JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

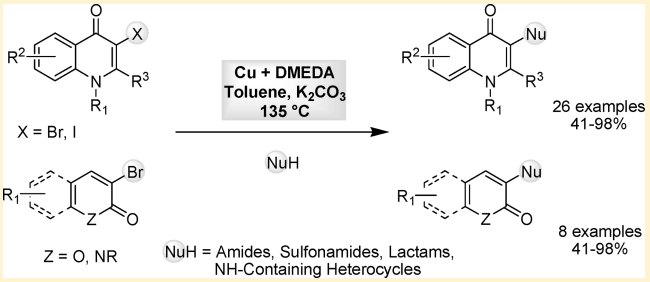
A General Copper Powder-Catalyzed Ullmann-Type Reaction of 3-Halo-4(1*H*)-quinolones With Various Nitrogen-Containing Nucleophiles

Davide Audisio, Samir Messaoudi,* Jean-François Peyrat, Jean-Daniel Brion, and Mouâd Alami*

1Univ Paris-Sud, 2CNRS, BioCIS UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 5 rue J.-B. Clément, Châtenay-Malabry, F-92296, France

Supporting Information

ABSTRACT: 3-(*N*-Substituted) 4(1*H*)-quinolinones were synthesized using the copper-catalyzed Ullmann C−N bond forming strategy in moderate to quantitative yields. Starting from 3-halo-4(1*H*)-quinolones, various nucleophiles including amides, lactams, sulfonamides and NH-containing azoles have been used successfully. In all cases, the reactions take place rapidly in toluene and proceed by using copper powder as a catalyst, DMEDA as a ligand and K_2CO_3 as a base. In addition, other related heterocycles such as 3-bromoquinolin-2(1*H*)-ones, 3-bromocoumarin, and 3,5-dibromo-2-pyridone show good to very high reactivity with various nucleophiles under our Cu/DMEDA catalyst system.



1. INTRODUCTION

3-Substituted 4(1*H*)-quinolinones represent an important class of heteroaromatic compounds, which have attracted a lot of attention because of their pharmacological properties.[1] In addition, these heterocyclic structures are common scaffolds found in various natural products.[2] One of the most important subfamilies of 4(1*H*)-quinolinones is 3-aminoquinolin-4(1*H*)-ones, whose derivatives show promising biological activities, including cannabinoid type 2 receptor agonists[3] and hepatite C antivirals.[4] While these derivatives clearly hold great potential in organic synthesis, a careful examination of the literature reveals lack methods for their preparation. Most routes to prepare 3-aminoquinolin-4(1*H*)-ones involve from 4(1*H*)-quinolinone-3-carboxylic acid derivatives a Curtius reaction using diphenylphosphorylazide followed by further *N*-functionalization,[3] or the sequential nitro-decarboxylation/reduction processes.[5] Alternative route consists on the cyclization of a suitable phenacyl anthranilamide in the presence of (poly)phosphoric acid under extremely harsh conditions.[6] All these multistep procedures, however, are often moderate to low yielding, difficult to handle for large-scale operations, the variety of substrates is narrow, and thus finds limited application in library synthesis. Therefore, the search for new selective, and simple procedures, as well as diversity oriented reactions such as metal-catalyzed couplings, presents an interesting challenge.

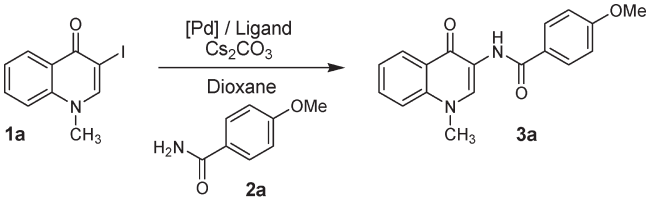
In an ongoing medicinal chemistry program[7] directed toward hsp90, an exciting new target in cancer drug discovery,[8] we reported the synthesis of 3-(*N*-substituted)-quinolin-2(1*H*)-ones and coumarins based on the metal-catalyzed C−N bond coupling reaction of 3-bromoquinolin-2(1*H*)-ones and 3-bromocoumarins[9] with various nitrogen nucleophiles,[10] including amines, amides, sulfonamides, carbamates, ureas, and azide anion. As part of our continuing effort at the construction of heterocycles via transition metal-catalyzed reactions, combined with our interest in discovering new hsp90 inhibitors,[11] we decided to explore the ability of the 3-haloquinolin-4(1*H*)-ones to participate in metal-catalyzed C−N cross-coupling reactions with various nitrogen nucleophiles. From a synthetic viewpoint, this coupling should be the shortest and most efficient route to 3-(*N*-substituted)-quinolin-4(1*H*)-ones for the purpose of medicinal chemistry screening programs. To the best of our knowledge, there is no report describing the formation of 3-(*N*-substitued)-quinolin-4(1*H*)-ones using this idea.

Initial studies focused on the palladium-catalyzed coupling of 3-iodoquinolinone **1a** with 4-methoxybenzamide **2a** under our previous conditions ($Pd(OAc)_2$/Xantphos, Cs_2CO_3, dioxane, 100 °C).[10a] However, this transformation was inefficient to provide **3a**, and all our attempts to react **1a** with **2a** using various combinations of palladium/ligand/base mixtures resulted, unfortunately, in unsatisfactory results (data not shown). The highest yield was achieved by using $Pd(OH)_2/C$ as the catalyst, and Xantphos as the ligand in dioxane at 140 °C. Under these conditions, the targeted 3-carboxamide-4-quinolinone **3a** was formed in a moderate 49% yield (Scheme 1).

