Hydration–Condensation–Double Cyclization of Pyridine-Substituted 2-Alkynylanilines: An Efficient Approach to Quinoline-Based Heterocycles

Lijie Peng, Honggen Wang, Changlan Peng, Ke Ding,* Qiang Zhu*

State Key Laboratory of Respiratory Disease, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, P. R. of China
Fax +86(20)32015299; E-mail: ding_ke@gibh.ac.cn; E-mail: zhu_qiang@gibh.ac.cn
Received 1 March 2011; revised 26 March 2011

Abstract: An environmentally benign and atom-economical process to construct a unique quinoline-based tetracyclic scaffold, through sequential hydration–condensation–double cyclization reactions, has been described. The reaction starts with readily available pyridine-substituted *o*-alkynylanilines and β-keto esters, promoted by *p*-toluenesulfonic acid in ethanol in one pot. In the absence of β-keto esters, multisubstituted quinolines are formed bimolecularly in reasonable yields.

Key words: alkynes, cyclization, heterocycles, quinoline, tandem reaction

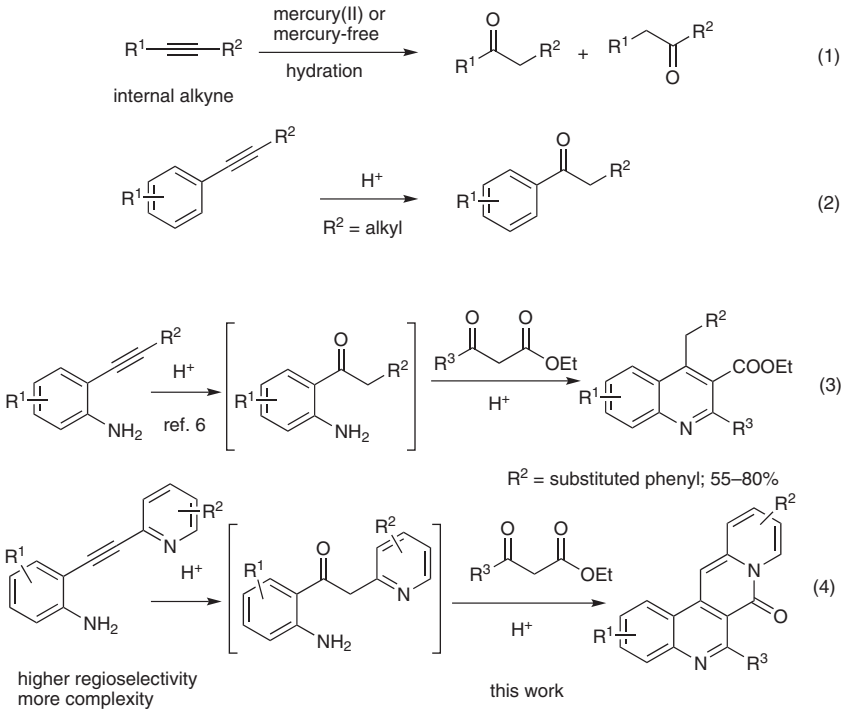
The addition of water to C≡C bonds catalyzed by mercury(II), known as hydration of alkynes for more than a century ago, produces the corresponding carbonyl compounds under mild conditions.[1] Over the last 30 years, much attention has been paid to the development of mercury-free catalysts with improved efficiency and regioselectivity and applying the process to tandem reactions involving carbonyl compounds due to the environmental concern and the convenient accessibility of alkynes.[1] A mixture of two ketones is usually obtained from asymmetric internal alkynes when substitution patterns are similar (Scheme 1, Equation 1). Regioselective hydration of arylalkynes bearing alkyl groups at the other end of the triple bond can be achieved via Brønsted acid catalyzed hydration, affording 2-substituted acetophenones (Scheme 1, Equation 2).[2] For asymmetric diarylalkynes, the selectivity is usually poor unless one of the aromatic ring is electron-rich and the other one is electron-poor or at least electron-neutral. Therefore, the electron-rich *o*-alkynylanilines are ideal precursors for 2-substituted 2′-aminoacetophenones upon hydration in the presence of Brønsted acids (Scheme 1, Equation 3).[3] The resulting 2-substituted 2′-aminoacetophenones can serve as versatile building blocks in the synthesis of N-heterocycles.[3,4]

As part of our continuing interest in diversified quinoline synthesis,[5] we reported a Friedländer type reaction for the synthesis of multisubstituted 4-alkylquinolines from *o*-alkynylanilines and activated ketones in the presence of *p*-toluenesulfonic acid in ethanol under reflux (Scheme 1, Equation 3).[6] When R^2 is a phenyl, the yield is relatively low, which can be explained by the poor regioselectivity during the hydration process. We conceived that higher efficiency could be achieved by introduction of an electron-deficient pyridine at the other end of the triple bond. Furthermore, the pyridine motif could serve as a nucleophile, cyclizing the pyridine nitrogen with the carboxylic ester at C-3 (Scheme 1, equation 4). Thus, additional complexity can be introduced to the quinoline scaffold. In addition, the pyridine moiety is ubiquitously distributed in natural products and synthetic compounds of pharmaceutical interests.[7] And the resulting multicyclic heterocycles containing both pyridine and quinoline moieties are expected to be biologically active.[8] In this proposed reaction, three chemical bonds – C=N, C=C, C–N – will be formed sequentially in one operation with high bond-forming efficiency and atom-economy.

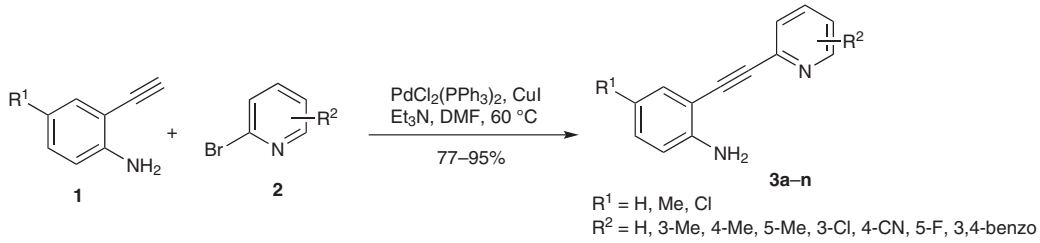
The pyridine-substituted *o*-alkynylanilines **3** with electron-donating and -withdrawing groups on both of the aromatic rings were readily accessible from Sonogashira coupling of *o*-ethynylanilines **1**[5a,b] and substituted 2-bromopyridines **2** in good to excellent yields as outlined in Scheme 2.

