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Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones *via* Pd-catalyzed cross-coupling reaction and cyclization†

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Biologically active 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones have been synthesized in an efficient and concise manner utilizing readily available 4-hydroxyquinolin-2(1*H*)-ones as the starting material. The key strategy relies on the construction of the pyrrole ring through the palladium catalyzed sequential cross-coupling reaction and cyclization process.

Introduction

Drug discovery research constantly calls for large collections of small molecules to look for lead structures active in biological assays. Thus, the pursuit of practical and efficient approaches for rapid chemical synthesis of natural product-like compounds is in great demand and attractive.[1] Tremendous efforts have been devoted by organic chemists to the development of new methodologies for the synthesis of the intriguing molecules individually; however, it is highly desirable to develop even more effective and flexible synthetic methodologies for heterocycle formation in order to build up complex natural product-like molecules in a combinatorial format.[2]

Nitrogen-containing heterocycles are of great importance in the pharmaceutical industry since they often exhibit interesting biological activities. The pyrrole moiety constitutes the key structure of a wide range of compounds that have shown a diverse range of bioactivities.[3,4] For example, ningalin B and lamellarin D are two members of novel marine natural products containing a highly substituted coumarin[3,4-*b*]pyrrolo core (Fig. 1).[3b] Ningalin B[4a–d] has been reported to act as a nontoxic inhibitor of MDR in various cancer cell lines. Lamellarin D[4e–n] is a potent inhibitor of human topoisomerase I and was recently shown to act on mitochondria to induce apoptosis. As coumarin isosteres, quinolin-2(1*H*)-ones are ubiquitous subunits of a range of pharmaceuticals and natural products with myriad biological activities.[5] A number of analogues of this family have wide applications in medical chemistry, being used as anticancer, antiviral, and antihypertensive agents.

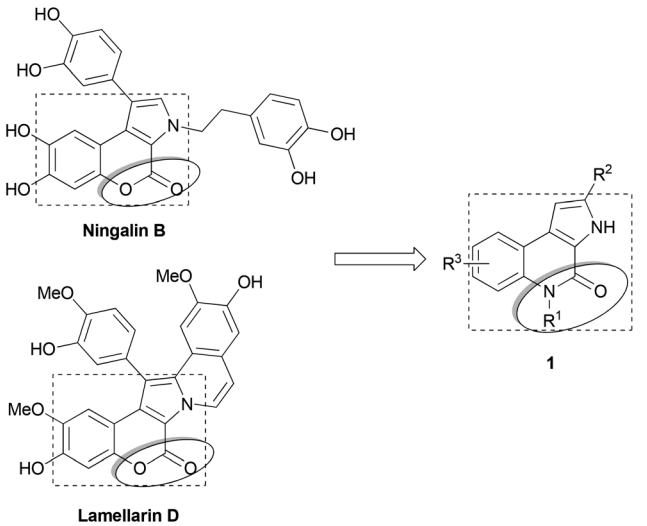

Fig. 1 Natural coumarin[3,4-*b*]pyrroles (left) and proposed pyrrolo[2,3-*c*]quinolin-4-one analogue (right).

For instance, 4-arylquinolin-2(1*H*)-one derivatives have been reported to be lead compounds or are currently in clinical trials (Fig. 2, compounds **A**,[5a–c] **B**[5d–e] and **C**[5f]). 3-(1*H*-Indol-2-yl)-quinolin-2(1*H*)-one **D**[5g–l] has been identified by Merck as potent KDR kinase inhibitors useful for cancer therapy. Moreover, quinolin-2(1*H*)-ones are also valuable intermediates in organic synthesis because they can be easily converted into 2-haloquinolines, which can undergo further functionalization.[6] As part of our continuing efforts at construction of libraries of quinolin-2(1*H*)-one compounds used in different biological assays,[7] we proposed to construct ningalin B and lamellarin D analogues with the coumarin core modified into a quinolin-2-(1*H*)-one scaffold of type **1** (Fig. 1).

Although a number of approaches are available for the generation of quinolin-2(1*H*)-one derivatives with broad structural diversity,[8] synthetic pathways for the efficient and

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†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c3ob41629a

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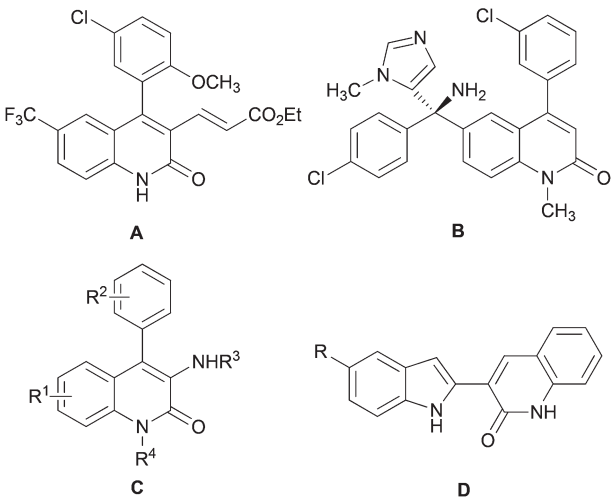
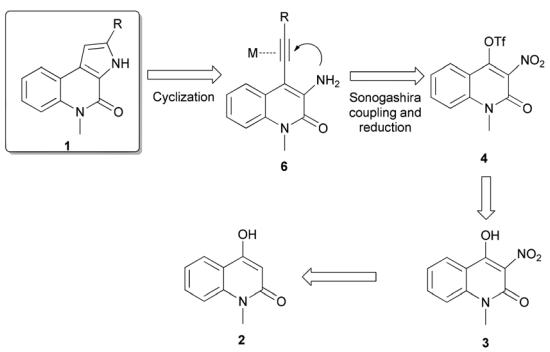