Difficulties in obtaining 4-quinolinones **3a** in good yield under palladium-catalysis led us to explore alterantive procedures. We felt that the copper-based protocols may be readily extended to the

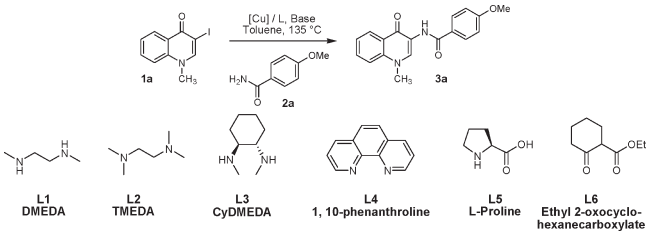
Received: April 1, 2011
Published: April 27, 2011

Scheme 1. Palladium-Catalyzed Amidation of 3-Iodo-4-quinolinone 1a



[Pd]	Isolated yield (%)
$Pd(OAc)_2$/Xantphos, 100 °C	<5
$Pd(OH)_2$/C/Xantphos, 140 °C	49

Table 1. Optimization Coupling Reaction of 1a with Amide 2a under Various Conditions[a]



entry	[Cu]	ligand	base	conv[b] (%)	yield[c] (%)
1	Cu	DMEDA	Na_2CO_3	21	nd
2	Cu	DMEDA	K_3PO_4	24	nd
3	Cu	DMEDA	Et_3N	15	nd
4	Cu	DMEDA	Cs_2CO_3	100	87
5	**Cu**	**DMEDA**	**K_2CO_3**	**100**	**96[d]**
6	Cu	L2	K_2CO_3	10	nd
7	Cu	L3	K_2CO_3	100	90
8	Cu	L4	K_2CO_3	28	nd
9	Cu	L5	K_2CO_3	21	nd
10	Cu	L6	K_2CO_3	10	nd
11	$CuSO_4$	DMEDA	K_2CO_3	100	94
12	CuI	DMEDA	K_2CO_3	100	94
13	CuBr	DMEDA	K_2CO_3	100	93
14	CuTC	DMEDA	K_2CO_3	100	91

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), [Cu] (10 mol %), ligand (20 mol %), base (1.5 equiv) in toluene were heated in a sealed Schlenk tube at 135 °C. [b] Conversion was determined by ^{1}H NMR on the crude reaction mixture and is based on remaining **1a**. [c] Isolated yields of **3a**. [d] For control experiments, no conversion at all was observed in the absence of ligand or Cu(0) and in the absence of Cu(0) and ligand.

synthesis of 3-carboxamide-4-quinolinone derivatives **3**. Recently, copper has emerged as a promising alternative as a catalyst for direct C−N bond forming reactions due to their low cost, toxicity, and offer attractive industrial possibilities in terms of sustainable chemistry.[12] Herein, we report on a copper catalyst system and reaction conditions that allow, for the first time, the cross-coupling of *N*-containing nitrogen nucleophile with 3-haloquinolin-4(1*H*)-ones. The reaction proceeds rapidly under relatively mild conditions providing direct access to various 3-(*N*-substituted)-quinolin-4(1*H*)-ones in good to excellent yields.

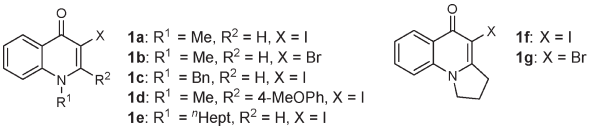


Figure 1. 3-Halo-4-quinolinones **1** used in this study.

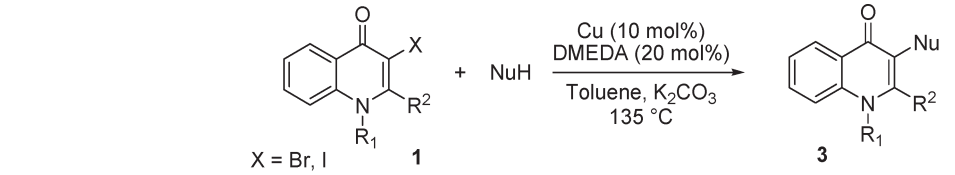
2. RESULTS AND DISCUSSION

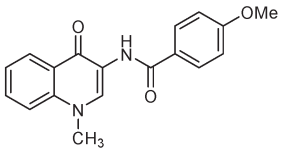
Very recently, we have developed the copper(0) powder catalyzed C(sp^2)-NH_2 bond formation to provides 3-aminoquinolin-2(1*H*)-one and 3-aminocoumarins as well as anilines.[10c] Thus, it was a natural extension for us to use initially this air-stable and inexpensive Cu(0) powder for preparing 3-carboxamide-4-quinolinone **3a** through the coupling of **1a** (1 mmol) with **2a** (1.2 mmol) as a model reaction. As summarized in Table 1, we found in this study that the nature of the base and the ligand were crucial to the outcome of the coupling. For the optimization process, we first screened a variety of bases (1.5 equiv) using Cu(0) powder (10 mol %) as the catalyst, and *N*,*N*′-dimethylethylenediamine (DMEDA, 20 mol %) as the ligand in toluene at 135 °C. It was observed that the reaction was dramatically facilitated when using K_2CO_3 or Cs_2CO_3, as the bases, thus providing the desired 4-quinolinone **3a** in excellent yields (87−96%, entries 4 and 5). Other bases such as Na_2CO_3, K_3PO_4, and Et_3N were less effective (entries 1−3). We then examined a variety of ligands. Changing DMEDA to the (±)-*trans*-cyclohexane-1,2-diamine-based ligand **L3** also led to total conversion although the yield of **3a** was slightly lower (entry 7). The use of other ligands such as TMEDA, 1,10-phenanthroline, L-proline or ethyl 2-oxocyclohexanecarboxylate, however, induced a lowering of the conversion rate (entries 6 and 8−10). It is interesting to note that in the coupling of **1a** with **2a**, the source of copper used has no influence on the reaction rate, since $CuSO_4$, CuI, CuBr and CuTC (entries 11−14) gave similar results than that of Cu(0) powder (entry 5). In summary, the best conditions were found to require **1a** (1 equiv), **2a** (1.2 equiv), Cu powder (10 mol %), DMEDA (20 mol %), K_2CO_3 (1.5 equiv), toluene in a sealed tube at 135 °C for 1 h (entry 5).