The proposed reaction was tested between *o*-[2-(pyridin-2-yl)ethynyl]aniline (**3a**; R^1, R^2 = H) and ethyl acetoacetate (**4a**; R^3 = Me) under the conditions reported previously by us.[6] The desired cyclization did take place by forming an amide bond between the pyridine nitrogen and the carboxylic ester in high yield in the presence of *p*-toluenesulfonic acid (**5a**, Table 1). The unique tetracyclic heterocycle was constructed via sequential formations of three chemical bonds with one molecule of ethanol and water as the only waste products. Substrates with methyl groups at three out of the four possible positions on the pyridine ring were successfully applied (**5b**–**d**, Table 1). 6-Methyl-substituted pyridine failed to cyclize due to the steric hindrance around nitrogen. Surprisingly, the quinoline intermediate before cyclization was not isolated either. Although the nucleophilicity of pyridine nitrogen was reduced by electron-withdrawing groups, such as Cl and CN, corresponding products were obtained in excellent yields (**5e**–**f**, Table 1). And more importantly, these functionalities provided handles for further modification on the scaffold. The fluoro substitution at C-5 also delivered the corresponding product **5g** in reasonable yield. The unprecedented pentacyclic heterocycle containing a

SYNTHESIS 2011, No. 11, pp 1723–1732
Advanced online publication: 15.04.2011
DOI: 10.1055/s-0030-1260001; Art ID: H23611SS



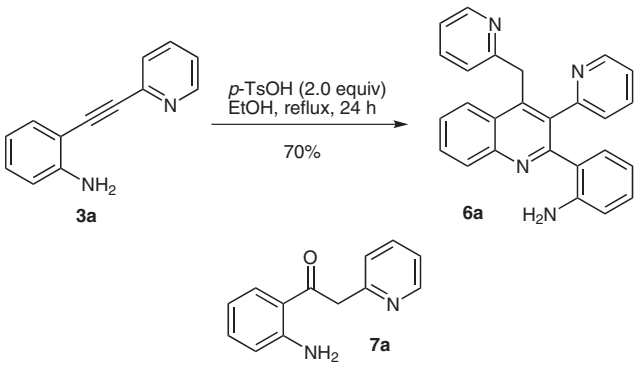
Scheme 1 Hydration of alkynes and its application



Scheme 2 Synthesis of pyridine substituted *o*-alkynylanilines

quinoline and an isoquinoline moiety was obtained in excellent yield (**5h**, Table 1). Quinoline-substituted *o*-alkynylaniline did not furnish a similar product as **5h** probably for steric reasons. Alteration of substituents on the aromatic ring of aniline did not affect the efficiency of cyclization, yielding **5i** and **5j** almost quantitatively. Reactions of **3a** with ethyl 3-oxohexanoate (**4b**) and ethyl 3-oxo-5-phenylpentanoate (**4c**) provided the corresponding *n*-propyl- and phenethyl-substituted **5k** and **5l** in excellent yields. The unexpected lower yield of **5m** and **5n** was probably due to the steric hindrance of the benzyl group as well as the activity of the methylene group under the reaction conditions. Variation of R^3 from alkyl groups to aryl ones **5o**,**p** were also successful, albeit longer reaction times were required. As expected, 3-oxobutanamide (**4h**) and 3-oxo-3-phenylpropanenitrile (**4i**) could be used as surrogates of β-keto esters **4a** and **4f**, providing respective **5a** and **5o** in good yields.

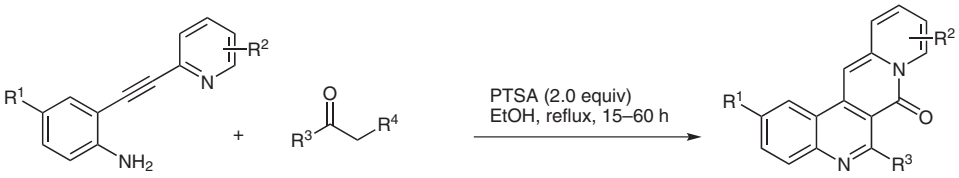
To our surprise, a new product was separated from the reaction of **3a** and ethyl 4,4,4-trifluoroacetoacetate (**4j**) under the same reaction conditions as described above. The structure was identified as multisubstituted quinoline **6a**, in which the other reactant, 4,4,4-trifluoroacetoacetate, was not incorporated. A reasonable explanation was that the diethoxyketal of the highly electrophilic trifluoromethyl ketone was formed in ethanol catalyzed by PTSA before it could condense with the amino group. The presence of **4j** had nothing to do with the formation of **6a**. Indeed, the same product **6a** was obtained in 70% yield when **3a** was the only substrate in the reaction mixture (Scheme 3). Obviously, **6a** was formed bimolecularly through Friedländer reaction of the hydrated intermediate



Scheme 3 Formation of multisubstituted quinoline **6a**

7a, which was detected during the reaction. The methylene group in **7a** was double activated by the carbonyl group and the pyridine ring, which facilitated the Friedländer reaction under the mild conditions.[4] The complex quinoline scaffold was constructed in an atom-economic manner from two molecules of simple pyridine-substituted *o*-alkynylanilines, without wasting any atoms in substrate **3a**.

