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Regioselective functionalization of quinolin-4(1*H*)-ones via sequential palladium-catalyzed reactions

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ABSTRACT

A practical and general synthesis of 1,3,6-trisubstituted quinolin-4(1*H*)-ones starting from 1-alkyl-6-bromo-3-iodoquinolin-4(1*H*)-one is described, based on regioselective sequential palladium-catalyzed cross-coupling reactions, namely Suzuki–Miyaura, Sonogashira and aminocarbonylation reactions, under microwave irradiation. Good substrate generality, ease of execution and practicability make this method exploitable for the generation of libraries of chemically diverse 4-quinolones.

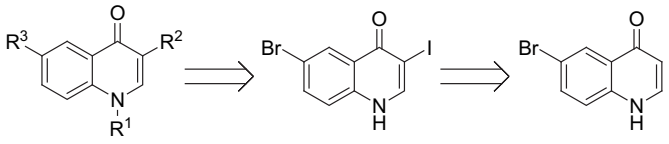
1. Introduction

Quinolin-4(1*H*)-ones constitute a major class of nitrogen containing heterocycles,[1] resulting among the most common frameworks present in the bioactive molecules.[2] While 4-quinolone-3-carboxylic acids are one of the largest classes of antimicrobial agents used worldwide, variously substituted quinolin-4(1*H*)-one derivatives have shown a wide range of different pharmacological activities,[3] such as, for instance, antiinflammatory,[4] antitumour,[5] anxiolytic,[6] antiischemic,[7] antiviral activity.[8,9] Due to their synthetic accessibility and to the possibility of functionalization at different position of the molecule, quinolin-4(1*H*)-ones represent an attractive platform for the design of combinatorial libraries.[10]

In the context of our ongoing research in the area of 4-quinolones as anti-HIV-1 agents[11] and cannabinoid ligands,[12] we became interested in the development of an efficient synthetic methodology enabling the rapid access to a number of 3,6-disubstituted 1-alkylquinolin-4(1*H*)-ones of general structure **1** (Scheme 1).

Although the halide selectivity (I>Br) for various Pd-mediated C–C bond forming reactions is well known, to our knowledge it has not been exploited to carry out site-selective functionalization of the 4-quinolone scaffold.[13]

It was speculated that 6-bromo-3-iodoquinolin-4(1*H*)-one **2**, generated from 6-bromoquinolin-4(1*H*)-one **3**, could represent the key intermediate for the preparation of compounds characterized by different substituents at the 1, 3 and 6-positions through N-alkylation followed by sequential regioselective MW-assisted palladium-catalyzed reactions.[14,15] Such an approach would offer the distinctive advantage of enhancing chemical diversity in the last three synthetic steps, affording combinatorial libraries of 4-quinolone derivatives.



1 **2** **3**

Scheme 1. Retrosynthetic analysis.

2. Results and discussion

6-Bromoquinolin-4(1*H*)-one **3**[16] was initially prepared according to the classic method for the synthesis of 4-quinolones, which relies on the Gould–Jacobs reaction between a suitably substituted aniline and a dialkyl alkoxymethylenemalonate followed by Lappin cyclization, hydrolysis of the ester function and decarboxylation. Despite the good efficiency of this reaction sequence in terms of yield (67%) and ease of execution, we found that the whole process was time consuming and not in line with an expeditious preparation of the target compounds. Accordingly, a two-step MW-assisted synthesis

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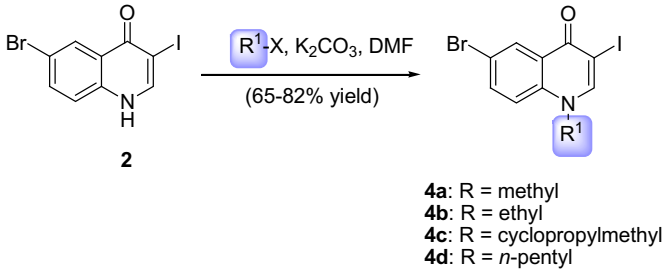
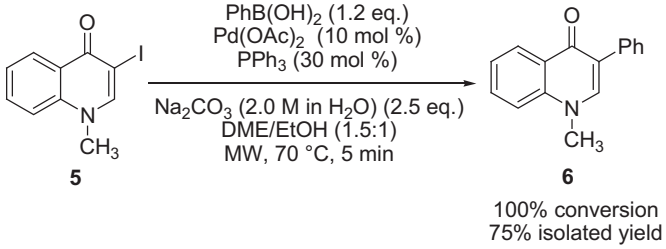
was set up, reacting commercially available 4-bromoaniline and ethyl propiolate to give the corresponding 3-anilinoacrylate, which was then cyclized to give the final compound **3** in 35% overall yield (Scheme 2).[17] Although the yield may appear modest if compared with the one obtained with the classical approach, this procedure has the advantage of ensuring a very fast access (40 min total reaction time for the two steps) to the target compound. Treatment of **3** with *N*-iodosuccinimide (NIS) for 3 min at room temperature provided the intermediate **2**, which delivered the corresponding *N*-alkylated products **4a**–**d** by reaction with the appropriate alkyl halide.



Scheme 2. Synthesis of 1-alkyl-6-bromo-3-iodoquinolones **4a**–**d**.

As a first step, we started to set up the mildest reaction conditions able to ensure the complete conversion of the starting material by replacement of iodine at 3-position using $Pd(OAC)_2$ as the catalyst. To our delight, we found that the model substrate 3-iodo-1-methylquinolin-4(1*H*)-one **5**[18] could be converted to the corresponding 3-phenyl derivative **6** (Scheme 3) in 75% isolated yield and with 100% conversion of the starting material **5** via Suzuki–Miyaura reaction with phenylboronic acid under standard conditions [$Pd(OAc)_2$ (10 mol %), PPh_3 (30 mol %), 2.0 M Na_2CO_3 (2.5 equiv), DME/EtOH (1.5:1), MW, 5 min, 70 °C].



Scheme 3. Suzuki–Miyaura reaction on the model substrate 5.

Next, we tested the chemoselectivity of the cross-coupling reaction between 6-bromo-3-iodoquinolin-4(1*H*)-one **4a** and phenylboronic acid without further optimization of the reaction conditions, and the results are shown in Table 1 (entry 1).

The expected compound **7a** was obtained in 80% isolated yield without concurrent formation of regioisomeric and/or bis-coupling products, demonstrating the chemoselective functionalization of 3-position. With this promising result in hand, we applied the same reaction protocol to substrates **4a**–**c** and various boronic acids (Table 1, entries 2–6).