Fig. 2 Biologically active molecules with quinolin-2(1*H*)-one subunit.

straightforward construction of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one units have been scarce.[9] It is well-known that transition metal catalyzed cyclization of alkynes with a nucleophile in proximity to the triple bond is an important method to construct various heterocycles in an efficient and atom-economic way.[10] For instance, 2-substituted indoles can be formed through palladium-[10a–d] or copper-catalyzed[10e] intramolecular cyclization of *o*-alkynylanilines. Inspired by these results, we envisioned that the construction of the pyrrole ring in **1** could be realised by intramolecular cyclisation of the key intermediate **6** (Scheme 1). In turn, **6** could be generated from the corresponding 1-methyl-3-nitro-4-trifloxyquinolin-2(1*H*)-one **4** by Sonogashira coupling and reduction of the nitro group. Finally **4** could be synthesised by means of a two step procedure from the easily available 4-hydroxy-1-methylquinolin-2-(1*H*)-one **2**. Herein, we describe a novel and flexible synthetic protocol for the synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one derivatives utilizing the palladium-catalyzed sequential coupling–cyclization strategy.



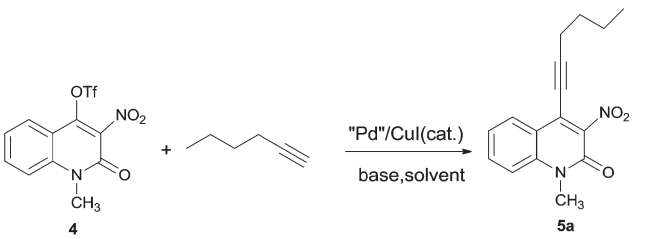
Scheme 1 Proposed synthetic route for generation of diverse 3*H*-pyrrolo[2,3-*c*]-quinolin-4(5*H*)-ones **1**.

Results and discussion

As described above, to verify the practicability of the projected route as shown in Scheme 1, initial model studies for the synthesis of **1** were carried out using the readily available 4-hydoxyquinolin-2(1*H*)-one **2** as the starting material.[11] The Sonogashira coupling precursor **4** was easily synthesized in high yield (82%) by treatment of 4-hydoxyquinolin-2(1*H*)-one **2** with HNO_3/AcOH and trifluoromethanesulfonic anhydride subsequently.[12] Thus, we started to explore the possibility of Sonogashira coupling reaction; 3-nitro-4-trifloxyquinolin-2(1*H*)-one **4** and 1-hexyne were used as the model substrates (Table 1). The reaction was initially performed in the presence of 5 mol% $Pd(PPh_3)_2Cl_2$/CuI in THF at room temperature, using K_2CO_3 as the base. Gratifyingly, we observed the formation of desired product **5a** although the yield was low (30%, Table 1, entry 1). The result was dramatically improved when the amount of catalyst loading was increased to 10 mol% (88%, Table 1, entry 2). A lower yield was obtained at higher reaction temperature (Table 1, entry 3). Further screening revealed that attempts to change the palladium catalysts or using other solvents and bases were ineffective and led to a lower yield (Table 1, entries 4–8).

With the optimized conditions identified, we started to investigate the reaction scope with 3-nitro-4-trifloxyquinolin-2(1*H*)-one **4** and various alkynes. It was found that aliphatic alkynes are excellent partners in the reactions, leading to the desired alkynyl derivatives **5a–c** in moderate to good yields. Conversely, no product was detected when aromatic alkynes were employed in the reaction of 3-nitro-4-trifloxyquinolin-2(1*H*)-one **4**. We also screened this reaction with various palladium catalysts, ligands, bases and solvents. However,

Table 1 Condition screening for Sonogashira coupling[a]



4 5a

Entry	Catalytic system (mol%)	Base	Solvent	*T* (°C)	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$/CuI (5)	K_2CO_3	THF	r.t.	30
2	$Pd(PPh_3)_2Cl_2$/CuI (10)	K_2CO_3	THF	r.t.	88
3	$Pd(PPh_3)_2Cl_2$/CuI (10)	K_2CO_3	THF	50	77
4	$Pd(OAc)_2/PPh_3$/CuI (10)	K_2CO_3	THF	r.t.	46
5	$Pd(PPh_3)_4$/CuI (10)	K_2CO_3	THF	r.t.	49
6	$Pd(PPh_3)_2Cl_2$/CuI (10)	Cs_2CO_3	THF	r.t.	20
7	$Pd(PPh_3)_2Cl_2$/CuI (10)	K_2CO_3	DMF	r.t.	Trace
8	$Pd(PPh_3)_2Cl_2$/CuI (10)	K_2CO_3	MeCN	r.t.	Trace

[a] All of the reactions were carried out with **4** (0.3 mmol), 1-hexyne (0.36 mmol), metal catalyst, and base (3.0 equiv.) in solvent (5.0 mL) under argon. [b] Isolated yield based on 3-nitro-4-trifloxyquinolin-2(1*H*)-one **4**.

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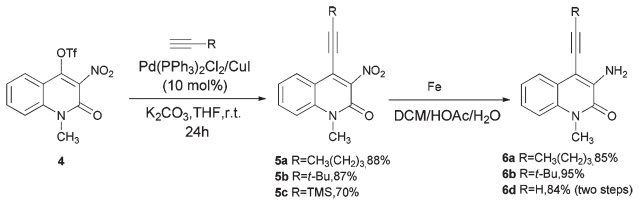


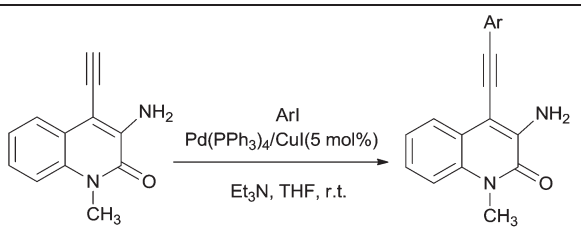
Scheme 2 Sonogashira coupling with aliphatic alkynes and reduction.

the results were inferior. This might be due to the inefficient transmetallation of aromatic copper(I) acetylide with Pd(0) species. Subsequently, mediated by iron powder in $AcOH/H_2O$ at room temperature, the reduction reaction was performed to generate the 4-alkynyl-3-amino-quinolin-2(1*H*)-ones in excellent yield (Scheme 2).