Table 1 Synthesis of Multicyclic Heterocycles Containing Pyridines and Quinolines in One Pot[a]



3 **4** R^4 = COOEt, $CONH_2$, CN **5**

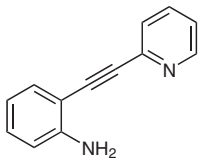
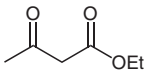
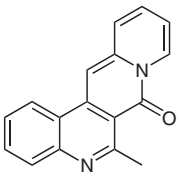
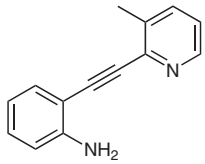
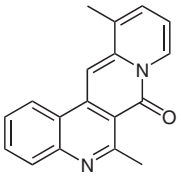
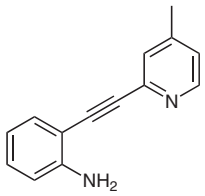
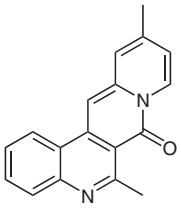
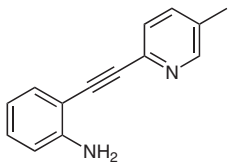
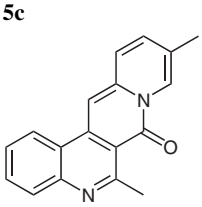
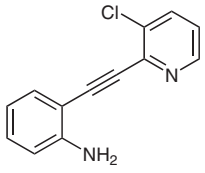
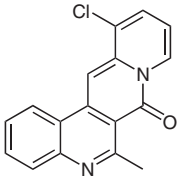
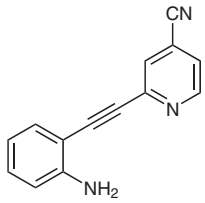
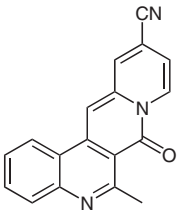
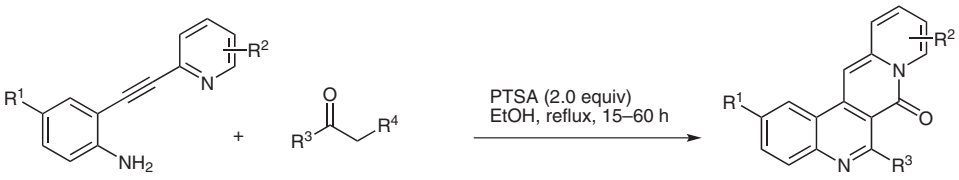
Entry	Substrate **3**	Substrate **4**	Product **5**	Time (h)	Yield (%)[b]
1	 **3a**	 **4a**	 **5a**	15	92
2	 **3b**	**4a**	 **5b**	15	93
3	 **3c**	**4a**	 **5c**	15	92
4	 **3d**	**4a**	 **5d**	15	85
5	 **3e**	**4a**	 **5e**	15	90
6	 **3f**	**4a**	 **5f**	15	90

Table 1 Synthesis of Multicyclic Heterocycles Containing Pyridines and Quinolines in One Pot[a] (continued)



3 **4** R^4 = COOEt, $CONH_2$, CN **5**

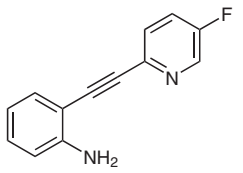
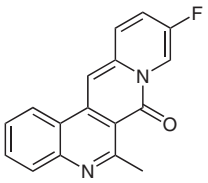
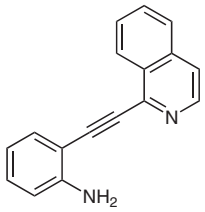
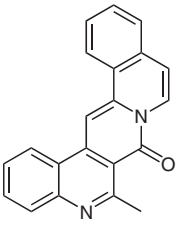
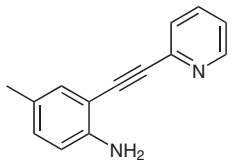
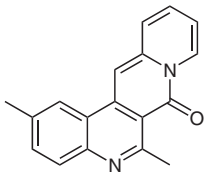
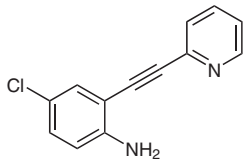
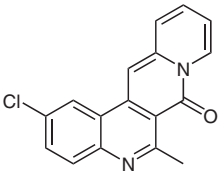
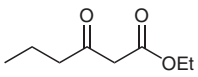
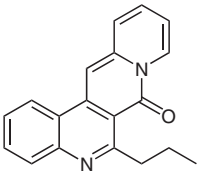
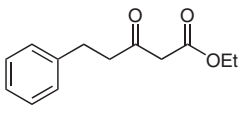
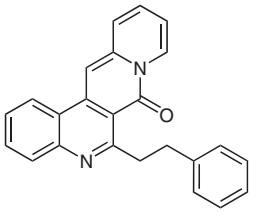
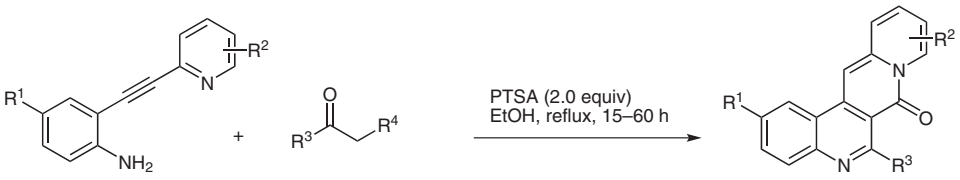
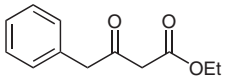
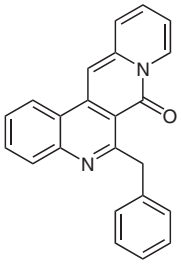
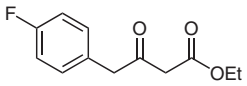
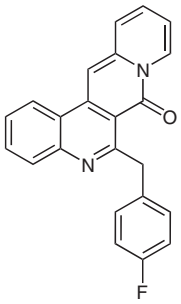
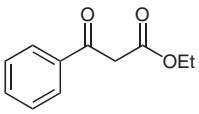
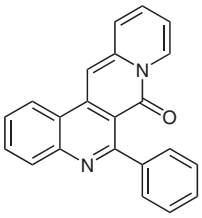
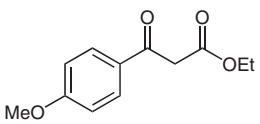
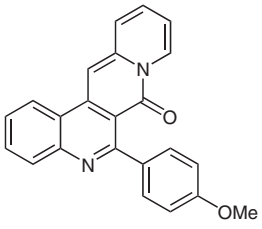
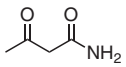
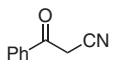
Entry	Substrate **3**	Substrate **4**	Product **5**	Time (h)	Yield (%)[b]
7	 **3g**	**4a**	 **5g**	15	70
8	 **3h**	**4a**	 **5h**	15	92
9	 **3i**	**4a**	 **5i**	15	96
10	 **3j**	**4a**	 **5j**	15	95
11	**3a**	 **4b**	 **5k**	36	88
12	**3a**	 **4c**	 **5l**	20	96