All the reactions afforded the desired products **7b**–**f** in good isolated yield, with the exception of those employing 2-furanboronic acid (entry 3) and 4-methoxyphenylvinylboronic acid (entry 4), where **7c** and **7d** were obtained in moderate yield along with not identified degradation products. The less reactive alkenylboronic acid required to increase the reaction temperature to 90 °C, but this Suzuki–Miyaura reaction afforded compound **7d** in a yield (47%) that is in line with the yield (42–65%) reported recently for the preparation of (*E*)-1-methyl-3-styrylquinolin-4(1*H*)-ones by a Heck reaction,[19] with the advantage of avoiding the possible concurrent formation of branched regioisomers. In all cases, complete conversion of substrates **4a**–**c** was observed by ^1H NMR of the crude reaction mixture, accompanied by formation of the target compounds **7b**–**f**. However, when a slightly higher excess (1.5 equiv) of boronic acid was used, traces of 3,6-disubstituted product also formed, as expected.

Further elaboration of compounds **7a**–**e** into trisubstituted quinolones **1a**–**g** was accomplished through sequential Suzuki–Miyaura cross-coupling reactions by exploiting the reactivity of bromine at 6-position. After some preliminary tests, we found that this reaction could be performed under the same conditions used to generate compounds **7**, by increasing the reaction temperature to 80 °C (Table 2).

The reactions proceeded smoothly to furnish the final trisubstituted quinolones in moderate (**1a**) or good yield (**1b**–**g**), with complete conversion of the substrate **7** to product.

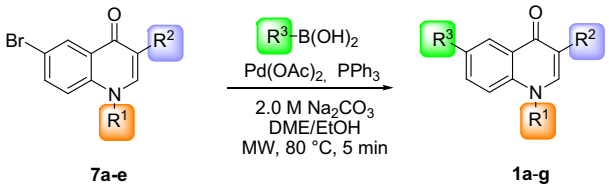
These results demonstrated that sequential Suzuki–Miyaura arylation at 3- and 6-position of 1-substituted 6-bromo-3-iodoquinolin-4(1*H*)-ones can be carried out regioselectively provided the reaction temperature be carefully controlled. From the viewpoint of efficiency, one-pot sequential reactions of easily available (hetero)aryl dihalides with a single catalyst are desirable, and so far not many successful examples have been reported.[20] Therefore, we considered the possibility to introduce chemical diversity at 3- and 6-position of compound **4b** by one-pot sequential Suzuki–Miyaura reactions. Accordingly, taking advantage of the possibility to attain complete conversion of **4a** after the first

Table 1
Cross-coupling reactions between 1-substituted 6-bromo-3-iodoquinolin-4(1*H*)-ones **4a**–**c** and boronic acids

Entry	Substrate	R^2-B(OH)$_2$	4-Quinolone-R^1,R^2	Yield[a] (%)
1	**4a**	R^2=phenyl	**7a**: R^1=Me, R^2=phenyl	80
2	**4a**	R^2=4-tolyl	**7b**: R^1=Me, R^2=4-tolyl	83
3	**4a**	R^2=2-furyl	**7c**: R^1=Me, R^2=2-furyl	49
4	**4a**	R^2=(*E*)-2-(4-methoxyphenyl)vinyl	**7d**: R^1=Me, R^2=(*E*)-2-(4-methoxyphenyl)vinyl	47[b]
5	**4b**	R^2=4-tolyl	**7e**: R^1=Et, R^2=4-tolyl	83
6	**4c**	R^2=4-chlorophenyl	**7f**: R^1=cyclopropylmethyl, R^2=4-chlorophenyl	84

[a] Isolated yield based on substrate **4**.
[b] Reaction performed at 90 °C.

Table 2
Synthesis of 1-alkyl-3,6-diarylquinolin-4(1*H*)-ones **1a**–**g**



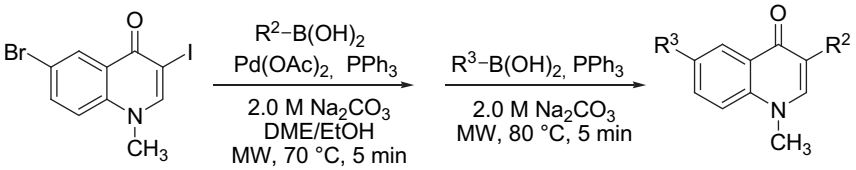
7a-e **1a-g**

Entry	Substrate	R^3-B(OH)$_2$	4-Quinolone-R^1,R^2,R^3	Yield[a] (%)
1	**7a**	R^3=4-(trifluoromethoxy)phenyl	**1a**: R^1=Me, R^2=phenyl, R^3=4-(trifluoromethoxy)phenyl	50
2	**7a**	R^3=3-pyridinyl	**1b**: R^1=Me, R^2=phenyl, R^3=3-pyridinyl	99
3	**7a**	R^3=3-chlorophenyl	**1c**: R^1=Me, R^2=phenyl, R^3=3-chlorophenyl	88
4	**7b**	R^3=4-cyanophenyl	**1d**: R^1=Me, R^2=4-tolyl, R^3=4-cyanophenyl	87
5	**7c**	R^3=3-chlorophenyl	**1e**: R^1=Me, R^2=2-furyl, R^3=3-chlorophenyl	98
6	**7d**	R^3=3-chlorophenyl	**1f**: R^1=Me, R^2=(*E*)-2-(4-methoxyphenyl)vinyl, R^3=3-chlorophenyl	67
7	**7e**	R^3=3-chlorophenyl	**1g**: R^1=Et, R^2=4-tolyl, R^3=3-chlorophenyl	76

[a] Isolated yield based on substrate **7**.

arylation reaction, the preparation of compounds **1c** and **1d** from **4a** without isolation and purification of the intermediates **7a** and **7b** was investigated (Table 3).

Table 3
One-pot double Suzuki reactions of **4a** with different arylboronic acids



4a **1c,d**

Entry	R^2-B(OH)$_2$	R^3-B(OH)$_2$	4-Quinolone-R^2, R^3	Yield[a] (%)
1	R^2=phenyl	R^3=3-chlorophenyl	**1c**: R^2=phenyl, R^3=3-chlorophenyl	69
2	R^3=4-tolyl	R^3=4-cyanophenyl	**1d**: R^3=4-tolyl, R^3=4-cyanophenyl	55

[a] Overall isolated yield based on substrate **4a**.

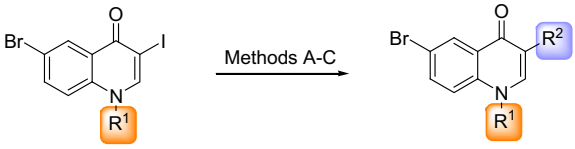
Thus, **4a** and phenylboronic acid (entry 1) were reacted under the conditions described in Table 1 and thereafter 3-chlorophenylboronic acid (1.2 equiv) was added to the crude reaction mixture, along with more triphenylphosphine (30 mol %) (to avoid catalyst decomposition) and base (2 M Na_2CO_3, 2.5 equiv), and the mixture was subjected to MW irradiation at 80 °C for 5 min to give compound **1c** in 69% overall yield. Similarly, compound **1d** (entry 2) was obtained in 55% overall yield through the one-pot sequential reaction of **4a** with 4-methylphenylboronic acid first and then with 4-cyanophenylboronic acid. The one-pot procedure allowed the preparation of the desired trisubstituted derivatives in overall yields comparable to or slightly lower than those obtained in the stepwise synthesis (70% for **1c** and 72% for **1d**), but with a total reaction time of only 10 min without isolation of the monoarylated intermediate.