Moreover, to install the desired aromatic substituents at the alkynes moiety at the C4 of the quinolinone core, **6c** was desilylatied giving rise to compound **6d** (84% yield, in two steps from **5c**) which in turn was subjected to Sonogashira coupling with aryl iodides. To our delight, the cross-coupling reactions proceeded smoothly to furnish the desired 3-amino-4-arylethynyl-quinolin-2(1*H*)-ones in high yields when various aryl iodides were used under the standard Sonogashira coupling conditions (2 mol% $Pd(PPh_3)_4$, 2 mol% CuI, 3.0 equiv. of Et_3N, THF, rt) (Table 2).

With a variety of 3-amino-4-arylethynylquinolin-2(1*H*)-ones in hand, we turned our attention to the key cyclization for constructing the corresponding pyrrolquinolinone backbone. The intramolecular hydroamination reaction of 3-amino-4-arylethynylquinolin-2(1*H*)-one **6f** was initially optimized. To find the optimum reaction conditions, **6f** was subjected to different metal-catalysts, solvents and reaction temperatures. The results

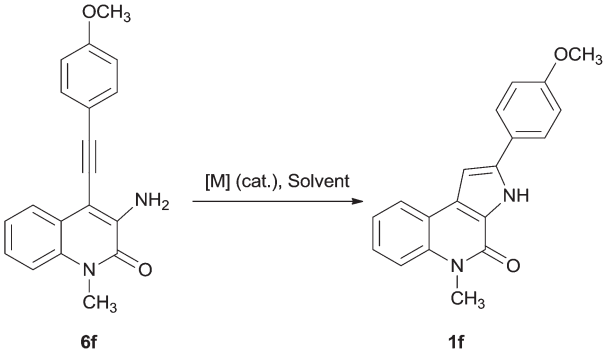
Table 2 Synthesis of 3-amino-4-arylethynylquinolin-2(1*H*)-ones **6a**[a]



Entry	Ar	6	Yield[b] (%)
1	C_6H_5	**6e**	86
2	4-$MeOC_6H_4$	**6f**	96
3	4-MeC_6H_4	**6g**	97
4	4-ClC_6H_4	**6h**	90
5	3-FC_6H_4	**6i**	98
6	2-MeC_6H_4	**6j**	94
7	2-ClC_6H_4	**6k**	83

[a] All of the reactions were carried out with **6d** (0.3 mmol), aryl iodide (0.36 mmol), $Pd(PPh_3)_4$ (0.015 mmol), CuI (0.015 mmol), and Et_3N (3.0 equiv.) in THF (3 mL) under argon at room temperature. [b] Isolated yield based on 3-amino-4-ethynylquinolin-2(1*H*)-one **6d**.

Table 3 Condition screening for intramolecular hydro-amination[a]



Entry	[M] (mol%)	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$ (10)	DMF	160	3	87
2	$Pd(OAc)_2$ (10)	DMF	160	3	22
3	$PdCl_2$ (10)	DMF	160	2	95
4	CuI (20)	DMF	160	3	78
5	CuI (100)	DMF	160	3	67
6	$PdCl_2$ (10)	DMF	100	2	89
7	$PdCl_2$ (10)	MeCN	80	3	76

[a] All of the reactions were carried out with **6f** (0.3 mmol) and metal catalyst in solvent (2.0 mL) under argon. [b] Isolated yield based on 4-acetylenyl-3-aminoquinolin-2(1*H*)-one **6f**.

of condition screening are shown in Table 3. A good result was obtained when the reaction took place in DMF under reflux, in the presence of $PdCl_2$ (Table 3, entry 3). Compound **1f** was characterized by ^1H NMR, ^{13}C NMR and mass spectral data analysis.

The scope of this palladium-catalyzed intramolecular cyclization reaction of 3-amino-4-arylethynylquinolin-2(1*H*)-ones **6** was then examined under optimized conditions (10 mol% $PdCl_2$, DMF, reflux). The results are summarized in Table 4. We noticed that all reactions worked well to generate the desired product in moderate to good yields. The reactions were very clean and usually completed in three hours. For instance, reactions of the 3-amino-4-arylethynylquinolin-2(1*H*)-ones **6a–b** with an alkyl group attached to the triple bond gave rise to the corresponding 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones in excellent yields (Table 4, entries 1 and 2). Moreover, it was found that the arylacetylenic substrates with electron-withdrawing groups on the R position were less reactive to some extent than those with the electron-donating groups. For example, reaction of **6h** or **6i** afforded the desired products **1** in 76% or 65% yield, respectively (Table 4, entries 6 and 7). For the 4-methoxy- or 2-methyl-substituted substrates **6f** or **6j**, the corresponding yield was 95% or 93%, respectively (Table 4, entries 4 and 8).

To make our strategy more attractive and straightforward as a synthetic methodology, we also tested the one-pot (stepwise) reaction of 3-amino-4-ethynylquinolin-2(1*H*)-one **6d** with *p*-iodoanisole for the synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4-(5*H*)-ones **1f**.[13] Gratifyingly, the reaction also proceeded well to generate the desired product in 71% yield (Scheme 3).