Table 1 Synthesis of Multicyclic Heterocycles Containing Pyridines and Quinolines in One Pot[a] (continued)



3 **4** R^4 = COOEt, $CONH_2$, CN **5**

Entry	Substrate **3**	Substrate **4**	Product **5**	Time (h)	Yield (%)[b]
13	**3a**	 **4d**	 **5m**	60	35
14	**3a**	 **4e**	 **5n**	60	74
15	**3a**	 **4f**	 **5o**	60	70
16	**3a**	 **4g**	 **5p**	48	58
17	**3a**	 **4h**	**5a**	15	68
18	**3a**	 **4i**	**5o**	42	75

[a] Reaction conditions: **3** (0.5 mmol), **4** (0.75 mmol), PTSA (1.0 mmol), EtOH (4.0 mL), reflux, 15–60 h.
[b] Yield of isolated **5**.

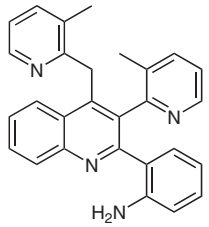
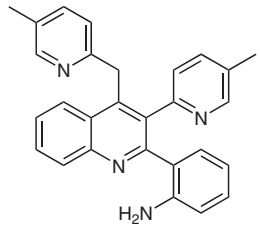
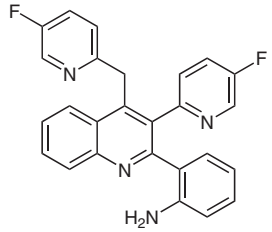
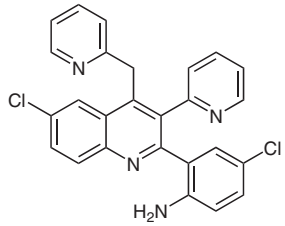
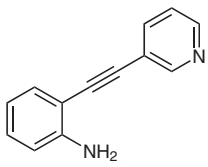
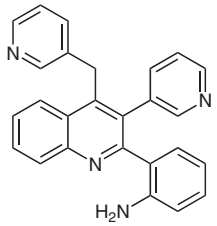
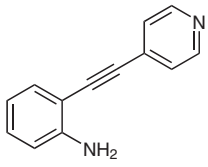
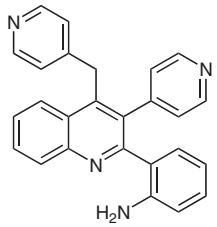
A few of pyridine-substituted *o*-alkynylanilines **3** were selected to examine the generality of the reaction and the results are listed in Table 2. The transformation was applicable to substrates with various substitutions on the pyridine ring to give **6b–d**. Chloro substitution on the aniline ring also provided **6e** in moderate yield. *o*-[2-(Pyridin-3-yl)ethynyl]aniline (**3k**) and *o*-[2-(pyridin-4-yl)ethynyl]aniline (**3l**), variants of **3a** in terms of the nitrogen position in the pyridine substituent, delivered corresponding products **6f** and **6g** in moderate yields.

To simplify the diagram, **3a** is used to elucidate the reaction pathways to **5a** and **6a** in the presence and absence of **4a**, respectively (Scheme 4). Regioselective hydration of **3a** triggers the sequential reactions via the protonated intermediate **A**, which is stabilized by the aniline ring. Condensation of the resulting **7a** with β-keto ester **4a** forms the imine intermediate **C** and its enamine tautomer **D**. Subsequent cyclocondensation and dehydrative aromatization delivers the quinoline intermediate **E** under the aid of acid. A second cyclization takes place by nucleophilic attack of the pyridine nitrogen at 3-carboxylic ester, forming the final tetracyclic product **5a** after deprotonation from intermediate **F**. Four individual reactions take place in order under the same conditions. When **4a** is absent, the amino group in **7a** condenses with the ketone moiety of another molecule of **7a**, resulting in dimeric intermediate **G**. Following a classical Friedländer quinoline synthesis, multisubstituted quinoline **6a** is formed.

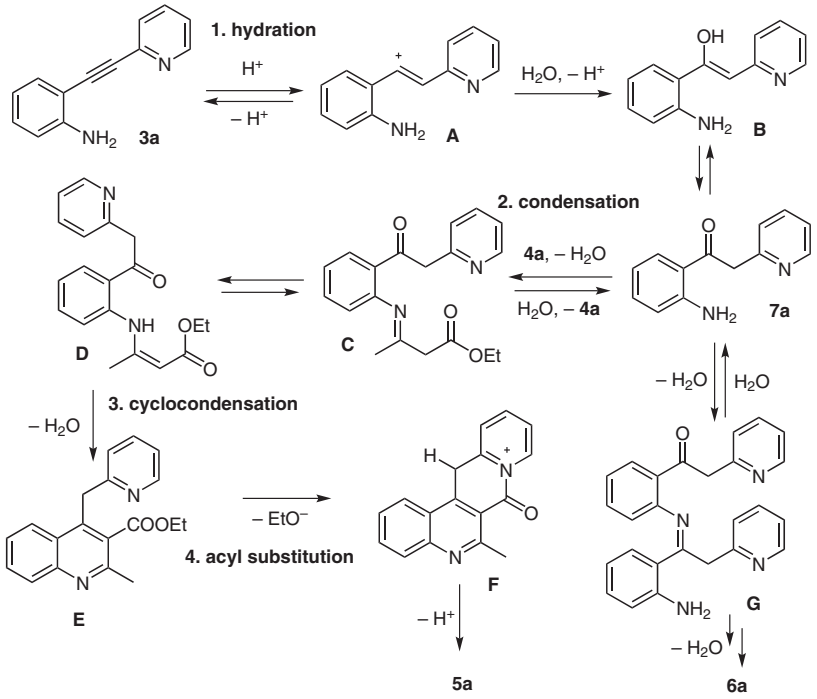
In summary, a unique quinoline-based tetracyclic scaffold is constructed through sequential hydration–condensation–double cyclization reactions starting with readily available pyridine-substituted *o*-alkynylanilines and β-keto esters in one pot promoted by *p*-toluenesulfonic acid in ethanol. It is an environmentally benign and atom-economical process since no metal catalyst is involved and the only wastes are alcohol and water. A C=N bond, a C=C bond, and a C–N bond are formed sequentially in one operation. In the absence of β-keto esters, the hydrated intermediates condense with themselves to produce multisubstituted quinolines with no atom wasted. Biological activity evaluation of these heterocycles containing both the quinoline and pyridine motifs is underway in our laboratories.