Once we had demonstrated that different aryl groups can be regioselectively introduced at 3- and 6-position of the 4-quinolone scaffold by Suzuki–Miyaura reactions, we considered other palladium-catalyzed reactions to be used to decorate the bicyclic core in order to enhance the chemical diversity. The results of these experiments are reported in Table 4. Although Sonogashira reactions on both 3-iodoquinolin-4(1*H*)-ones and 4-bromoquinolin-2(1*H*)-ones have been already reported,[21,22] in the reaction between **4a** and trimetylsilylacetylene (TMSA) (entry 1) the best conversions and isolated product yields were achieved by employing the procedure developed by Babudri et al.,[23] based on the use of a large excess (250 equiv) of diisopropylamine as base, though we replaced toluene with 1,4-dioxane as a solvent and used MW irradiation (120 °C, 5 min) instead of conventional heating (reflux, 2 h). Under these conditions, product **7f** was obtained in 58% yield. This reaction worked in a satisfactory manner even on substrate **2** (entry 6), delivering product **8** in 65% yield, with no further conversion to furo[3,2-*c*]quinoline derivatives.[21]

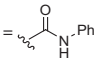
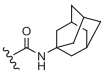
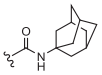
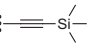
Pd-catalyzed carbonylation of aryl halides in the presence of primary or secondary amines provides different benzoic acid amides in a smooth manner. The combination of microwave heating and in situ release of CO from $Mo(CO)_6$ has been proven to enable the fast development of new easy-to-execute carbonylation protocols.[24–26] Based on our previous applications of aminocarbonylation reactions on quinolone derivatives,[11] we initially adopted the experimental protocol reported by Larhed et al.[27] Thus, substrate **4a** (entry 2) was reacted with aniline according to method B to provide compound **7h** in 38% yield. Similarly, the conversion of **4d** (entry 5) into **7k** was accomplished in a moderate yield of 25%. Slight modifications of the experimental conditions, such as in entry 3, did not improve the reaction yield and compound **7i** was isolated in 36% yield. Even when the procedure recently described by Salvadori et al.,[28] based on the use of gaseous CO and Pd/C as the catalyst (method C), was applied to substrate **4c** (entry 4), the aminocarbonylation product **7j** was obtained in a similar yield of 35%.

Cross-coupling reactions at 6-position of substrates **7a**,**f**–**i**,**k** to produce the trisubstituted 4-quinolones **1h**–**o** were carried out using the same procedures adopted to displace iodine at 3-position, although some modifications were usually required due to the lower reactivity of bromine compared to iodine (Table 5). In all cases MW irradiation time and/or temperature had to be

Table 4
Sonogashira and aminocarbonylation reactions of substrates **2**, and **4a**,**b**,**d**



2, **4a**,**b**,**d** **7g-k**, **8**

Entry	Substrate	Product	Method	Yield[a] (%)
1	**4a**: R^1=Me	**7g**: R^1 = Me, R^2 = 	A	58
2	**4a**: R^1=Me	**7h**: R^1 = Me, R^2 = 	B	38
3	**4a**: R^1=Me	**7i**: R^1 = Me, R^2 = 	B[b]	36
4	**4b**: R^1=Et	**7j**: R^1 = Et, R^2 = 	C	35
5	**4d**: R^1=*n*-pentyl	**7k**: R^1 = *n*-pentyl, R^2 = 	B	25
6	**2**: R^1=H	**8**: R^1 = H, R^2 = 	A	65

Reagents and conditions: method A: TMSA, CuI, $Pd(PPh_3)_2Cl_2$, *i*-Pr_2NH, dioxane, MW, 120 °C, 5 min; method B: appropriate amine, $Pd(OAc)_2$, $Mo(CO)_6$, DBU, THF, MW, 110 °C, 10 min; method C: morpholine, Pd/C, CO (130 psi), DBU, DMF, MW, 100 °C, 10 min.

[a] Isolated yield based on substrates **2** and **4a**,**b**,**d**.

[b] Irradiation time: 5 min.

optimized, while for the conversion of **7a** into **1h** by Sonogashira coupling (entry 1), the reaction was best performed under conventional heating (reflux, 24 h). Generally, harder conditions were necessary to functionalize the 6-position while, on the other hand, the increased structural complexity made substrates **7** more prone to decomposition and side-products formation. As a result, cross-coupling reactions at 6-position proceeded with slightly lower efficiency, leading to products **1h**–**o** in 27–81% yield. It is worth noting that attempts to perform the aminocarbonylation reaction on substrate **7f** with 4-methoxybenzylamine according to method D only afforded the debrominated quinolone along with decomposition products, while compound **1i** (entry 2) could be obtained using the procedure described under method B in 30% yield together with 53% of starting material **7f**, which was easily separated by chromatography and reused in another run.

Finally, we wish to underline that the two-step transformation of **4d** into **1o** by sequential aminocarbonylation and Suzuki–Miyaura reactions represents a new synthesis of *N*-(adamantan-1-yl)-6-(furan-2-yl)-4-oxo-1-pentyl-1,4-dihydroquinoline-3-carboxamide (**1o**), possibly the highest affinity and most selective cannabinoid type 2 receptor ligand developed to date, which compares favourably in terms of ease of execution and overall yield (6%) with the previous synthesis (8%).[12]

3. Conclusion

In summary, the sequential palladium-catalyzed cross-coupling reactions of 1-alkyl-6-bromo-3-iodoquinolin-4(1*H*)-one disclosed herein represent a general and practical synthesis of 1,3,6-trisubstituted quinolin-4(1*H*)-ones of potential pharmaceutical interest. Good substrate generality, ease of execution and practicability make this method exploitable for the generation of libraries of 4-quinolones characterized by remarkable chemical diversity.

4. Experimental section

4.1. General

Merck silica gel 60 was used for flash chromatography (23–400 mesh). IR spectra were recorded on a Perkin–Elmer BX FT-IR system using $CHCl_3$ as the solvent or a Nujol dispersion. ^1H NMR and ^{13}C NMR were recorded at 200 MHz and 50 MHz, respectively, on a Brucker AC200F spectrometer and at 400 MHz and 100 MHz on a Brucker Advance DPX400. Chemical shifts are reported relative to tetramethylsilane at 0.00 ppm. Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Microwave irradiations were conducted using a CEM Discover Synthesis Unit. Elemental analyses were performed on a Perkin–Elmer PE 2004 Elemental Analyzer and the data for C, H and N are within 0.4% of the theoretical values.