With a viable coupling procedure in hand, attention was turned to the generality of the process, and the couplings of structurally diverse nucleophiles with some 3-halo-4-quinolinones **1**[13] were studied (Figure 1).

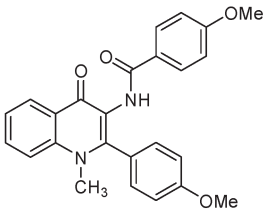
Results summarized in Table 2, show that the optimized conditions described above proved to be general for the coupling with a large variety of nucleophiles. The coupling was found to be compatible with primary substituted (hetero)aromatic and aliphatic amides providing the corresponding coupling products **3a**−**l** in good to excellent yields. Interestingly, product **3d** revealed an excellent chemical selectivity at benzamide over aniline, which could enjoy further metal-catalyzed fuctionalization processes. Although the yield of **3d** was moderate, no compounds resulting from the coupling at the aniline, neither the disubstitued product have been isolated. One can note that compound **3i** which was obtained in a 83% yield, may be regarded as an analogue of DH4TCNA,[11b] a potent hsp90 inhibitor. The reaction was also effective with cyclic amides[14] providing the corresponding lactames *N*−containing quinolinones **3m** and **3n** in excellent 89% and 97% yields, respectively. Finally, C−N bond forming reaction was also studied with the less nucleophilic alkyl- or arylsulfonamides. These substrates were found to be suitable nucleophiles for the coupling reaction, although a longer reaction time were required to obtain total conversion, and in most cases, satisfactory yields of coupling products **3o,p** were obtained.

Table 2. Copper-Catalyzed Amidation of 4-Haloquinolinones 1: Synthesis of Functionalized 3-(*N*-Substitued) aminoquinolinones 3.[a]

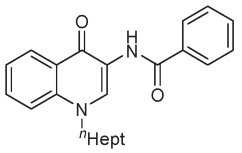




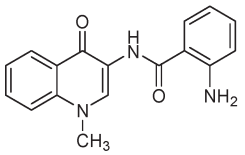
3a, 96%[b] (X = I, 1 h)
83%[b] (X = Br, 1 h)



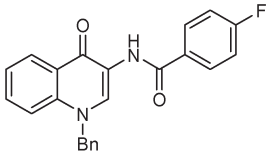
3b, 65%[b, c] (X = I, 5 h)



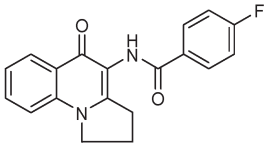
3c, 88%[b] (X = I, 1 h)



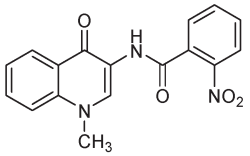
3d, 41%[b] (X = I, 14 h)



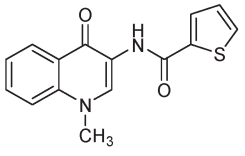
3e, 98%[b] (X = I, 1 h)



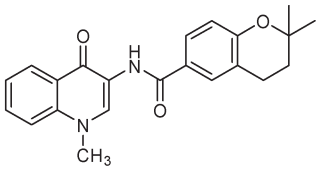
3f, 96%[b] (X = I, 3 h)



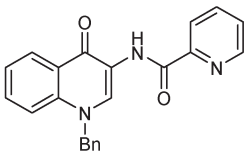
3g, 64%[b] (X = I, 16 h)



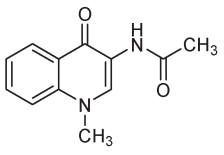
3h, 90%[b] (X = I, 1 h)



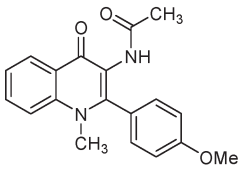
3i, 83%[b] (X = I, 5 h)



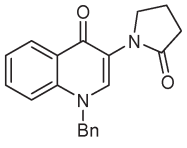
3j, 75%[b] (X = I, 10 h)



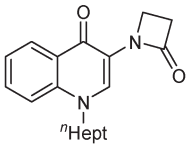
3k, 94%[b] (X = I, 1 h)



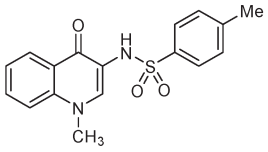
3l, 56%[b] (X = I, 7 h)



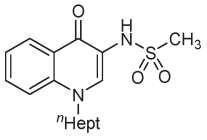
3m, 89%[b] (X = I, 1 h)



3n, 97%[b] (X = I, 1 h)



3o, 53%[b] (X = I, 48 h)



3p, 65%[b] (X = I, 60 h)

[a] Reactions of **1** (1.0 mmol) with amide/lactam/sulfonamide (1.2 mmol) were performed in a sealed Schlenk tube at 135 °C in toluene (2 mL) by using Cu (10 mol %), DMEDA (20 mol %) and K_2CO_3 (1.5 mmol). [b] Isolated yields. [c] A 10% yield of the dehalogenated quinolinone was isolated.