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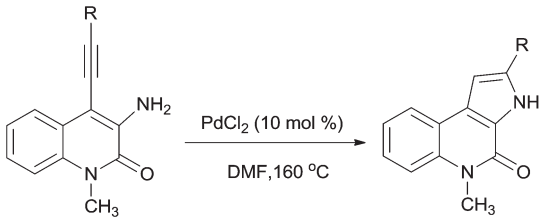
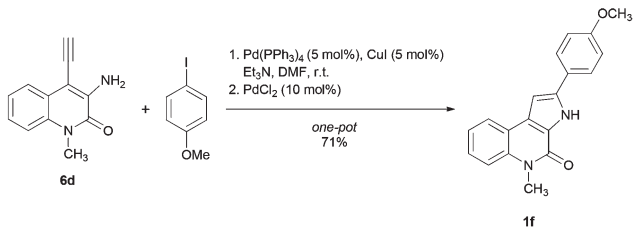
Table 4 Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones **1**[a]



Entry	6	R	1	Yield[b] (%)
1	**6a**	$CH_3(CH_2)_3$	**1a**	89
2	**6b**	*t*-Bu	**1b**	89
3	**6e**	C_6H_5	**1e**	90
4	**6f**	4-$MeOC_6H_4$	**1f**	95
5	**6g**	4-MeC_6H_4	**1g**	85
6	**6h**	4-ClC_6H_4	**1h**	76
7	**6i**	3-FC_6H_4	**1i**	65
8	**6j**	2-MeC_6H_4	**1j**	93
9	**6k**	2-ClC_6H_4	**1k**	78

[a] All of the reactions were carried out with **6** (0.3 mmol) and $PdCl_2$ (0.03 mmol) in DMF (2.0 mL) under argon for 2–3 h under reflux. [b] Isolated yield based on 4-acetylenyl-3-aminoquinolin-2(1*H*)-one **6**.



Scheme 3 Synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one **1f** from **6f** under one-pot conditions.

Conclusions

In conclusion, this paper presented an efficient and novel route for the synthesis of an interesting class of pyrroloquinolinone compounds 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones *via* palladium catalyzed cross-coupling reaction and cyclization process, starting from 4-hydoxyquinolin-2(1*H*)-one. A wide substrate scope with good functional group tolerance has been demonstrated. Introducing more diversity in the scaffold and evaluation of all these small molecules for biological effects are currently underway in our laboratory.

Experimental section

General information

NMR spectra were recorded using a 500 or 600 spectrometer (500 or 600 MHz for ^{1}H, 125 or 150 MHz for ^{13}C) with chloroform-*d* or dimethyl sulfoxide-d_6 as a solvent at 20–25 °C. High-resolution mass spectra (HRMS) were obtained with a Q-TOF MS spectrometer. All anaerobic manipulations were carried out with standard Schlenk techniques under an inert atmosphere of argon. All commercial materials were used without further purification. Column chromatography was performed using silica gel (300–400 mesh).

Preparation of 1-methyl-3-nitro-2-oxo-1,2-dihydroquinolin-4-yl trifluoromethanesulfonate (4)

To a solution of 4-hydoxyquinolin-2(1*H*)-one **2** (875 mg, 5 mmol) in acetic acid (10 mL) was added concentrated nitric acid (13.5 mmol) and sodium nitrite (28 mg, 0.4 mmol) at room temperature. The mixture was left for 0.5 h under stirring at room temperature. Then it was poured slowly onto ice-water under vigorous stirring to give a yellow precipitate. The precipitate was washed with water and dried to give crude compound **3**. The crude compound **3** (*ca.* 5 mmol), Et_3N (1.01 g, 10 mmol) and DCM (50 mL) were combined in a 100 mL round-bottom flask with a magnetic stir bar and allowed to cool to 0 °C. With vigorous magnetic stirring, Tf_2O (2.11 g, 7.5 mmol) was added dropwise from a syringe. After the mixture was stirred overnight at room temperature, ethyl acetate was added, the organic layer was washed with aqueous HCl (1 M), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to yield **4** as a yellow solid (1.44 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–8.02 (m, 1H), 7.89–7.85 (m, 1H), 7.55–7.50 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.2, 144.6, 139.3, 135.2, 134.2, 125.2, 124.6, 118.2 (q, J = 319 Hz), 115.2, 113.3, 30.9. HRMS (ESI) calcd for $C_{11}H_8F_3N_2O_6S$ $[M + H]^+$ 353.0055, found 353.0048.

General procedure for synthesis of 4-acetylenyl-3-nitroquinolin-2(1*H*)-ones 5

To a mixture of 3-nitro-4-trifloxyquinolin-2(1*H*)-one **4** (106 mg, 0.3 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol), K_2CO_3 (124 mg, 0.9 mmol) in a Schlenk flask under an argon atmosphere was added 5 mL of freshly distilled THF and terminal alkyne (0.36 mmol). The mixture was stirred for 24 hours until TLC indicated completion of reaction. The reaction solution was concentrated under vacuum and the residue was purified by column chromatography on silica gel to afford product **5a–5c**.

4-(Hex-1-yn-1-yl)-1-methyl-3-nitroquinolin-2(1*H*)-one 5a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.73–7.70 (m, 1H), 7.42–7.37 (m, 2H), 3.76 (s, 3H), 2.58 (t, J = 7.0 Hz, 2H), 1.68–1.64 (m, 2H), 1.52–1.48 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 143.8, 138.9, 133.0, 129.0, 125.7, 123.5, 117.8, 114.6, 110.8, 70.1, 30.0, 29.8, 21.9, 19.6, 13.4; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3$ $[M + H]^+$ 285.1239, found 285.1236.