All reagents were purchased and used without further purification unless otherwise noted. DMF was distilled under reduced pressure before use. Reactions were monitored using TLC on commercial silica gel plates (GF254). Visualization of the developed plates was performed under UV light (254 nm, 365 nm). Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were measured on a OptiMelt MPA 100 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 or 500 MHz spectrometer. Chemical shifts (δ) were reported in ppm referenced to an internal TMS ($CDCl_3$) or the residual peak of solvents (DMSO-d_6: δ = 2.50; acetone-d_6: δ = 2.05; acetic acid-d_4: δ = 2.04) for ^{1}H NMR. Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ = 77.0), DMSO-d_6 (δ = 39.5) or acetone-d_6 (δ = 29.8). For some cases, about 10–20% of MeOH or AcOH was added to improve the solubility for ^{13}C NMR. Coupling

Table 2 Synthesis of Multisubstituted Quinoline **6**[a]

Entry	Substrate **3**	Product **6**	Yield (%)[b]
1	**3b**	 **6b**	60
2	**3d**	 **6c**	64
3	**3g**	 **6d**	60
4	**3j**	 **6e**	42
5	 **3k**	 **6f**	31
6	 **3l**	 **6g**	59

[a] Reaction conditions: **3** (0.5 mmol), PTSA (1.0 mmol), EtOH (4.0 mL), reflux, 24 h.
[b] Yield of isolated **6**.



Scheme 4 Proposed reaction pathways to **5a** and **6a**

constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Q-STAR Elite ESI-LC-MS/MS Spectrometer.

Compounds 5a–n; General Procedure

To a solution of *o*-[2-(pyridin-2-yl)ethynyl]aniline **3** (0.5 mmol) and **4** (0.75 mmol) in anhyd EtOH (4 mL), was added PTSA·H_2O (190 mg, 1.0 mmol), and the mixture was stirred at reflux under air. When TLC (CH_2Cl_2–MeOH; 50:1) showed that almost all of the raw material **3** was consumed, CH_2Cl_2 (60 mL) was added. The organic layer was washed with sat. aq $NaHCO_3$ (3 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). The residue obtained by the removal of the solvent by rotary evaporation was purified by column chromatography over silica gel using CH_2Cl_2–MeOH (100:1 to 50:1) as eluent to provide the desired product (Table 1).

6-Methyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5a)

Yield: 120 mg (92%); yellow solid; mp 243–244 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.08 (d, *J* = 7.2 Hz, 1 H), 8.59 (d, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.85 (s, 1 H), 7.83–7.79 (m, 2 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.56–7.52 (m, 1 H), 7.09 (t, *J* = 7.2 Hz, 1 H), 3.16 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 158.5, 146.0, 141.8, 140.8, 131.1, 130.4, 129.0, 127.4, 125.9, 125.5, 123.1, 121.3, 113.6, 109.5, 95.2, 28.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022; found: 261.1026.

6,12-Dimethyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5b)

Yield: 127 mg (93%); yellow solid; mp 220–221 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.04 (d, *J* = 7.6 Hz, 1 H), 8.68 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.80 (t, *J* = 7.2 Hz, 1 H), 7.73 (s, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.02 (t, *J* = 7.2 Hz, 1 H), 3.16 (s, 3 H), 2.67 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + MeOH): δ = 161.8, 158.9, 145.5, 142.2, 140.2, 132.0, 131.2, 130.5, 128.4, 126.0, 125.9, 122.9, 121.5, 113.4, 109.0, 91.9, 28.0, 19.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1185.

6,11-Dimethyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5c)

Yield: 126 mg (92%); yellow solid; mp 232–233 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.99 (d, *J* = 7.6 Hz, 1 H), 8.54 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.78 (t, *J* = 7.6 Hz, 1 H), 7.68 (s, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.55 (s, 1 H), 6.95 (dd, *J* = 7.2, 1.8 Hz, 1 H), 3.14 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + MeOH): δ = 161.8, 158.4, 144.8, 142.8, 142.2, 140.9, 131.1, 127.5, 126.6, 126.0, 123.1, 123.0, 121.3, 117.1, 108.3, 94.2, 27.4, 20.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1180.

6,10-Dimethyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5d)

Yield: 116 mg (85%); yellow solid; mp 211–212 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.88 (s, 1 H), 8.56 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.81–7.73 (m, 3 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.43 (dd, *J* = 9.2, 1.6 Hz, 1 H), 3.16 (s, 3 H), 2.41 (d, *J* = 0.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + MeOH): δ = 161.9, 158.2, 145.2, 140.8, 140.2, 134.1, 131.1, 128.2, 126.0, 125.0, 124.4, 124.1, 123.0, 121.4, 109.1, 95.1, 28.0, 18.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1182.