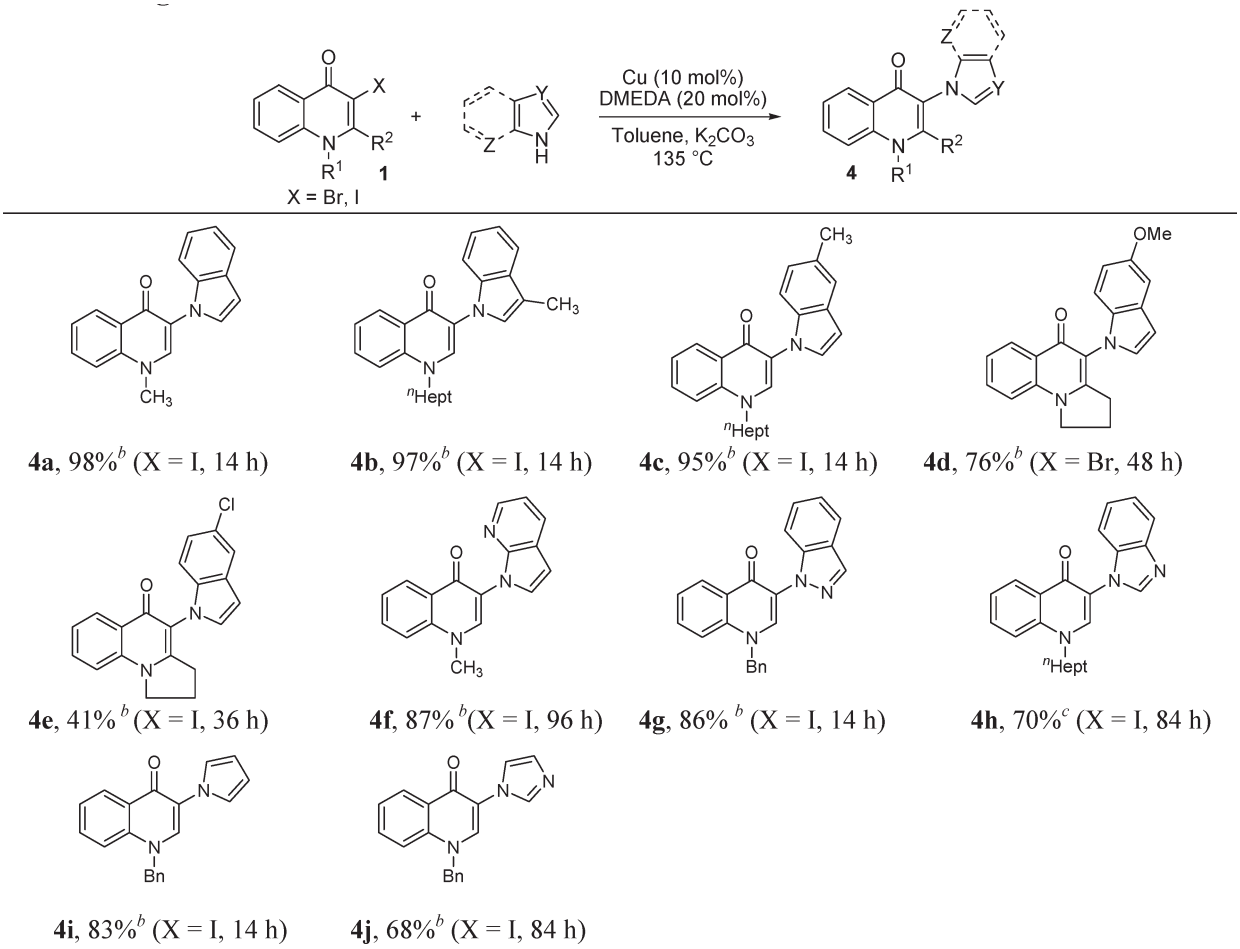
The development of chemistry that could emanate from a single method for each of the major classes of nitrogen nucleophiles has been seriously inhibited so far. In an endeavor to expand the scope of the methodology, we found that our new catalytic system was also suitable for π-electron-rich nitrogen-containing heterocycles (e.g., indoles, pyrroles, azaindoles, indazoles, imidazoles...; Table 3) despite the fact that the reaction require longer time to total completion.

Several interesting features are apparent from the results in Table 3. The reaction works well with electron-neutral, electron-rich and electron-deficient indoles to give the corresponding products in satisfactory to excellent yields (**4a**−**e**). Additionally, it was found that chlorine atom at C-5 position of the indole was tolerated, yielding **4e**, which may be useful for further metal-catalyzed fuctionalization processes.[15] As with indole, other nitrogen-containing heterocycles, including 7-azaindole, pyrrole, benzimidazole and imidazoles were tolerated under the reaction conditions providing **4f**, **4i**, **4h** and **4j** in good yields. Extending this chemistry to include indazoles as substrates proved to be quite successful. Thus, the reaction of iodoquinolinone **1c** with indazole was readily accomplished, and excellent regioselectivity for the *N*-1 arylation product **4g** was observed.[16]

Motivated by these results, we then examined under our optimized conditions the efficiency of our catalytic system on the coupling of various nitrogen nucleophiles with other electrophilic coupling partners, such as 3-bromoquinolin-2(1*H*)-ones **5a**−**c**, 3-bromocoumarin **5d**, and 3,5-dibromo-2-pyridone **5e** (Figure 2). As summarized in Table 4, these electrophilic substrates **5** efficiently undergo the coupling reaction with various nucleophiles under the catalytic system Cu/DMEDA, providing the corresponding *N*-coupling products in yield ranging from 41 to 98%. The representative examples depicted in Table 4 clearly demonstrated the generality of this reaction.

dx.doi.org/10.1021/jo200680j |*J. Org. Chem.* 2011, 76, 4995–5005

Table 3. Copper-Catalyzed C−N Coupling of 4-Haloquinolinones 1 with NH-Containing Azoles[a]



[a] Reactions of **1** (1.0 mmol) with NH-containing azoles (1.2 mmol) were performed in a sealed Schlenk tube at 135 °C in toluene (2 mL) by using Cu (10 mol %), DMEDA (20 mol %) and K_2CO_3 (1.5 mmol). [b] Isolated yields. [c] Yield calculated by NMR.