4-(3,3-Dimethylbut-1-yn-1-yl)-1-methyl-3-nitroquinolin-2(1*H*)-one 5b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–8.01 (m, 1H), 7.73–7.70 (m, 1H), 7.41–7.38 (m, 2H), 3.75 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 143.7, 138.9, 133.1, 128.9, 125.7, 123.5, 118.2, 117.7, 114.6, 69.0, 30.1, 30.0, 28.8; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3$ $[M + H]^+$ 285.1239, found 285.1237.

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1-Methyl-3-nitro-4-((trimethylsilyl)ethynyl)quinolin-2(1*H*)-one 5c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.07 (m, 1H), 7.74–7.71 (m, 1H), 7.42–7.38 (m, 2H), 3.76 (s, 3H), 0.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 144.2, 139.0, 133.3, 129.1, 124.6, 123.8, 117.4, 115.9, 114.7, 92.4, 30.2, −0.8; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_3Si$ $[M + H]^+$ 301.1008, found 301.1022.

General procedure for synthesis of 4-acetylenyl-3-aminoquinolin-2(1*H*)-ones (6a–6b)

To a solution of 4-acetylenyl-3-nitroquinolin-2(1*H*)-ones **5a** or **5b** (0.20 mmol) in DCM (1 mL) were added HOAc (1 mL), H_2O (1 mL) and reduced iron powder (56 mg, 1 mmol). After TLC indicated completion of reaction, the reaction solution was poured into water. Na_2CO_3 was added into the solution portion by portion until the pH of the solution became weak basic (pH = 8–9). The neutralized solution was filtered, and the filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford product **6a** or **6b**.

3-Amino-4-(hex-1-yn-1-yl)-1-methylquinolin-2(1*H*)-one 6a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 1H), 7.34–7.24 (m, 3H), 4.99 (s, 2H), 3.77 (s, 3H), 2.61 (t, J = 6.5 Hz, 2H), 1.71–1.68 (m, 2H), 1.57–1.53 (m, 2H), 0.99 (t, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 138.5, 133.5, 125.7, 124.6, 122.7, 121.6, 113.8, 104.0, 101.8, 73.5, 31.0, 30.0, 22.1, 19.7, 13.6; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1495.

3-Amino-4-(3,3-dimethylbut-1-yn-1-yl)-1-methylquinolin-2(1H)-one 6b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.81 (m, 1H), 7.36–7.32 (m, 1H), 7.29–7.24 (m, 2H), 4.96 (bs, 2H), 3.78 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 138.2, 133.5, 125.7, 124.6, 122.7, 121.5, 113.8, 112.4, 101.7, 72.0, 31.2, 30.0, 28.7; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1493.

Preparation of 3-amino-4-ethynyl-1-methylquinolin-2(1*H*)-one 6d. To a solution of 4-acetylenyl-3-nitroquinolin-2(1*H*)-one **5c** (301 mg, 1 mmol) in DCM (2 mL) were added HOAc (4 mL), H_2O (4 mL) and reduced iron powder (280 mg, 5 mmol). After TLC indicated completion of reaction, the reaction solution was poured into water. Na_2CO_3 was added into the solution portion by portion until the pH of the solution became weak basic (pH = 8–9). The neutralized solution was filtered, and the filtrate was extracted with EtOAc. The combined organic layers were concentrated under vacuum to afford crude **6c**. The crude **6c** was added to a solution of K_2CO_3 (207 mg, 1.5 mmol) in CH_3OH–DCM (5 mL/2 mL). After stirring for another 30 min, the reaction solution was poured into water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford **6d** as a pale yellow solid (167 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 1H), 7.33–7.30 (m, 1H), 7.26–7.22 (m, 2H), 5.18 (s, 2H), 3.86 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 140.1, 133.2, 125.8, 124.3, 123.0, 120.9, 113.9, 98.8, 89.9, 77.0, 30.0; HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$ 199.0871, found 199.0873.

General procedure for synthesis of 3-amino-4-arylethynylquinolin-2(1*H*)-ones (6e–6k)

To a mixture of 3-amino-4-ethynyl-1-methylquinolin-2(1*H*)-one **6d** (198 mg, 0.3 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), CuI (3 mg, 0.015 mmol), Et_3N (91 mg, 0.9 mmol) in a Schlenk flask under an argon atmosphere were added 3 mL of freshly distilled THF and aryl iodide (0.36 mmol). After TLC indicated completion of reaction, the reaction solution was concentrated under vacuum and the residue was purified by column chromatography on silica gel to afford products **6e–6k**.

3-Amino-1-methyl-4-(phenylethynyl)quinolin-2(1*H*)-one 6e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.93 (m, 1H), 7.62–7.60 (m, 2H), 7.41–7.26 (m, 6H), 5.18 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 138.7, 133.4, 131.5, 128.7, 128.4, 125.8, 124.5, 122.9, 122.7, 121.0, 113.9, 102.2, 100.4, 82.2, 30.0; HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$ 275.1184, found 275.1174.

3-Amino-4-((4-methoxyphenyl)ethynyl)-1-methylquinolin-2(1*H*)-one 6f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.91 (m, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.36–7.24 (m, 3H), 6.90 (d, J = 8.5 Hz, 2H), 5.14 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.2, 138.4, 133.5, 133.0, 125.8, 124.7, 122.8, 121.2, 114.8, 114.1, 113.9, 102.4, 101.0, 80.9, 55.3, 30.0; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2$ $[M + H]^+$ 305.1290, found 305.1287.

3-Amino-1-methyl-4-(*p*-tolylethynyl)quinolin-2(1*H*)-one 6g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.90 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.34–7.30 (m, 1H), 7.26–7.23 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 5.16 (s, 2H), 3.75 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 138.9, 138.6, 133.4, 131.3, 129.2, 125.8, 124.6, 122.8, 121.1, 119.7, 113.8, 102.5, 100.7, 81.6, 30.0, 21.5; HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1341, found 289.1337.