4.2. General procedure for the synthesis of 3-substituted quinolin-4(1*H*)-ones 7a–f

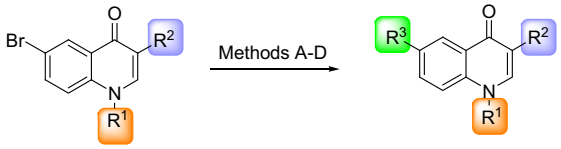
A microwave vial was charged with **4a**–**c** (0.20 mmol), the appropriate arylboronic acid (0.24 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), PPh_3 (16 mg, 0.06 mmol), 2 M Na_2CO_3 (0.25 mL), DME (0.75 mL), EtOH (0.5 mL) and exposed to microwave irradiation at 70 °C for 5 min. After cooling, the reaction mixture was diluted with dichloromethane and filtered through Celite. The organic layer was washed with brine, dried and concentrated to a residue, which was purified by flash chromatography [silica gel, 95/5 (v/v) dichloromethane/methanol] to provide the title compounds **7a**–**f**.

*4.2.1. 6-Bromo-1-methyl-3-phenylquinolin-4(1H)-one (**7a**).* R_f 0.70 (CH_2Cl_2/MeOH 95/5); mp 185–186 °C (MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J=2.1 Hz, 1H), 7.70 (dd, J_{ortho}=8.9 Hz, J_{meta}=2.1 Hz, 1H), 7.64–7.63 (m, 2H), 7.61 (s, 1H), 7.42–7.38 (m, 2H), 7.33–7.29 (m, 1H), 7.26 (d, J_{ortho}=8.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 142.7, 138.7, 135.0, 134.9, 130.0, 128.5, 128.3, 127.3, 122.2, 117.5, 117.2, 40.8; IR ($CHCl_3$): ν 1626 cm^{-1}; MS: m/z (M^++1) 315. Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46; found: C, 61.35; H, 3.91; N, 4.36.

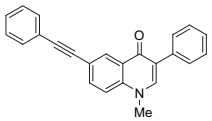
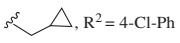
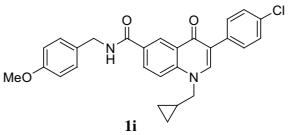
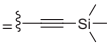
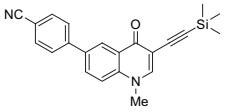
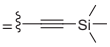
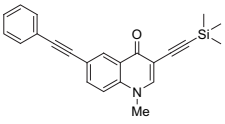
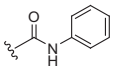
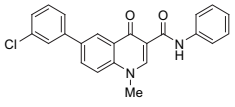
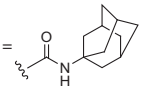
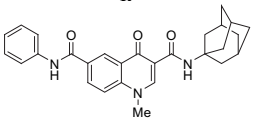
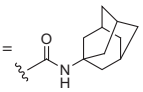
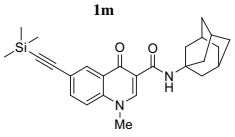
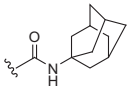
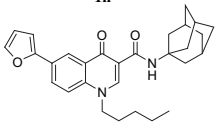
*4.2.2. 6-Bromo-1-methyl-3-(4-methylphenyl)quinolin-4(1H)-one (**7b**).* R_f 0.87 (CH_2Cl_2/MeOH 95/5); mp 226–227 °C (MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 8.59 (d, J=2.8 Hz, 1H), 7.64 (dd, J_{ortho}=8.8 Hz, J_{meta}=1.8 Hz, 1H), 7.59 (s, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.24–7.15 (m, 4H), 3.76 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 142.6, 138.9, 137.3, 135.1, 132.2, 130.4, 129.3, 128.6, 122.8, 117.7, 117.2, 112.5, 41.0, 21.5; IR ($CHCl_3$): ν 1625 cm^{-1}; MS: m/z (M^++1) 329. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27; found: C, 62.50; H, 4.39; N, 4.12.

*4.2.3. 6-Bromo-1-methyl-3-(furan-2-yl)quinolin-4(1H)-one (**7c**).* R_f 0.75 (CH_2Cl_2/MeOH 95/5); mp 209–210 °C (MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 8.59 (d, J=2.0 Hz, 1H), 8.05 (s, 1H), 7.66 (dd, J_{ortho}=9.5 Hz, J_{meta}=2.6 Hz, 1H), 7.35 (d, J=3.5 Hz, 1H), 7.25–7.21 (m, 2H), 6.51–6.48 (m, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.2, 140.2, 139.5, 137.8, 134.6, 123.5, 127.6, 117.7, 117.3, 111.8, 109.2, 41.2; IR ($CHCl_3$): ν 1632 cm^{-1}; MS: m/z (M^++1) 305.

Table 5
Synthesis of trisubstituted quinolones **1h**–**o** by various Pd-catalyzed reactions



7a, **7f-i**, **7k** **1h-o**

Entry	Substrate	Product	Method	Yield[a] (%)
1	**7a**: R^1=Me, R^2=Ph	 **1h**	A[b]	56
2	**7f**: R^1 =  , R^2 = 4-Cl-Ph	 **1i**	B	30[c]
3	**7g**: R^1 = Me, R^2 = 	 **1j**	C	44
4	**7g**: R^1 = Me, R^2 = 	 **1k**	A	27
5	**7h**: R^1 = Me, R^2 = 	 **1l**	C[d]	55
6	**7i**: R^1 = Me, R^2 = 	 **1m**	D	30
7	**7i**: R^1 = Me, R^2 = 	 **1n**	A[e]	52
8	**7k**: R^1 = *n*-pentyl, R^2 = 	 **1o**	C[f]	81

Reagents and conditions: method A: appropriate alkyne, CuI, $Pd(PPh_3)_2Cl_2$, *i*-Pr_2NH, dioxane, MW, 150 °C, 30 min; method B: 4-methoxybenzylamine, $Pd(PPh_3)_2Cl_2$, CO (120 psi), DIPEA, THF, MW, 130 °C, 2×20 min; method C: boronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, DME/EtOH, MW, 80 °C, 5 min; method D: appropriate amine, $Pd(OAc)_2$, $Mo(CO)_6$, DBU, THF, MW, 150 °C, 5 min.

[a] Isolated yield based on substrates **7a**, **7f**–**i**, **7k**.
[b] Reaction performed under conventional heating (reflux, 24 h).
[c] Compound **7f** (53%) was recovered.
[d] Irradiation time: 10 min.
[e] Reaction performed at 120 °C for 5 min.
[f] Reaction performed at 150 °C for 10 min; see Ref. 12.

Anal. Calcd for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61; found: C, 55.00; H, 3.20; N, 4.77.