In addition, under our optimal conditions, the reaction selectivity was investigated with substrates **5c** and **5e** containing two carbon−bromine bonds. The amination proceeded at the more activated C-3 position and yielded the monoaminated products **6d**−**g** in satisfactory yields (42−68%), despite the fact that the reaction conditions had never been optimized. One can note that compound **6d** which was obtained in a 65% yield may be regarded as an analogue of 6BrCaQ, a potent hsp90 inhibitor recently identified in our laboratory.[11j] Finally, a comparative study with 3-bromocoumarin **5d** gave a slight reduction in yield of **6h** (41%) in comparaison to the result obtained by palladium catalysis, as we previously reported.[10a]

3. CONCLUSION

In conclusion, we have demonstrated that the catalytic system used allows the first general C−N bond forming reaction between 3-haloquinolin-4(1*H*)-ones and various nucleophiles including amides, lactams, sulphonamides and *N*-containing heterocycles. For the first time, the C−N bond was formed directly by using the inexpensive copper powder as the catalyst, DMEDA as the ligand and toluene as the solvent. Consequently, various 3-(*N*-substituted) 4(1*H*)-quinolinones were prepared in good to excellent yields. In addition, expanding the scope of the method to other related

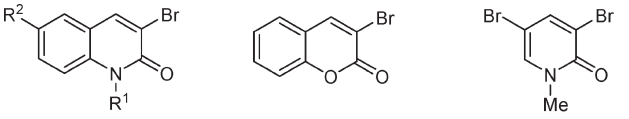


Figure 2. Other electrophilic coupling partners **5a**−**e** used in this study.

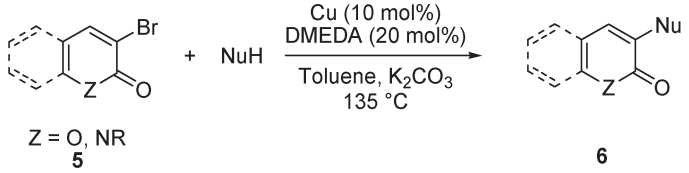
heterocycles was demonstrated by coupling diverses 3-bromoquinolin-2(1*H*)-ones, 3-bromocoumarin and 3,5-dibromo-2-pyridone with various nucleophiles under our Cu/DMEDA catalyst system. Owing to their practical advantages and low environmental impact, we believe that the reaction described here could be an attractive alternative for the preparation of potentially bioactive compounds.

4. EXPERIMENTAL SECTION

General. The compounds were all identified by usual physical methods, that is, ^{1}H NMR, ^{13}C NMR, IR, elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a 300 MHz spectrometer. ^{1}H chemical shifts are reported in ppm from an internal

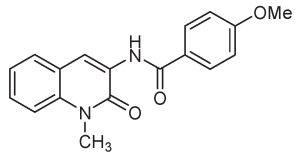
dx.doi.org/10.1021/jo200680j |*J. Org. Chem.* 2011, 76, 4995–5005

Table 4. Copper-Catalyzed *N*-Functionalization of Other Heterocyclic Halides 5[a]

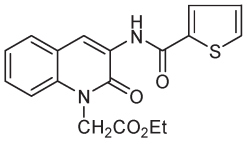


Z = O, NR
5

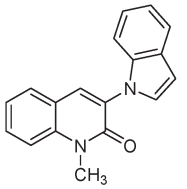
6



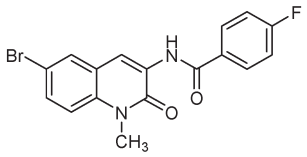
6a, 98%[b] (2 h)



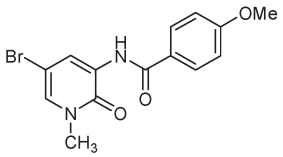
6b, 74%[b] (12 h)



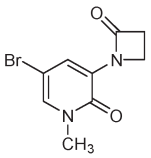
6c, 54%[b] (12 h)



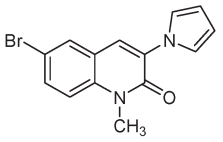
6d, 65%[b] (3 h)



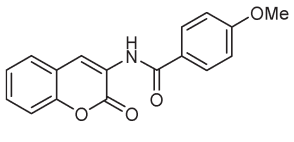
6e, 68%[b,c] (3 h)



6f, 57%[b] (12 h)



6g, 42%[b] (18 h)



6h, 41%[b] (1.5 h)

[a] Reactions of **1** (1.0 mmol) with amide/lactam/azole (1.2 mmol) were performed in a sealed Schlenk tube at 135 °C in toluene (2 mL) by using Cu (10 mol %), DMEDA (20 mol %) and K_2CO_3 (1.5 mmol). [b] Isolated yields.

standard TMS or of residual chloroform (7.27 ppm). The following abreviation are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet), td (triplet of doublet). ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.14).

Materials. Unless otherwise noted, reagents were commercially avialble and were used without purification. R_f values refer to TLC on 0.25 mm silica gel plates (60-F254, Merck KGaA). Flash chromatography was performed on silica gel 60 (0.040−0.063 mm, Merck KGaA). IR spectra were acquired on a FT-IR and are reported in wave numbers (cm-1). Elemental analyses were performed with a Perkin-Elmer 240 analyzer. Melting points (m.p.) were determined on a capillary melting point apparatus and were uncorrected.

Starting Materials Synthesis. *3-Iodo-1-methylquinolin-4(1H)-one (**1a**).* To a suspension of 3-iodoquinolin-4(1*H*)-one[13c,d] (3 g, 11.1 mmol, 1.0 equiv) in dry THF (50 mL) was added NaH (670 mg of a 65% oil dispersion, 16.6 mmol, 1.5 equiv) under argon atmosphere. After 30 min, methyl iodide (700 μL, 16.6 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for 1.5 h at room temperature, before being quenched with saturated NaCl aqueous solution and the aqueous layer extracted with DCM (5 times) and EtOAc (2 times). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1a** as a light-yellow solid.

Yield 75%, light-yellow solid, mp 196−198 °C, R_f = 0.50 (CH_2Cl_2/MeOH 95:5). IR 3025, 1578, 1545, 1494, 1467, 1430, 1363, 1261, 1166, 1146, 1118, 1079, 1038, 956, 830, 784, 753, 689, 621 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.40 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 8.02 (s, 1H), 7.67 (td, 1H, J_1 = 8.5 Hz, J_2 = 1.6 Hz), 7.42−7.34 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 174.0, 148.3, 140.0, 132.3, 127.6, 124.6, 123.4, 115.4, 80.7, 40.7. MS (ESI^+) *m*/*z*: 286.0 $(M + H)^+$. Anal. Calcd for $C_{10}H_8INO$ (284.97): C 42.13, H 2.83, N 4.91; found: C 42.17, H 2.88, N 4.99.