3-Amino-4-((4-chlorophenyl)ethynyl)-1-methylquinolin-2(1*H*)-one 6h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 6.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.37–7.29 (m, 5H), 5.19 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 138.9, 134.8, 133.5, 132.7, 128.9, 126.0, 124.5, 123.0, 121.2, 120.9, 114.0, 101.0, 100.1, 83.2, 30.1; HRMS (ESI) calcd for $C_{18}H_{14}ClN_2O$ $[M + H]^+$ 309.0794, found 309.0783.

3-Amino-4-((3-fluorophenyl)ethynyl)-1-methylquinolin-2(1*H*)-one 6i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 1H), 7.40–7.29 (m, 6H), 7.12–7.09 (m, 1H), 5.21 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{CF}$ = 245 Hz), 157.1, 139.1, 133.5, 130.1 (d, $^3J_{CF}$ = 9 Hz), 127.4, 126.0, 124.6, 124.5, 123.0, 120.9, 118.2 (d, $^2J_{CF}$ = 22 Hz), 116.0 (d, $^2J_{CF}$ = 21 Hz), 114.0, 100.8, 99.8, 83.2, 30.1; HRMS (ESI) calcd for $C_{18}H_{14}FN_2O$ $[M + H]^+$ 293.1090, found 293.1087.

3-Amino-1-methyl-4-(*o*-tolylethynyl)quinolin-2(1*H*)-one 6j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.96 (m, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.40–7.28 (m, 5H), 7.25–7.21 (m, 1H), 5.18 (s, 2H), 3.81 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 139.6, 138.6, 133.6, 131.9, 129.7, 128.8, 125.9, 125.8, 124.6,

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123.0, 122.7, 121.1, 114.0, 101.3, 100.9, 86.1, 30.1, 21.2; HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1341, found 289.1336.

3-Amino-4-((2-chlorophenyl)ethynyl)-1-methylquinolin-2(1*H*)-one 6k. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.99 (m, 1H), 7.67–7.65 (m, 1H), 7.50–7.48 (m, 1H), 7.39–7.29 (m, 5H), 5.37 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 139.5, 135.3, 133.4, 132.9, 129.6, 129.3, 126.7, 125.9, 124.6, 123.0, 122.8, 120.7, 114.0, 99.7, 98.9, 87.9, 30.1; HRMS (ESI) calcd for $C_{18}H_{14}ClN_2O$ $[M + H]^+$ 309.0794, found 309.0788.

General procedure for synthesis of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1 *via* $PdCl_2$-mediated cyclization

A mixture of $PdCl_2$ (5.3 mg, 0.03 mmol) and **6** (0.30 mmol) in DMF (2 mL) was stirred at 160 °C under a nitrogen atmosphere. After completion of the reaction as monitored by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the corresponding product **1**.

2-Butyl-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.98–7.96 (m, 1H), 7.91 (d, J = 7.0 Hz. 1H), 7.44 (s, 2H), 7.28 (s, 1H), 6.53 (s, 1H), 3.87 (s, 3H), 2.86 (t, J = 7.5 Hz. 2H), 1.79–1.76 (m, 2H), 1.44–1.41 (m, 2H), 0.95 (t, J = 7.0 Hz. 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 142.9, 136.5, 127.7, 126.5, 123.6, 122.1, 121.5, 118.9, 115.1, 99.6, 31.6, 29.7, 27.9, 22.4, 13.8; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1486.

2-(*tert*-Butyl)-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1b. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (s, 1H), 7.98–7.96 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.43–7.40 (m, 1H), 7.25 (t, J = 7.0 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 3.70 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.4, 154.5, 151.1, 136.3, 126.5, 125.8, 123.3, 121.7, 118.2, 115.3, 97.3, 32.0, 29.9, 28.7; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1494.

5-Methyl-2-phenyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 7.0 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.49–7.44 (m, 3H), 7.41 (s, 1H), 7.35–7.30 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.5, 139. 5, 136.5, 131.3, 128.8, 127.8, 127.1, 127.0, 125.6, 123.5, 123.1, 121.9, 117.8, 115.4, 100.0, 28.8; HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$ 275.1184, found 275.1185.

2-(4-Methoxyphenyl)-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1f. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.43 (s, 1H), 8.04 (d, J = 7.0 Hz. 1H), 7.96 (d, J = 8.5 Hz. 2H), 7.55–7.45 (m, 2H), 7.32–7.29 (m, 2H), 7.02 (d, J = 8.5 Hz. 2H), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 154.4, 139.569, 136.5, 127.2, 127.0, 126.8, 124.0, 123.4, 122.6, 121.8, 117.8, 115.4, 114.2, 98.8, 55.2, 28.7; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2$ $[M + H]^+$ 305.1290, found 305.1281.

5-Methyl-2-(*p*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1g. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.05 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.55–7.47 (m, 2H), 7.36–7.25 (m, 4H), 3.73 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.5, 139.7, 137.3, 136.5, 129.4, 128.6, 127.2, 127.0, 125.6, 123.5, 122.8, 121.9, 117.8, 115.5, 99.5, 28.8, 20.9; HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1341, found 289.1337.

2-(4-Chlorophenyl)-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1h. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.62 (s, 1H), 8.03 (d, J = 8 Hz, 3H), 7.56–7.45 (m, 5H), 7.31 (t, J = 7.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.6, 138.2, 136.7, 132.4, 130.4, 129.0, 127.4, 127.2, 123.6, 123.5, 122.1, 117.9, 115.6, 100.6, 29.0; HRMS (ESI) calcd for $C_{18}H_{14}ClN_2O$ $[M + H]^+$ 309.0794, found 309.0790.