*4.2.4. 6-Bromo-3-[2-(4-methoxyphenyl)ethen-1-yl]-1-methylquinolin-4(1H)-one (**7d**).* R_f 0.83 (CH_2Cl_2/MeOH 99/1); mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J=4.0 Hz, 1H), 7.71–7.70 (m, 1H), 7.69 (s, 1H), 7.53 (d, J=16.0 Hz, 1H), 7.45 (d, J=8.0 Hz, 2H), 7.26 (m, 1H), 6.99 (d, J=16.0 Hz, 1H), 6.88 (d, J=8.0 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 159.3, 143.2, 141.8, 138.2, 134.8, 130.1, 129.5, 128.0, 119.6, 117.9, 117.5, 117.4, 114.3, 114.1, 55.5, 41.2, 40.9, 29.9; IR ($CHCl_3$): ν 1618 cm^{-1}; MS: m/z (M^++1) 371. Anal. Calcd for $C_{19}H_{16}BrNO_2$: C, 61.64; H, 4.36; N, 3.78; found: C, 61.98; H, 4.50; N, 3.51.

*4.2.5. 6-Bromo-1-ethyl-3-(4-methylphenyl)quinolin-4(1H)-one (**7e**).* R_f 0.75 (CH_2Cl_2/MeOH 95/5); mp 146–147 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J=2.4 Hz, 1H), 7.66 (dd, J_{ortho}=13.2 Hz, J_{meta}=2.5 Hz, 1H), 7.54 (d, J=7.9 Hz, 2H), 7.28 (d, J=9.0 Hz, 1H), 7.21 (d, J=7.8 Hz, 2H), 4.16 (q, J=7.3 Hz, 2H) 2.37 (s, 3H), 1.48 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 141.2, 137.6, 137.0, 134.7, 132.2, 130.3, 129.1, 128.8, 128.4, 122.6, 117.1, 117.0, 48.2, 21.2, 14.5; IR ($CHCl_3$): ν 1634 cm^{-1}; MS: m/z (M^++1) 343. Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09; found: C, 63.40; H, 4.55; N, 4.21.

*4.2.6. 6-Bromo-3-(4-chlorophenyl)-1-cyclopropylmethylquinolin-4(1H)-one (**7f**).* R_f 0.73 (AcOEt/hexanes 1/1); mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.75 (s, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.58 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 1H), 7.34 (d, J=8.0 Hz, 2H) 4.00 (d, J=4.0, 2H), 1.32 (m, 1H), 0.73 (m, 2H), 0.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 141.4, 138.2, 134.9, 133.7, 132.9, 130.1, 129.8, 129.1, 128.6, 128.4, 120.9, 117.5, 117.3, 57.4, 10.2, 4.5; IR ($CHCl_3$): ν 1622 cm^{-1}; MS: m/z (M^++1) 389. Anal. Calcd for $C_{19}H_{15}BrClNO$: C, 58.71; H, 3.89; N, 3.60; found: C, 58.42; H, 3.78; N, 3.79.

4.3. General procedure for the synthesis of 3,6-disubstituted quinolin-4(1*H*)-ones 1a–g, 1j, 1l and 1o by Suzuki–Miyaura cross-coupling reaction

The title compounds were prepared from **7a**–**e**, **7g**, **7h** and **7k** according to the same procedure described for the synthesis of compounds **7a**–**f**, by microwave irradiation at 80 °C for 5 min, unless otherwise reported below.

*4.3.1. 1-Methyl-3-phenyl-6-[(4-trifluoromethoxy)phenyl]quinolin-4(1H)-one (**1a**).* R_f 0.70 (CH_2Cl_2/MeOH 95/5); mp 200–201 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.75 (d, J=2.4 Hz, 1H), 7.87 (dd, J_{ortho}=8.8 Hz, J_{meta}=2.0 Hz, 1H) 7.72 (s, 2H), 7.67 (s, 1H), 7.63 (s, 2H), 7.47 (d, J=8.9 Hz, 1H), 7.43–7.29 (m, 5H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 149.1, 142.8, 139.7, 138.7, 135.5, 135.4, 130.9, 128.9, 128.7, 128.6, 127.7, 127.4, 125.8, 122.6, 121.6, 116.2, 112.5, 41.1; IR ($CHCl_3$): ν 1630 cm^{-1}; MS: m/z (M^++1) 396. Anal. Calcd for $C_{23}H_{16}F_3NO_2$: C, 69.87; H, 4.08; N, 3.54; found: C, 70.11; H, 4.00; N, 3.35.

*4.3.2. 1-Methyl-3-phenyl-6-(pyridin-3-yl)quinolin-4(1H)-one (**1b**).* R_f 0.38 (CH_2Cl_2/MeOH 95/5); mp 168–169 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.77 (d, J=1.8 Hz, 1H), 8.60 (s, 1H), 7.99 (d, J=7.9 Hz, 1H), 7.90 (dd, J_{ortho}=8.6 Hz, J_{meta}=2.2 Hz, 1H), 7.60 (s, 1H), 7.65 (d, J=7.2 Hz, 1H), 7.51 (d, J=8.8, 1H), 7.43–7.30 (m, 5H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 148.9, 148.4, 139.9, 135.4, 134.6, 133.4, 130.8, 128.9, 128.6, 127.9, 127.5, 126.0, 122.6, 116.5, 41.1; IR ($CHCl_3$): ν 1631 cm^{-1}; MS: m/z (M^++1) 313. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; found: C, 80.55; H, 5.25; N, 9.15.

*4.3.3. 6-(3-Chlorophenyl)-1-methyl-3-phenylquinolin-4(1H)-one (**1c**).* R_f 0.61 (CH_2Cl_2/MeOH 95/5); mp 210–211 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J=2.0 Hz, 1H), 7.84 (dd, J_{ortho}=9.0 Hz, J_{meta}=2.1 Hz, 1H), 7.70–7.65 (m, 4H), 7.56 (dd, J_{ortho}=7.6 Hz, J_{meta}=6.4 Hz, 1H), 7.44 (d, J=8.7 Hz, 1H), 7.41–7.28 (m, 5H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 142.8, 141.7, 139.8, 135.2, 135.1, 130.9, 130.4, 128.9, 128.6, 127.8, 127.6, 127.4, 125.8, 125.5, 122.5, 116.2, 41.1; IR ($CHCl_3$): ν 1630 cm^{-1}; MS: m/z (M^++1) 346. Anal. Calcd for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05; found: C, 76.18; H, 4.54; N, 4.21.

*4.3.4. 6-(4-Cyanophenyl)-1-methyl-3-(4-methylphenyl)quinolin-4(1H)-one (**1d**).* R_f 0.70 (CH_2Cl_2/MeOH 95/5); mp 257–258 °C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J=1.9 Hz, 1H), 7.92 (dd, J_{ortho}=8.8 Hz, J_{meta}=1.8 Hz, 1H), 7.81 (d, J=8.4, 2H), 7.74 (d, J=8.4 Hz, 2H), 7.74 (s, 1H), 7.58 (d, J=7.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 1H), 7.24 (d, J=7.8 Hz, 2H), 3.90 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 144.4, 142.6, 140.2, 137.3, 134.4, 133.0, 132.3, 130.7, 129.3, 128.7, 127.9, 127.6, 126.4, 122.9, 119.1, 116.4, 11.3, 41.1, 21.5; IR ($CHCl_3$): ν 2230, 1625 cm^{-1}; MS: m/z (M^++1) 351. Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99; found: C, 82.47; H, 5.02; N, 8.22.