12-Chloro-6-methyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5e)

Yield: 132 mg (90%); yellow solid; mp 330–332 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.06 (d, J = 7.6 Hz, 1 H), 8.74 (s, 1 H), 8.08 (s, 1 H), 7.95 (d, J = 8.4 Hz, 1 H), 7.86–7.83 (m, 2 H), 7.68–7.64 (m, 1 H), 7.20 (t, J = 6.8 Hz, 1 H), 3.12 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.7, 157.2, 145.7, 139.6, 136.6, 134.2, 134.0, 133.1, 128.5, 126.2, 123.3, 122.9, 122.7, 117.3, 105.8, 96.3, 23.0.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{12}ClN_2O$: 295.0633; found: 295.0628.

6-Methyl-7-oxo-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridine-11-carbonitrile (5f)

Yield: 128 mg (90%); orange solid; mp 309–310 °C.

^{1}H NMR (400 MHz, acetic acid-d_4): δ = 9.18 (d, J = 7.2 Hz, 1 H), 8.63 (d, J = 8.4 Hz, 1 H), 8.36 (s, 1 H), 8.19 (d, J = 8.4 Hz, 1 H), 8.00 (t, J = 7.6 Hz, 1 H), 7.94 (s, 1 H), 7.85 (t, J = 7.6 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 3.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.4, 157.0, 142.7, 142.3, 137.4, 133.5, 132.8, 129.0, 128.4, 123.8, 122.4, 121.4, 117.1, 115.2, 113.7, 109.2, 98.4, 23.5.

HRMS: m/z [M + H]$^+$ calcd for $C_{18}H_{12}N_3O$: 286.0975; found: 286.0976.

10-Fluoro-6-methyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5g)

Yield: 77 mg (70%); yellow solid; mp 228–229 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.96 (dd, J = 6.0, 2.4 Hz, 1 H), 8.59 (d, J = 8.0 Hz, 1 H), 7.99–7.90 (m, 3 H), 7.82 (t, J = 7.6 Hz, 1 H), 7.64 (t, J = 7.6 Hz, 1 H), 7.60–7.56 (m, 1 H), 3.17 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.8, 156.9, 156.1, 154.1, 143.6, 140.7, 135.1, 133.2, 128.6, 128.5, 128.4, 123.9, 121.5, 120.9, 114.7, 114.4, 105.8, 96.9, 30.2.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{12}FN_2O$: 279.0928; found: 279.0926.

6-Methyl-7*H*-benzo[*f*]isoquinolino[2,1-*b*][2,7]naphthyridin-7-one (5h)

Yield: 143 mg (92%); yellow solid; mp 259–260 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09–9.03 (m, 2 H), 8.76 (d, J = 8.0 Hz, 1 H), 8.60 (s, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 7.87–7.69 (m, 5 H), 7.28 (d, J = 8.0 Hz, 1 H), 3.11 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 161.6, 158.0, 142.8, 141.5, 139.4, 132.7, 132.6, 131.5, 129.2, 127.7, 127.3, 125.1, 125.0, 123.8, 123.5, 122.2, 121.4, 115.2, 109.1, 92.2, 24.2.

HRMS: m/z [M + H]$^+$ calcd for $C_{21}H_{15}N_2O$: 311.1179; found: 311.1179.

2,6-Dimethyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5i)

Yield: 132 mg (96%); yellow solid; mp 243–244 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.97 (d, J = 7.2 Hz, 1 H), 8.37 (s, 1 H), 7.88 (s, 1 H), 7.81–7.77 (m, 2 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.10 (t, J = 6.8 Hz, 1 H), 3.07 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 161.1, 157.4, 144.4, 140.5, 138.3, 135.9, 134.4, 134.0, 127.6, 126.2, 123.1, 122.4, 121.1, 116.0, 106.6, 95.9, 23.9, 21.6.

HRMS: m/z [M + H]$^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1177.

2-Chloro-6-methyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5j)

Yield: 140 mg (95%); yellow solid; mp 239–240 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (d, J = 8.0 Hz, 1 H), 8.67 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.94 (s, 1 H), 7.90–7.86 (m, 2 H), 7.70 (t, J = 7.6 Hz, 1 H), 7.10 (t, J = 7.2 Hz, 1 H), 3.12 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.2, 157.8, 141.3, 141.2, 140.8, 132.6, 132.2, 129.3, 127.5, 127.0, 125.3, 123.4, 121.4, 113.3, 108.3, 92.9, 25.2.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{12}ClN_2O$: 295.0633; found: 295.0631.

6-Propyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5k)

Yield: 127 mg (88%); yellow solid; mp 162–164 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.02 (d, J = 7.2 Hz, 1 H), 8.60 (d, J = 8.0 Hz, 1 H), 7.95–7.92 (m, 2 H), 7.83–7.79 (m, 2 H), 7.64 (t, J = 7.6 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.12 (t, J = 6.8 Hz, 1 H), 3.53–3.49 (m, 2 H), 1.83–1.74 (m, 2 H), 1.04 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 157.9, 141.7, 141.1, 131.0, 130.4, 129.1, 127.5, 125.9, 125.4, 123.0, 121.3, 113.6, 108.9, 95.3, 42.1, 23.0, 14.6.

HRMS: m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1337.

6-Phenethyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5l)

Yield: 168 mg (96%); orange solid; mp 183–184 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.06 (d, J = 7.6 Hz, 1 H), 8.61 (d, J = 8.4 Hz, 1 H), 7.97–7.95 (m, 2 H), 7.85–7.81 (m, 2 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 7.42 (d, J = 7.2 Hz, 2 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.13 (t, J = 7.2 Hz, 1 H), 3.84–3.79 (m, 2 H), 3.09–3.05 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 157.9, 146.0, 142.8, 141.7, 141.0, 131.0, 130.4, 129.2, 128.9, 128.2, 127.5, 126.0, 125.6, 125.4, 123.1, 121.3, 113.5, 108.9, 95.2, 42.1, 35.4.

HRMS: m/z [M + H]$^+$ calcd for $C_{24}H_{19}N_2O$: 351.1492; found: 351.1490.