*3-Bromo-1-methylquinolin-4(1H)-one (**1b**).* To a suspension of 3-bromoquinolin-4(1*H*)-one (0.8 g, 3.6 mmol, 1.0 equiv) in dry THF (15 mL) was added NaH (128 mg of a 65% oil dispersion, 5.36 mmol, 1.5 equiv) in one portion, under argon atmosphere. After 30 min, dimethyl sulfate (508 μL, 5.36 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for 4 h at room temperature, before being quenched with saturated NaCl aqueous solution and the aqueous layer extracted with DCM (5 times). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1b**.

Yield 84%, beige solid, mp 234−236 °C, R_f = 0.54 (CH_2Cl_2/MeOH: 95/5). IR 3029, 1582, 1548, 1498, 1470, 1364, 1263, 1170, 1150, 1121, 1082, 1039, 957, 843, 785, 754, 691, 619, 584, 573 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.48 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.1 Hz), 7.93 (s, 1H), 7.69 (td, 1H, J_1 = 8.6 Hz, J_2 = 1.6 Hz), 7.42 (td, 1H, J_1 = 8.1 Hz, J_2 = 0.9 Hz), 7.40 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 170.8, 145.1, 139.7, 132.1, 125.8, 124.7, 124.2, 116.9, 103.3, 40.0. MS ($APCI^+$) *m*/*z*: 238.0 ($[M + H]^+$, ^{79}Br), 240.0 ($[M + H]^+$, ^{81}Br). Anal. Calcd for $C_{10}H_8BrNO$ (236.98): C 50.45, H 3.39, N 5.88; found: C 50.48, H 3.41, N 5.90.

*1-Benzyl-3-iodoquinolin-4(1H)-one (**1c**).* To a suspension of 3-iodoquinolin-4(1*H*)-one[13c] (1.8 g, 6.64 mmol, 1.0 equiv) in dry THF (25 mL) was added NaH (400 mg of a 65% oil dispersion, 9.96 mmol, 1.5 equiv) under argon atmosphere. After 30 min, benzyl bromide (1.6 mL, 13.3 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 12 h at room temperature, before being quenched with saturated NaCl aqueous solution and the aqueous layer extracted with DCM (5 times) and EtOAc (2 times). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1c**.

Yield 72%, white solid, mp 203−205 °C, R_f = 0.65 (CH_2Cl_2/MeOH: 95/5). IR 1615, 1592, 1541, 1484, 1369, 1267, 1228, 831, 758, 739, 688, 620, 590, 572, 560 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.46 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 8.18 (s, 1H), 7.54 (td, 1H, J_1 = 8.6 Hz, J_2 = 1.6 Hz), 7.38−7.28 (m, 5H), 7.15−7.12 (m, 2H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 174.1, 148.1, 139.6, 134.6, 132.3, 129.3 (2C), 128.5, 127.9, 126.0 (2C), 124.6, 123.9, 116.1, 81.5, 56.5. MS ($APCI^+$) *m*/*z*: 362.0 $[M + H]^+$. Anal. Calcd for $C_{16}H_{12}INO$ (361): C 53.21, H 3.35, N 3.88; found: C 53.21, H 3.35, N 3.88.

dx.doi.org/10.1021/jo200680j |*J. Org. Chem.* 2011, 76, 4995–5005

*3-Iodo-2-(4-methoxyphenyl)-1-methylquinolin-4(1H)-one (**1d**).* To a suspension of 3-iodo-2-(4-methoxyphenyl)quinolin-4(1*H*)-one[17,18] (1.12 g, 3.07 mmol, 1.0 equiv) in dry THF was added NaH (184 mg of a 65% oil dispersion, 4.60 mmol, 1.5 equiv) in one portion, under argon atmosphere. After 30 min, methyl iodide (300 μL, 4.60 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred for 2 h at room temperature, before being quenched with saturated NaCl and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1d**.

Yield 91%, brown solid, mp 189−191 °C, R_f = 0.63 (*c*-hexane/AcOEt: 2/8). IR 2923, 1614, 1591, 1502, 1459, 1391, 1288, 1245, 1178, 1150, 1109, 1077, 1028, 853, 824, 787, 766, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.41 (dd, 1H, H_5, J_1 = 8.0 Hz, J_2 = 0.8 Hz), 7.61 (t, 1H, H_7, J = 8.4 Hz), 7.46 (d, 1H, H_8, J = 8.6 Hz), 7.32 (t, 1H, H_6, J = 7.5 Hz), 7.14 (d, 2H, H_{13}, J = 8.6 Hz), 7.02 (d, 2H, H_{14}, J = 8.6 Hz), 3.84 (s, 3H, H_{16}), 3.54 (s, 3H, H_{11}). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 173.8, 160.2, 155.1, 140.5, 132.3, 131.5, 129.5 (2C), 127.3, 124.1, 122.6 (C_{10}), 115.7, 114.3 (2C), 89.7, 55.2, 39.1. MS (APCI$^+$) *m*/*z*: 392.0 $[M + H]^+$. Anal. Calcd for $C_{17}H_{14}INO_2$ (391.01): C 52.19, H 3.61, N 3.58; found: C 52.23, H 3.65, N 3.62.

*1-Heptyl-3-iodoquinoléin-4(1H)-one (**1e**).* To a suspension of 3-iodoquinolin-4(1*H*)-one (1 g, 3.69 mmol, 1.0 equiv) in dry THF (20 mL) was added NaH (440 mg of a 65% oil dispersion, 11.0 mmol, 3.0 equiv) under argon atmosphere. After 30 min, 7-iodoheptane (3.0 μL, 18.4 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred for 24 h at room temperature, before being quenched with saturated NaCl aqueous solution and the aqueous layer extracted with DCM (3 times). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1e**.