*4.3.5. 6-(3-Chlorophenyl)-3-(furan-2-yl)-1-methylquinolin-4(1H)-one (**1e**).* R_f 0.85 (CH_2Cl_2/MeOH 98/2); mp 253–254 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.98 (s, 1H), 7.75 (d, J=8.5 Hz, 1H), 7.62 (s, 1H), 7.52 (d, J=7.2 Hz, 1H), 7.41–7.31 (m, 5H), 6.53 (s, 1H), 3.81(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 148.5, 141.2, 140.0, 139.4, 138.6, 134.8, 134.7, 130.2, 130.1, 127.6, 127.0, 126.5, 125.1, 124.7, 116.3, 113.0, 111.9, 109.0, 41.1; IR ($CHCl_3$): ν 1625 cm^{-1}; MS: m/z (M^++1) 336. Anal. Calcd for $C_{20}H_{14}ClNO_2$: C, 71.54; H, 4.20; N, 4.17; found: C, 71.86; H, 4.32; N, 4.01.

*4.3.6. 6-(3-Chlorophenyl)-3-[2-(4-methoxyphenyl)ethen-1-yl]-1-methylquinolin-4(1H)-one (**1f**).* R_f 0.53 (CH_2Cl_2/MeOH 99/1); mp 192–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (m, 1H), 7.84 (dd, J_{ortho}=8.0 Hz, J_{meta}=4.0 Hz, 1H), 7.71–7.69 (m, 2H), 7.60–7.56 (m, 2H), 7.48–7.30 (m, 5H), 7.04 (d, J=16.0 Hz, 1H), 6.89 (d, J=8.0 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 159.1, 141.5, 138.8, 134.9, 131.0, 130.2, 130.1, 128.0, 127.5, 127.1, 126.7, 125.2, 120.3, 119.1, 116.1, 114.1, 55.3, 40.9; IR ($CHCl_3$): ν 1630, 1608 cm^{-1}; MS: m/z (M^++1) 403. Anal. Calcd for $C_{25}H_{20}ClNO_2$: C, 74.71; H, 5.02; N, 3.49; found: C, 75.01; H, 5.11; N, 3.29.

*4.3.7. 6-(3-Chlorophenyl)-1-ethyl-3-(4-methylphenyl)quinolin-4(1H)-one (**1g**).* R_f 0.80 (CH_2Cl_2/MeOH 95/5); mp 137–138 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J=1.7 Hz, 1H), 7.87 (dd, J_{ortho}=8.9 Hz, J_{meta}=2.1 Hz, 1H), 7.71 (d, J=8.0 Hz, 2H), 7.60 (d, J=7.8 Hz, 41 2H), 7.52 (d, J=8.8 Hz, 1H), 7.42–7.33 (m, 3H), 7.24 (d, J=7.8 Hz, 2H) 4.26 (q, J=7.2 Hz, 2H), 2.39 (s, 3H), 1.55 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 138.5, 136.9, 134.9, 134.7, 132.5, 130.5, 130.2, 129.7, 129.0, 128.5, 127.8, 127.5, 127.2, 125.9, 125.2, 122.5, 115.7, 48.2, 21.2, 14.6; IR ($CHCl_3$): ν 1635 cm^{-1}; MS: m/z (M^++1) 374. Anal. Calcd for $C_{24}H_{20}ClNO$: C, 77.10; H, 5.39; N, 3.75; found: C, 77.40; H, 5.51; N, 3.48.

*4.3.8. 6-(4-Cyanophenyl)-1-methyl-3-(trimethylsilylethynyl)quinolin-4(1H)-one (**1j**).* R_f 0.36 (CH_2Cl_2/MeOH, 97/3); mp 230–231 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.86 (dd, J_{ortho}=9.0 Hz, J_{meta}=2.0 Hz, 4H), 7.72 (s, 1H), 7.47 (d, J=9.0 Hz, 1H), 7.24 (s, 1H), 3.83 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0,

147.4, 143.6, 139.4, 134.8, 132.6, 130.7, 127.5, 126.4, 125.4, 118.6, 116.5, 111.2, 106.7, 98.6, 98.3, 41.0, 29.6; IR ($CHCl_3$): ν 2240, 1630 cm^{-1}; MS: m/z (M^++1) 357. Anal. Calcd for $C_{22}H_{20}N_2OSi$: C, 74.12; H, 5.65; N, 7.86; found: C, 74.47; H, 5.55; N, 8.10.

*4.3.9. 6-(3-Chlorophenyl)-1-methyl-N-phenylquinolin-4(1H)-one-3-carboxamide (**1l**).* Irradiation time: 2×5 min. R_f 0.51 (CH_2Cl_2/MeOH 98/2); mp 243–244 °C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.20 (s, 1H), 8.85 (s, 1H), 8.71 (d, J=2.0 Hz, 1H), 7.97 (dd, J_{ortho}=8.8 Hz, J_{meta}=2.0 Hz, 1H), 7.79–7.68 (m, 3H), 7.60–7.50 (m, 2H), 7.45–7.31 (m, 4H), 7.14–7.07 (m, 1H), 3.99 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 176.9, 163.0, 148.8, 142.8, 141.0, 139.6, 138.9, 137.2, 135.3, 130.5, 129.5, 128.9, 128.1, 127.7, 125.6, 124.1, 120.6, 116.2, 112.5, 41.9; IR ($CHCl_3$): ν 1664, 1605 cm^{-1}; MS: m/z (M^++1) 389. Anal. Calcd for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41; N, 7.20; found: C, 71.34; H, 4.53; N, 6.87.

*4.3.10. N-(Adamantan-1-yl)-6-(furan-2-yl)-1-pentylquinolin-4(1H)-one-3-carboxamide (**1o**).* Prepared as described in Ref. 12.

4.4. General procedure for the synthesis of 7g, 8, 1h, 1k, 1n by Sonogashira coupling

A mixture of the appropriate substrate **2b**, **4b**, **7a**, **7g**, **7i** (0.2 mmol), CuI (8 mg, 0.04 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), diisopropylamine (7 mL, 50 mmol), the proper alkyne (phenylacetylene: 55 μL, 0.5 mmol; TMSA: 40 μL, 0.26 mmol), and 1,4-dioxane (5 mL) was heated by microwaves irradiation at 120 °C for 5 min (150 °C, 3×10 min for **1l**) or refluxed for 24 h (for **1i**). After cooling, the reaction mixture was diluted with dichloromethane and filtered through Celite. The organic layer was washed with 1 N HCl, then with brine, dried and concentrated to a residue, which was purified by flash chromatography [silica gel, 98/2 (v/v) dichloromethane/methanol] to give the title compound as a solid.