2-(3-Fluorophenyl)-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1i. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.51–7.47 (m, 3H), 7.32 (t, J = 7.5 Hz, 1H), 7.18–7.14 (m, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162. 7 (d, $^1J_{CF}$ = 241 Hz), 154.6, 138.0, 136.6, 133.7, 133.7, 130.9 (d, $^3J_{CF}$ = 9 Hz), 127.2, 127.1, 123.5, 122.1, 121.7, 117.7, 115.5, 114.5 (d, $^2J_{CF}$ = 21 Hz), 112.1 (d, $^2J_{CF}$ = 22 Hz), 101.0, 28.9; HRMS (ESI) calcd for $C_{18}H_{14}FN_2O$ $[M + H]^+$ 293.1090, found 293.1089.

5-Methyl-2-(*o*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.36 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.57–7.46 (m, 3H), 7.33–7.27 (m, 4H), 7.04 (s, 1H), 3.74 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 139.3, 136.5, 135.8, 131.8, 130.6, 129.7, 128.1, 126.8, 126.6, 125.8, 123.5, 122.4, 121.8, 117.9, 115.4, 102.7, 28.8, 20.8; HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1341, found 289.1336.

2-(2-Chlorophenyl)-5-methyl-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one 1k. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.53 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.75–7.73 (m, 1H), 7.61–7.55 (m, 2H), 7.49–7.41 (m, 3H), 7.29 (t, J = 7.0 Hz, 1H), 7.25 (s, 1H), 3.74 (s, 3H);. ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.5, 136.5, 136.1, 131.5, 131.5, 130.6, 130.2, 129.6, 127.2, 126.9, 126.2, 123.5, 122.7, 121.9, 117.8, 115.4, 103.7, 28.8; HRMS (ESI) calcd for $C_{18}H_{14}ClN_2O$ $[M + H]^+$ 309.0794, found 309.0794.

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Notes and references

1 (*a*) S. Wetzel, R. S. Bon, K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 10800; (*b*) D. P. Walsh and Y.-T. Chang, *Chem. Rev.*, 2006, **106**, 2476; (*c*) P. Arya,

Published on 03 September 2013. Downloaded by Michigan Technological University on 22/10/2014 19:54:05.

D. T. H. Chou and M.-G. Baek, *Angew. Chem., Int. Ed.*, 2001, **40**, 339; (*d*) S. L. Schreiber, *Science*, 2000, **287**, 1964.

2 For selected recent reviews on the synthesis of heterocycles, see: (*a*) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084; (*b*) X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1; (*c*) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937.

3 For selected recent reviews on pyrrole-derived alkaloids, see: (*a*) J.-F. Hu, H. Fan, J. Xiong and S.-B. Wu, *Chem. Rev.*, 2011, **111**, 5465; (*b*) H. Fan, J.-N. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.

4 For selected examples, see: (*a*) D. L. Boger, D. R. Soenen, C. W. Boyce, M. P. Hedrick and Q. Jin, *J. Org. Chem.*, 2000, **65**, 2479; (*b*) D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Sehon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54; (*c*) H. Tao, I. Hwang and D. L. Boger, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5979; (*d*) P. Y. Zhang, I. L. K. Wong, C. S. W. Yan, X. Y. Zhang, T. Jiang, L. M. C. Chow and S. B. Wan, *J. Med. Chem.*, 2010, **53**, 5108; (*e*) T. Ohta, T. Fukuda, F. Ishibashi and M. Iwao, *J. Org. Chem.*, 2009, **74**, 8143; (*f*) J. C. Liermann and T. Opatz, *J. Org. Chem.*, 2008, **73**, 4526; (*g*) D. Pla, A. Marchal, C. A. Olsen, A. Francesch, C. Cuevas, F. Albericio and M. lvarez, *J. Med. Chem.*, 2006, **49**, 3257; (*h*) C. Tardy, M. Facompré, W. Laine, B. Baldeyrou, D. García-Gravalos, A. Francesch, C. Mateo, A. Pastor, J. A. Jiménez, I. Manzanares, C. Cuevasb and C. Bailly, *Bioorg. Med. Chem.*, 2004, **12**, 1697; (*i*) C. P. Ridley, M. V. R. Reddy, G. Rocha, F. D. Bushman and D. J. Faulknera, *Bioorg. Med. Chem.*, 2002, **10**, 3285; (*j*) S. Su and J. A. Porco Jr., *J. Am. Chem. Soc.*, 2007, **129**, 7744; (*k*) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly and F. Gago, *J. Med. Chem.*, 2005, **48**, 3796; (*l*) J. Kluza, M.-A. Gallego, A. Loyens, J.-C. Beauvillain, J.-M. F. Sousa-Faro, C. Cuevas, P. Marchetti and C. Bailly, *Cancer Res.*, 2006, **66**, 3177; (*m*) Q. Li, J. Jiang, A. Fan, Y. Cui and Y. Jia, *Org. Lett.*, 2011, **13**, 312; (*n*) L. Chen and M.-H. Xu, *Adv. Synth. Catal.*, 2009, **351**, 2005.