Yield 82%, brown solid, mp 83−85 °C, R_f = 0.65 (CH_2Cl_2/MeOH: 95/5). IR 3031, 2915, 2857, 1613, 1585, 1543, 1487, 1469, 1414, 1384, 1366, 1262, 1234, 1192, 1170, 1138, 1082, 1052, 947, 829, 803, 756, 728, 688, 626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.47 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 8.06 (s, 1H), 7.66 (td, 1H, J_1 = 8.8 Hz, J_2 = 1.7 Hz), 7.41−7.36 (m, 2H), 4.10 (t, 2H, J = 7.5 Hz), 1.85 (q, 2H, J = 7.5 Hz), 1.44−1.20 (m, 8H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.9, 147.6, 139.1, 132.1, 128.0, 124.4, 123.9, 115.3, 80.9, 53.4, 31.5, 29.0, 28.7, 26.6, 22.5, 14.0. MS (APCI$^+$) *m*/*z*: 370.0 $[M + H]^+$. Anal. Calcd for C_9H_5INO (269.94): C 40.03, H 1.87, N 5.19; found: C 40.10, H 2.02, N 5.23.

*4-Iodo-2,3-dihydropyrrolo[1,2-a]quinolin-5(1H)-one (**1f**).* To a suspension of 2,3-dihydropyrrolo[1,2-a]quinolin-5(1*H*)-one[13c,d] (0.2 g, 1.08 mmol, 1.0 equiv) in dry THF at room temperature were added I_2 (550 mg, 2.16 mmol, 2.0 equiv) and Na_2CO_3 (175 mg, 1.62 mmol, 1.5 equiv). The reaction mixture was stirred for 2 h at room temperature, before being quenched with saturated $Na_2S_2O_3$ aqueous solution and the aqueous layer was extracted with EtOAc (2 times) and DCM (5 times). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product **1f**.

Yield 77%, beige solid, mp 215−217 °C, R_f = 0.70 (CH_2Cl_2/MeOH: 95/5). IR 1614, 1590, 1536, 1498, 1420, 1252, 1157, 1078, 970, 766, 687 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.22 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.48 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.1 Hz, J_3 = 1.6 Hz), 7.24−7.18 (m, 1H), 7.09 (d, 1H, J = 8.4 Hz), 4.27 (t, 2H, J = 7.6 Hz), 3.10 (t, 2H, J = 7.6 Hz), 2.27 (q, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 174.0, 157.1, 137.8, 132.0, 127.4, 124.0, 122.1, 115.2, 78.6, 52.3, 38.1, 20.1. MS (APCI$^+$) *m*/*z*: 312.0 $[M + H]^+$. Anal. Calcd for $C_{12}H_{10}INO$ (310.98): C 46.33, H 3.24, N 4.50; found: C 46.36, H 3.29, N 4.52.

*4-Bromo-2,3-dihydropyrrolo[1,2-a]quinoléin-5(1H)-one (**1g**).* To a suspension of 2,3-dihydropyrrolo[1,2-a]quinolin-5(1*H*)-one, (400 mg, 2.16 mmol, 1.0 equiv) in dry THF at room temperature was added MPHT[19] (1.9 g, 4.3 mmol, 2.0 equiv). The reaction mixture was stirred for 2 h at 80 °C, before being quenched with saturated $Na_2S_2O_3$ aqueous solution. The mixture was left 12 h at r.t. and the solid formed was filtered and washed with *c*-hexane to yield the desired product **1g** as a white solid (460 mg, 1.74 mmol, 81%).

Yield 81%, white solid, mp 207−209 °C, R_f = 0.30 (CH_2Cl_2/MeOH: 95/5). IR 1616, 1572, 1541, 1503, 1468, 1422, 1257, 1162, 1081, 973, 812, 768, 689, 619 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.41 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.4 Hz), 7.61 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.1, J_3 = 1.5 Hz), 7.37−7.32 (m, 1H), 7.25 (d, 1H, J = 8.3 Hz), 4.37 (t, 2H, J = 7.5 Hz), 3.28 (t, 2H, J = 7.9 Hz), 2.41 (q, 2H, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 172.4, 154.2, 137.5, 131.9, 127.3, 124.3, 123.9, 115.4, 101.8, 51.9, 34.3, 20.4. MS (ES$^+$) *m*/*z*: 286.0 ($[M + Na]^+$, ^{79}Br), 288.0 ($[M + Na]^+$, ^{81}Br). Anal. Calcd for $C_{12}H_{10}BrNO$ (262.99): C 54.57, H 3.82, N 5.30; found: C 54.61, H 3.85, N 5.33.

General Procedure for Cu-Catalyzed Couplings of 3-Haloquinolones with Various Nucleophiles: Amides, Lactams, Sulfonamides, NH-Containing Azoles. A flame-dried resealable Schlenk tube was charged with Cu powder (10 mol %) the solid reactant(s) (1.0 mmol of the haloquinolone, 1.2 mmol of the amide/lactam/sulfonamide/azole) and K_2CO_3 (1.5 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. DMEDA (20 mol %), the liquid reactant(s) and toluene (2 mL) were added through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 135 °C for the indicated time. The resulting suspension was cooled to room temperature and filtred through Celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

*4-Methoxy-N-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl) benzamide (**3a**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 1 h according to the general procedure to obtain **3a** (104 mg, 0.34 mmol).