*4.4.1. 6-Bromo-1-methyl-3-(trimethylsilylethynyl)quinolin-4(1H)-one (**7g**).* R_f 0.84 (CH_2Cl_2/MeOH, 97/3); mp>300 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.55 (d, J=2.5 Hz, 1H), 7.81 (s, 1H), 7.73 (dd, J_{ortho}=8.5 Hz, J_{meta}=2.5 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 3.77 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 147.6, 138.0, 135.1, 129.1, 127.0, 118.2, 117.6, 106.2, 98.8, 98.2, 41.2, 0.2; IR ($CHCl_3$): ν 2150, 1635 cm^{-1}; MS: m/z (M^++1) 335. Anal. Calcd for $C_{15}H_{16}BrNOSi$: C, 53.89; H, 4.82; N, 4.19; found: C, 53.50; H, 4.70; N, 3.99.

*4.4.2. 6-Bromo-3-(trimethylsilylethynyl)quinolin-4(1H)-one (**8**).* R_f 0.60 (CH_2Cl_2/MeOH 9/1); mp 260–261 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.32 (s, 1H), 8.16 (d, J_{meta}=4.0 Hz, 1H), 7.82 (dd, J_{ortho}=8.0 Hz, J_{meta}=4.0 Hz, 1H), 7.55 (d, J_{ortho}=8.0 Hz, 1H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 222.2, 174.0, 144.1, 137.8, 134.6, 126.9, 126.2, 121.3, 116.6, 104.3, 101.1, 96.0; IR ($CHCl_3$): ν 2158, 1609 cm^{-1}; MS: m/z (M^++1) 321. Anal. Calcd for $C_{14}H_{14}BrNOSi$: C, 52.50; H, 4.41; N, 4.37; found: C, 52.81; H, 4.49; N, 4.22.

*4.4.3. 1-Methyl-3-phenyl-6-(phenylethynyl)quinolin-4(1H)-one (**1h**).* R_f 0.60 (CH_2Cl_2/MeOH 98/2); mp 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 2H), 7.55 (s, 1H), 7.49–7.48 (m, 2H), 7.36–7.23 (m, 7H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 142.6, 139.4, 135.2, 134.6, 131.7, 130.9, 128.6, 128.4, 128.3, 127.2, 123.1, 122.5, 118.8, 115.5, 90.1, 88.7, 40.8; IR ($CHCl_3$): ν 2145, 1631 cm^{-1}; MS: m/z (M^++1) 336. Anal. Calcd for $C_{24}H_{17}NO$: C, 85.94; H, 5.11; N, 4.18; found: C, 85.55; H, 5.02; N, 3.89.

*4.4.4. 1-Methyl-6-(phenylethynyl)-3-(trimethylsilylethynyl)quinolin-4(1H)-one (**1k**).* R_f 0.62 (CH_2Cl_2/MeOH, 98/2); mp 210–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, J=1.9 Hz, 1H), 7.73 (s, 1H), 7.68 (dd, J_{ortho}=8.7 Hz, J_{meta}=6.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.35–7.30 (m, 3H), 7.25 (d, J=3, 1H), 3.75 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 147.3, 138.7, 134.8, 131.5, 130.2, 128.4, 128.3, 125.8, 122.7, 119.4, 115.7, 106.5, 98.7, 98.0, 90.4, 88.2, 40.9, 29.6; IR ($CHCl_3$): ν 2149, 1637 cm^{-1}; MS: m/z (M^++1) 356. Anal. Calcd for $C_{23}H_{21}NOSi$: C, 77.71; H, 5.95; N, 3.94; found: C, 78.08; H, 6.10; N, 3.66.

*4.4.5. N-(Adamantan-1-yl)-1-methyl-6-(trimethylsilylethynyl)quinolin-4(1H)-one-3-carboxamide (**1n**).* R_f 0.71 (CH_2Cl_2/MeOH 98/2); mp 298–299 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.68 (s, 1H), 8.59 (m, 1H), 7.77–7.73 (m, 1H), 7.39 (d, J=8.8 Hz, 1H), 3.89 (s, 3H), 2.15–2.09 (m, 9H), 1.77–1.71 (m, 6H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 165.3, 148.8, 143.6, 139.4, 135.4, 131.3, 121.2, 115.8, 109.2, 63.7, 51.7, 41.8, 36.6, 29.7, 29.6, 29.4, 12.9; IR ($CHCl_3$): ν 1660 cm^{-1}; MS: m/z (M^++1) 432. Anal. Calcd for $C_{26}H_{32}N_2O_2Si$: C, 72.18; H, 7.46; N, 6.48; found: C, 72.37; H, 7.55; N, 6.26.

4.5. Synthesis of 7h, 7i, 7k and 1m by aminocarbonylation Reaction using $Mo(CO)_6$

A microwave vial was charged with the appropriate substrate **4b**, **4e**, **7i** (0.5 mmol), $Pd(OAc)_2$ (12.3 mg, 0.05 mmol), $Mo(CO)_6$ (67 mg, 0.25 mmol), DBU (224 μL, 1.5 mmol), the appropriate amine (0.75 mmol), dry THF (5 mL) and subjected to microwave irradiation at the temperature and for the time reported below. The reaction mixture was filtered through Celite and evaporated. The residue was taken up into dichloromethane, washed with brine and dried. Removal of the solvent left a residue, which was purified by flash chromatography on silica gel to provide the title compounds.

*4.5.1. 6-Bromo-1-methyl-N-phenylquinolin-4(1H)-one-3-carboxamide (**7h**).* R_f 0.33 (AcOEt/EP 2/1); mp 224–225 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.10 (s, 1H), 8.80 (s, 1H), 8.65 (d, J=2.0 Hz, 1H), 7.83 (dd, J_{ortho}=8.4 Hz, J_{meta}=2.0 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.41–7.30 (m, 4H), 7.13–7.05 (m, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 177.3, 163.0, 148.8, 144.0, 142.9, 138.6, 136.1, 129.9, 128.9, 128.0, 123.9, 120.4, 117.8, 41.7; IR ($CHCl_3$): ν 1665 cm^{-1}; MS: m/z (M^++1) 358. Anal. Calcd for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; N, 7.84; found: C, 57.46; H, 3.80; N, 7.50.