6-Benzyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5m)

Yield: 59 mg (35%); pale yellow solid; mp 254–255 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (d, J = 7.2 Hz, 1 H), 8.65 (d, J = 7.6 Hz, 1 H), 8.01–7.98 (m, 2 H), 7.88–7.82 (m, 2 H), 7.69 (t, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.2 Hz, 1 H), 7.29 (m, 2 H), 7.20 (t, J = 7.6 Hz, 2 H), 7.14–7.09 (m, 2 H), 4.99 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.9, 156.9, 144.0, 141.4, 137.1, 134.2, 132.3, 129.3, 128.3, 128.0, 127.6, 126.6, 125.8, 124.1, 123.3, 121.4, 115.6, 106.6, 95.5, 40.8.

HRMS: m/z [M + H]$^+$ calcd for $C_{23}H_{17}N_2O$: 337.1335; found: 337.1338.

6-(4-Fluorobenzyl)-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5n)

Yield: 131 mg (74%); pale yellow solid; mp 277–278 °C.

^{1}H NMR (400 MHz, $CDCl_3$ + acetic acid-d_4): δ = 9.00 (d, J = 6.4 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.13 (d, J = 8.4 Hz, 1 H), 7.70 (t, J = 6.8 Hz, 1 H), 7.65–7.58 (m, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.38–7.35 (m, 3 H), 7.07 (t, J = 4.8 Hz, 1 H), 6.85 (t, J = 7.6 Hz, 2 H), 5.01 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.7, 162.6, 160.8, 156.8, 145.3, 141.6, 136.5, 135.9, 133.0, 131.5, 130.8, 130.7, 128.4, 128.3, 126.0, 123.6, 122.2, 121.7, 116.6, 115.1, 114.9, 105.6, 96.2, 38.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}FN_2O$: 355.1241; found: 355.1245.

6-Phenyl-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5o)

Yield: 113 mg (70%); pale yellow solid; mp 265–266 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (d, *J* = 7.2 Hz, 1 H), 8.73 (d, *J* = 7.6 Hz, 1 H), 8.07 (s, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.91–7.86 (m, 2 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.62 (t, *J* = 7.2 Hz, 1 H), 7.52–7.49 (m, 2 H), 7.43–7.40 (m, 3 H), 7.10 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ = 162.0, 157.6, 143.4, 143.2, 141.4, 140.6, 132.1, 131.9, 128.4, 127.9, 127.7, 127.3, 125.6, 123.3, 121.7, 114.4, 107.5, 95.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}N_2O$: 323.1179; found: 323.1176.

6-(4-Methoxyphenyl)-7*H*-benzo[*f*]pyrido[1,2-*b*][2,7]naphthyridin-7-one (5p)

Yield: 102 mg (58%); yellow solid; mp 274–276 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (d, *J* = 7.6 Hz, 1 H), 8.71 (d, *J* = 8.0 Hz, 1 H), 8.04 (s, 1 H), 8.00 (d, *J* = 7.2 Hz, 1 H), 7.89–7.84 (m, 2 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.63–7.59 (m, 1 H), 7.50–7.48 (m, 2 H), 7.10 (t, *J* = 6.8 Hz, 1 H), 6.98–6.96 (m, 2 H), 3.84 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ + AcOH): δ =161.2, 160.8, 157.4, 144.5, 141.7, 139.8, 134.1, 132.6, 130.1, 129.2, 128.2, 127.9, 125.8, 124.9, 123.5, 121.7, 115.5, 113.3, 106.2, 95.9, 55.1.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{17}N_2O_2$: 353.1285; found: 353.1288.

Compounds 6a–f; General Procedure

To a solution of *o*-[2-(pyridin-2-yl)ethynyl]aniline **3** (0.5 mmol) in anhyd EtOH (4 mL), was added PTSA·H_2O (190 mg, 1.0 mmol), and the mixture was stirred at reflux under air. When TLC (CH_2Cl_2–MeOH; 50:1) showed that almost all of the raw material was consumed, CH_2Cl_2 (60 mL) added. The organic layer was washed with sat. aq $NaHCO_3$ (3 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). The solvent was evaporated by rotary evaporation to give a residue, which was purified by column chromatography over silica gel using CH_2Cl_2–MeOH (100:1) as eluent to provide the desired product (Table 2).

2-[3-(Pyridin-2-yl)-4-(pyridin-2-ylmethyl)quinolin-2-yl]aniline (6a)

Yield: 68 mg (70%); pale yellow solid; mp 80–81 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56 (d, *J* = 4.4 Hz, 1 H), 8.38 (d, *J* = 4.4 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.59–7.54 (m, 3 H), 7.23–7.20 (m, 1 H), 7.14–7.11 (m, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.88 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.66–6.63 (m, 2 H), 6.27 (t, *J* = 7.2 Hz, 1 H), 5.18 (br, 2 H), 4.50 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.2, 157.9, 157.3, 148.8, 148.7, 146.7, 146.3, 144.0, 136.5, 135.8, 134.5, 130.6, 129.5, 129.3, 128.4, 126.8, 126.0, 125.6, 125.3, 124.5, 122.8, 122.2, 121.4, 115.4, 115.3, 37.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}N_4$: 389.1761; found: 389.1759.

2-{3-(3-Methylpyridin-2-yl)-4-[(3-methylpyridin-2-yl)methyl]quinolin-2-yl}aniline (6b)

Yield: 62 mg (60%); pale yellow solid; mp 197–198 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.47 (d, *J* = 3.6 Hz, 1 H), 8.05 (t, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 3.6 Hz, 1 H), 7.78 (t, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 7.2 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 7.12 (dd, *J* = 7.6, 4.8 Hz, 1 H), 6.96 (dd, *J* = 7.2, 4.8 Hz, 1 H), 6.87 (td, *J* = 7.2, 1.2 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.17 (t, *J* = 7.2 Hz, 1 H), 5.50 (br, 2 H), 4.55 (d, *J* = 16.4 Hz, 1 H), 4.38 (d, *J* = 16.4 Hz, 1 H), 2.00 (s, 3 H), 1.49 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.2, 157.1, 156.8, 146.7, 146.3, 146.1, 145.9, 145.9, 137.4, 136.9, 133.6, 133.2, 130.8, 130.6, 129.3, 129.0, 128.6, 127.2, 126.4, 125.6, 123.6, 122.4, 121.1, 115.8, 115.0, 33.0, 18.1, 17.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{25}N_4$: 417.2074; found: 417.2076.