5 (*a*) P. Hewawasam, W. Fan, M. Ding, K. Flint, D. Cook, G. D. Goggings, R. A. Myers, V. K. Gribkoff, C. G. Boissard, S. I. Dworetzky, J. E. Starret and N. J. Lodge, *J. Med. Chem.*, 2003, **46**, 2819; (*b*) K. M. Boy, J. M. Guernon, S.-Y. Sit, K. Xie, P. Hewawasam, C. G. Boissard, S. I. Dworetzky, J. Natale, V. K. Gribkoff, N. Lodge and J. E. Starret, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5089; (*c*) P. Hewawasam, W. Fan, D. A. Cook, K. S. Newberry, C. B. Boissard, V. K. Gribkoff, J. Starret and N. J. Lodge, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4479; (*d*) P. R. Angibaud, M. G. Venet, W. Filliers, R. Broeckx, Y. A. Ligny, P. Muller, V. S. Poncelet and D. W. End, *Eur. J. Org. Chem.*, 2004, 479; (*e*) B. M. Andresen, M. Couturier, B. Cronin, M. D'Occhio, M. D. Ewing, M. Guinn, J. M. Hawkins, V. J. Jasys, S. D. LaGreca, J. P. Lyssikatos, G. Moraski, K. Ng, J. W. Raggon, A. M. Stewart, D. L. Tickner, J. L. Tucker, F. J. Urban, E. Vazquez and L. Wei, *Org. Process Res. Dev.*, 2004, **8**, 643; (*f*) P. Hewawasam, W. Fan, J. Knipe, S. L. Moon, C. G. Boissard, V. K. Gribkoff and J. E. Starret, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1779; (*g*) G. D. Yancopoulos, S. Davis, N. W. Gale, J. S. Rudge, S. J. Wiegand and J. Holash, *Nature*, 2000, **407**, 242; (*h*) P. Carmeliet and R. K. Jain, *Nature*, 2000, **407**, 249; (*i*) Y.-Q. Fang, R. Karisch and M. Lautens, *J. Org. Chem.*, 2007, **72**, 1341; (*j*) J. T. Kuethe, A. Wong, C. Qu, J. Smitrovich, I. W. Davies and D. L. Hughes, *J. Org. Chem.*, 2005, **70**, 2555; (*k*) J. F. Payack, E. Vazquez, L. Matty, M. H. Kress and J. McNamara, *J. Org. Chem.*, 2005, **70**, 175; (*l*) A. Wong, J. T. Kuethe, I. W. Davies and D. L. Hughes, *J. Org. Chem.*, 2004, **69**, 7761; (*m*) D. Audisio, S. Messaoudi, L. Cegielkowski, J.-F. Peyrat, J.-D. Brion, D. Methy-Gonnot, C. Radanyi, J.-M. Renoir and M. Alami, *ChemMedChem*, 2011, **6**, 804.

6 (*a*) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi and D. M. Ferguson, *J. Med. Chem.*, 2006, **49**, 2127; (*b*) A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna and P. Pace, *Synlett*, 1998, 446; (*c*) M. Anzini, A. Cappelli and S. Vomero, *J. Heterocycl. Chem.*, 1991, **28**, 1809; (*d*) A. Godard, J. M. Fourquez, R. Tamion, F. Marsais and G. Quéguiner, *Synlett*, 1994, 235.

7 (*a*) Z. Wang and J. Wu, *Tetrahedron*, 2008, **64**, 1736; (*b*) Z. Wang, B. Wang and J. Wu, *J. Comb. Chem.*, 2007, **9**, 811; (*c*) Z. Wang, R. Fan and J. Wu, *Adv. Synth. Catal.*, 2007, **349**, 1943.

8 For selected examples, see: (*a*) K. Inamoto, T. Saito, K. Hiroya and T. Doi, *J. Org. Chem.*, 2010, **75**, 3900; (*b*) D.-J. Tang, B.-X. Tang and J.-H. Li, *J. Org. Chem.*, 2009, **74**, 6749; (*c*) T. N. Glasnov, W. Stadlbauer and C. O. Kappe, *J. Org. Chem.*, 2005, **70**, 3864; (*d*) A. C. Tadd, A. Matsuno, M. R. Fielding and M. C. Willis, *Org. Lett.*, 2009, **11**, 583; (*e*) Z. Liu, C. Shi and Y. Chen, *Synlett*, 2008, 1734; (*f*) G. Battistuzzi, R. Bernini, S. Cacchi, I. De Salve and G. Fabrizi, *Adv. Synth. Catal.*, 2007, **349**, 297; (*g*) R. Bernini, S. Cacchi, G. Fabrizi and A. Sferrazza, *Heterocycles*, 2006, **69**, 99; (*h*) D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772; (*i*) M. Mori, K. Chiba, N. Ohta and Y. Ban, *Heterocycles*, 1979, **13**, 329; (*j*) N. A. Cortese, C. B. Ziegler Jr., B. J. Hrnjez and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2952.

9 (*a*) V. A. Vaillard, M. E. Budén, S. E. Martín and R. A. Rossi, *Tetrahedron Lett.*, 2009, **50**, 3829; (*b*) J. Bergman and S. Rehn, *Tetrahedron*, 2002, **45**, 9179.

10 For selected reviews, see: (*a*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215; (*b*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644; (*c*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (*d*) A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, 1989, **30**, 2581; (*e*) C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.

11 (*a*) T. Kappe, A. S. Karem and W. Stadlbauer, *J. Heterocycl. Chem.*, 1988, **25**, 857; (*b*) T. Kappe, *Farmaco*, 1999, **54**, 309; (*c*) E. Ziegler, R. Wolf and T. Kappe, *Monatsh. Chem.*, 1965, **96**, 418; (*d*) E. Ziegler and H. Junek, *Monatsh. Chem.*, 1959, **90**, 762; (*e*) H. Junek and K. Gelfert, *Monatsh. Chem.*, 1959,

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90, 822; (*f*) P. Roschger and W. Stadlbauer, *Liebigs Ann. Chem.*, 1990, 821.

12 D. Audisio, S. Messaoudi, S. Cojean, J.-F. Peyrat, J.-D. Brion, C. Bories, F. Huteau, P. M. Loiseau and M. Alami, *Eur. J. Med. Chem.*, 2010, **52**, 44.

13 The operation is simple: after completion of the reaction of 3-amino-4-ethynylquinolin-2(1*H*)-one **6d** with *p*-iodoanisole as indicated by TLC, $PdCl_2$ (10 mol%) was added directly in the reaction mixture and the mixture was stirred at 160 °C for another 2 hours.