*4.5.2. N-(Adamantan-1-yl)-6-bromo-1-methylquinolin-4(1H)-one-3-carboxamide (**7i**).* R_f 0.30 (CH_2Cl_2/MeOH 97/3); mp 191–192 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.87 (s, 1H), 8.77 (s, 1H), 8.64 (d, J=3.7 Hz, 1H), 7.76–7.63 (m, 1H), 7.3 (d, J=11.2 Hz, 1H), 3.93 (s, 3H), 2.90–2.18 (m, 9H), 1.78–1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 163.1, 148.3, 138.6, 135.7, 134.7, 129.8, 119.1, 117.7, 113.5, 46.1, 42.6, 41.8, 41.6, 41.5, 37.2, 36.5, 36.4, 30.0, 29.5, 29.4; IR (Nujol): ν 1661, 1634 cm^{-1}; MS: m/z (M^++1) 416. Anal. Calcd for $C_{21}H_{23}BrN_2O_2$: C, 60.73; H, 5.58; N, 6.74; found: C, 61.06; H, 5.68; N, 6.51.

*4.5.3. N-(Adamantan-1-yl)-6-bromo-1-pentylquinolin-4(1H)-one-3-carboxamide (**7k**).* R_f 0.64 (AcOEt/hexanes 1/1); mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.71 (s, 1H), 8.63 (d, J=2.0 Hz, 1H), 7.77 (dd, J_{ortho}=8.9 Hz, J_{meta}=2.1 Hz, 1H), 7.37 (d, J=8.9 Hz, 1H), 4.18 (t, J=7.4 Hz, 2H), 2.2–2.1 (m, 9H), 1.9–1.8 (m, 2H), 1.7–1.6 (m, 6H), 1.32–1.35 (m, 2H), 1.23 (t, J=6.9 Hz, 2H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 158.9, 144.1, 143.1, 138.3, 134.2, 129.3, 116.2, 112.0, 111.8, 46.2, 41.2, 37.8, 36.8, 29.7, 28.1, 27.8, 26.1, 22.5, 14.1; IR ($CHCl_3$): ν 1660, 1632 cm^{-1}; MS: m/z (M^++1) 472.

Anal. Calcd for $C_{25}H_{31}BrN_2O_2$: C, 63.69; H, 6.63; N, 5.94; found: C, 63.46; H, 6.50; N, 5.65.

*4.5.4. N^3-(Adamantan-1-yl)-1-methyl-N^6-phenylquinolin-4(1H)-one-3,6-dicarboxamide (**1m**).* R_f 0.54 (CH_2Cl_2/MeOH 98/2); mp 172–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.72 (s, 2H), 8.52–8.48 (m, 1H), 7.77–7.69 (m, 1H), 7.52–7.45 (m, 5H), 5.27 (s, 1H), 3.91 (s, 3H), 2.15–1.88 (m, 9H), 1.77–1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 169.3, 163.6, 148.1, 144.0, 139.9, 136.0, 132.8, 128.9, 127.8, 127.2, 125.1, 124.1, 122.5, 119.9, 115.8, 113.0, 51.9, 51.7, 41.8, 41.6, 41.4, 36.6, 36.4, 29.7, 29.6, 29.4, 24.7; IR ($CHCl_3$): ν 1659, 1638 cm^{-1}; MS: m/z (M^++1) 456. Anal. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22; found: C, 74.13; H, 6.30; N, 8.91.

4.6. Synthesis of 6-bromo-1-ethyl-3-[(morpholin-4-yl) carbonyl]-quinolin-4(1*H*)-one (7j)

A microwave vial was charged with **4c** (18.9 mg, 0.05 mmol), morpholine (4.6 μL, 0.05 mmol), DBU (23 μL, 0.15 mmol), DMF (100 μL) and 10% Pd/C (1 mg, 0.001 mmol). The reaction mixture was irradiated with microwaves at 100 °C under a CO pressure of 130 psi for 2×5 min. After cooling, the mixture was diluted with ethyl acetate, filtered on Celite and washed with 1 N HCl, then with brine. Removal of solvents gave a residue, which was purified by chromatography on silica gel (CH_2Cl_2/MeOH 94/6) to yield **7j** as a clear oil (7 mg, 30%). R_f 0.53 (CH_2Cl_2/MeOH 93/7); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.57 (d, J=2.3 Hz, 1H), 8.03 (s, 1H), 7.75 (dd, J_{ortho}=9.0 Hz, J_{meta}=2.3 Hz, 1H), 7.33 (d, J=8.9 Hz, 1H), 4.25–4.11 (m, 2H), 3.76 (s, 8H), 1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 165.9, 146.1, 137.9, 135.8, 130.5, 129.4, 118.9, 118.5, 117.9, 67.5, 67.0, 49.0, 48.3, 43.3, 14.7; IR ($CHCl_3$): ν 1631, 1620 cm^{-1}; MS: m/z (M^++1) 366. Anal. Calcd for $C_{16}H_{17}BrN_2O_3$: C, 52.62; H, 4.69; N, 7.67; found: C, 52.92; H, 4.59; N, 7.79.

4.7. Synthesis of 3-(4-chlorophenyl)-1-cyclopropylmethyl-*N*-(4-methoxybenzyl)quinolin-4(1*H*)-one-6-carboxamide (1i)

A microwave vial was charged with **7f** (19.4 mg, 0.05 mmol), 4-methoxybenzylamine (6.6 μL, 0.05 mmol), DIPEA (26 μL, 0.15 mmol), dry THF (200 μL) and $Pd(PPh_3)_2Cl_2$ (1.78 mg, 0.0025 mmol). The reaction mixture was irradiated with microwaves at 130 °C under a CO pressure of 120 psi for 2×20 min. After cooling, the mixture was diluted with ethyl acetate, filtered on Celite and washed with 1 N HCl, then with brine. Removal of solvents gave a residue, which was chromatographed on silica gel (CH_2Cl_2/MeOH 98/2) to give 10.3 mg (53%) of the starting material **7f** and subsequently 7.1 mg (30%) of the title compound **1i** as a colourless oil. R_f 0.30 (CH_2Cl_2/MeOH 98/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J=2.0 Hz, 1H), 8.27 (dd, J_{ortho}=8.0 Hz, J_{meta}=2.0 Hz, 1H), 7.73 (s, 1H), 7.57–7.52 (m, 3H), 7.32 (d, J=8.0 Hz, 2H), 7.23–7.19 (m, 2H), 6.80–6.78 (m, 2H), 4.52 (d, J=4.0 Hz, 2H), 4.01 (d, J=4.0 Hz, 2H), 3.73 (s, 3H), 1.31–1.28 (m, 1H), 0.71–0.67 (m, 2H), 0.41–0.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 166.1, 159.3, 141.9, 141.4, 133.7, 132.3, 130.1, 129.7, 129.6, 128.8, 126.6, 125.3, 116.2, 114.4, 57.8, 55.6, 44.0, 29.9, 10.5, 4.8; IR ($CHCl_3$): ν 1629, 1610 cm^{-1}; MS: m/z (M^++1) 474. Anal. Calcd for $C_{28}H_{25}ClN_2O_3$: C, 71.10; H, 5.33; N, 5.92; found: C, 71.41; H, 5.23; N, 5.70.

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Supplementary data

Synthetic procedures and spectroscopic data for compounds **2**–**4**, and elemental analyses data for all new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.05.134.

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