2-{3-(5-Methylpyridin-2-yl)-4-[(5-methylpyridin-2-yl)methyl]quinolin-2-yl}aniline (6c)

Yield: 67 mg (64%); pale yellow solid; mp 87–88 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (s, 1 H), 8.23 (s, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.75 (t, *J* = 7.6 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 6.67 (t, *J* = 8.4 Hz, 2 H), 6.30 (t, *J* = 7.6 Hz, 1 H), 5.14 (br, 2 H), 4.41 (s, 2 H), 2.23 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.0, 156.3, 154.5, 149.0, 148.9, 146.7, 146.2, 144.2, 137.0, 136.2, 134.4, 131.2, 130.6, 130.3, 129.4, 129.3, 128.4, 126.7, 126.0, 125.3, 125.1, 124.8, 122.2, 115.5, 115.4, 36.9, 17.6, 17.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{25}N_4$: 417.2074; found: 417.2080.

2-{3-(5-Fluoropyridin-2-yl)-4-[(5-fluoropyridin-2-yl)methyl]quinolin-2-yl}aniline (6d)

Yield: 64 mg (60%); pale yellow solid; mp 79–80 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (d, *J* = 2.8 Hz, 1 H), 8.36 (d, *J* = 2.8 Hz, 1 H), 8.14 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 7.79 (t, *J* = 7.2 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.55–7.49 (m, 2 H), 7.14–7.11 (m, 2 H), 6.91 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.67–6.61 (m, 2 H), 6.31 (t, *J* = 7.2 Hz, 1 H), 5.16 (br, 2 H), 4.50 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.9, 158.7, 157.9, 156.9, 156.7, 155.4, 155.4, 153.7, 153.7, 146.9, 146.2, 144.2, 136.7, 36.7, 136.6, 136.5, 133.6, 130.5, 129.7, 129.4, 128.5, 127.0, 127.0, 127.0, 126.0, 125.2, 124.3, 124.1, 124.1, 123.6, 123.5, 123.0, 122.9, 115.4, 115.3, 36.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{19}F_2N_4$: 425.1572; found: 425.1575.

4-Chloro-2-[6-chloro-3-(pyridin-2-yl)-4-(pyridin-2-ylmethyl)quinolin-2-yl]aniline (6e)

Yield: 48 mg (42%); pale yellow solid; mp 83–85 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.49 (dd, *J* = 4.4, 1.2 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 8.16 (dd, *J* = 4.4, 1.2 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 7.83 (td, *J* = 8.0, 0.8 Hz, 1 H), 7.73 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.65–7.61 (m, 2 H), 7.28 (dd, *J* = 8.4, 4.8 Hz, 1 H), 7.15 (dd, *J* = 8.0, 4.4 Hz, 1 H), 6.88 (td, *J* = 8.0, 1.2 Hz, 1 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 6.57 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.18 (td, *J* = 7.6, 0.8 Hz, 1 H), 5.43 (br, 2 H), 4.75 (d, *J* = 16.8 Hz, 1 H), 4.54 (d, *J* = 16.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.2, 155.2, 154.9, 147.4, 147.2, 146.9, 146.5, 145.1, 137.0, 136.5, 131.8, 131.7, 130.2, 129.8, 129.7, 129.0, 128.7, 126.9, 126.7, 125.7, 124.0, 123.0, 122.8, 115.8, 114.8, 33.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{19}Cl_2N_4$: 457.0981; found: 457.0978.

2-[3-(Pyridin-3-yl)-4-(pyridin-3-ylmethyl)quinolin-2-yl]aniline (6f)

Yield: 30 mg (31%); pale yellow solid; mp 92–93 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35–8.32 (m, 3 H), 8.27 (s, 1 H), 8.09 (d, *J* = 6.8 Hz, 1 H), 8.03 (d, *J* = 6.8 Hz, 1 H), 7.79 (t, *J* = 6.0 Hz, 1 H), 7.61–7.58 (m, 2 H), 7.37 (t, *J* = 6.4 Hz, 1 H), 7.22–7.20 (m, 2 H), 6.88 (t, *J* = 6.0 Hz, 1 H), 6.82 (d, *J* = 6.0 Hz, 1 H), 6.53 (d, *J* = 6.4 Hz, 1 H), 6.35 (t, *J* = 6.0 Hz, 1 H), 4.93 (s, 2 H), 4.35 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.5, 149.8, 149.1, 148.1, 147.3, 147.2, 145.6, 143.3, 137.0, 135.4, 135.1, 133.7, 132.6, 130.2, 129.7, 129.5, 128.3, 127.0, 125.7, 125.0, 124.9, 123.5, 122.5, 115.1, 114.8, 31.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}N_4$: 389.1761; found: 389.1763.

2-[3-(Pyridin-4-yl)-4-(pyridin-4-ylmethyl)quinolin-2-yl]aniline (6g)

Yield: 57 mg (59%); pale yellow solid; mp 202–203 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.39–8.37 (m, 4 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.80 (t, *J* = 7.2 Hz, 1 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 7.21 (d, *J* = 3.6 Hz, 2 H), 7.06 (d, *J* = 3.6 Hz, 2 H), 6.89 (t, *J* = 6.8 Hz, 1 H), 6.80 (d, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 6.34 (t, *J* = 7.2 Hz, 1 H), 4.98 (br, 2 H), 4.32 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.5, 149.4, 148.7, 148.2, 147.0, 145.9, 145.6, 141.7, 133.5, 130.0, 129.5, 128.3 127.0, 125.5, 124.8, 124.6, 124.5, 123.3, 114.9, 115.7, 33.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}N_4$: 389.1761; found: 389.1759.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

We are grateful for the support of this work by a Start-up Grant from Guangzhou Institutes of Biomedicine and Health (GIBH), and Guangzhou Municipal Foundation for Science and Technology (2010Y1-C241).

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