Yield 96%, white solid, mp 158−160 °C, R_f = 0.25 (CH_2Cl_2/AcOEt: 8/2). IR 1633, 1585, 1543, 1493, 1474, 1401, 1309, 1246, 1177, 1116, 1024, 890, 857, 746, 697, 623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.34 (s, 1H), 9.18 (s, 1H), 8.51 (d, 1H, J = 8.1 Hz), 7.93 (d, 2H, J = 8.4 Hz), 7.69 (t, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 8.7 Hz), 7.40 (t, 1H, J = 7.5 Hz), 6.98 (d, 2H, J = 8.4 Hz), 3.91 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.1, 164.9, 162.5, 138.6, 132.4, 131.9, 129.0 (2C), 126.7, 126.4, 123.7, 123.1, 122.6, 115.3, 113.9 (2C), 55.4, 41.2. MS (APCI$^+$) *m*/*z*: 309.0 $[M + H]^+$. Anal. Calcd.for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.83; H, 5.38; N, 8.87. Anal. Calcd for $C_{18}H_{16}N_2O_3$ (308.12): C 70.12, H 5.23, N 9.09; found: C 70.17, H 5.27, N 9.11.

*4-Methoxy-N-(2-(4-methoxyphényl)-1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzamide (**3b**).* The reaction was carried out with **1d** (100 mg, 0.26 mmol) for 5 h according to the general procedure to obtain **3b** (69 mg, 0.17 mmol):

Yield 65%, ochre solid, mp 190−192, °C, R_f = 0.10 (CH_2Cl_2/AcOEt: 5/5). IR 1670, 1592, 1491, 1289, 1248, 1175, 1025, 841, 761, 687 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.46 (d, 1H, J = 8.0 Hz), 8.12 (bs, 1H), 7.67−7.7.61 (m, 3H), 7.47−7.35 (m, 4H), 6.93 (d, 2H, J = 8.5 Hz), 6.69 (d, 2H, J = 8.6 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 174.1, 166.5, 161.8, 160.0, 152.6, 140.8, 132.1, 130.3 (2C), 129.2 (2C), 126.7, 126.0, 125.5, 123.5, 119.0, 116.0, 113.8 (2C), 113.2 (2C), 55.2 (2C), 37.5, one carbon is missed. MS (APCI$^+$) *m*/*z*: 415.0 $[M + H]^+$. Anal. Calcd for $C_{25}H_{22}N_2O_4$ (414.16): C 72.45, H 5.35, N 6.76; found: C 72.49, H 5.38, N 6.77.

*N-(1-Heptyl-4-oxo-1,4-dihydroquinolin-3-yl)benzamide (**3c**).* The reaction was carried out with **1e** (100 mg, 0.27 mmol) for 1 h according to the general procedure to obtain **3c** (87 mg, 0.24 mmol):

Yield 88%, beige solid, mp 107−109 °C, R_f = 0.47 (CH_2Cl_2/AcOEt: 8/2). IR 3362, 2928, 1659, 1630, 1571, 1538, 1472, 1412, 1394, 1321, 1223, 1136,

1057, 924, 901, 793, 749, 708, 696, 623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.40 (s, 1H), 9.30 (s, 1H), 8.54 (d, 1H, J = 8.1 Hz), 7.98 (d, 2H, J = 8.1 Hz), 7.68 (t, 1H, J = 8.4 Hz), 7.58−7.47 (m, 4H), 7.39 (t, 1H, J = 7.5 Hz), 4.23 (t, 2H, J = 7.6 Hz), 2.00−1.87 (m, 2H), 1.47−1.23 (m, 8H) 0.88 (t, 3H, J = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.0, 165.4, 137.9, 134.2, 132.0, 131.9, 131.8, 128.7 (2C), 127.2 (2C), 127.1, 124.1, 123.0, 122.5, 115.4, 54.0, 31.6, 29.1, 28.8, 26.7, 22.5, 14.0. MS ($APCI^+$) m/z: 363.0 $[M + H]^+$. Anal. Calcd for $C_{23}H_{26}N_2O_2$ (362.2) C 76.21, H 7.23, N 7.73; found: C 76.25, H 7.27, N 7.79.

*2-Amino-N-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzamide (**3d**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 14 h according to the general procedure to obtain **3d** (42 mg, 0.14 mmol):

Yield 41%, white solid, mp 155−157 °C, R_f = 0.33 (CH_2Cl_2/AcOEt: 8/2). IR 1610, 1574, 1536, 1473, 1401, 1317, 1225, 1155, 1120, 901, 755, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.24 (s, 1H), 9.10 (bs, 1H), 8.50 (d, 1H, J = 7.8 Hz), 7.70−7.64 (m, 2H), 7.46−7.37 (m, 2H), 7.28−7.23 (m, 1H), 6.75−6.71 (m, 2H) 5.35 (bs, 2H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.2, 167.4, 149.0, 138.6, 132.7, 132.1, 131.9, 127.7, 126.6, 123.7, 123.1, 122.6, 117.4, 116.9, 115.4, 115,3, 41.2. MS ($APCI^+$) m/z: 294.0 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.12) C 69.61, H 5.15, N 14.33; found: C 69.65, H 5.18, N 14.35.

*N-(1-Benzyl-4-oxo-1,4-dihydroquinolin-3-yl)-4-fluorobenzamide (**3e**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 1 h according to the general procedure to obtain **3e** (101 mg, 0.27 mmol):

Yield 98%, violet solid, mp 230−232 °C, R_f = 0.59 (CH_2Cl_2/AcOEt: 9/1). IR 1660, 1573, 1542, 1479, 1411, 1313, 1214, 1157, 906, 848, 762, 739, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.52 (s, 1H), 9.27 (s, 1H), 8.53 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.1 Hz), 8.00 (dd, 2H, J_1 = 8.8 Hz, J_2 = 5.2 Hz), 7.58 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz), 7.43−7.16 (m, 9H), 5.47 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.4, 165.0 (d, 1C, J_{C-F} = 252.6 Hz), 164.3, 138.4, 135.1, 132.5, 132.1, 130.4 (d, 1C, J_{C-F} = 2.6 Hz), 129.6, 129.5, 129.2 (2C), 128.3, 126.9, 126.0 (2C), 124.1, 123.3, 122.6, 116.2, 116.0, 115.7, 57.3. MS (ESI^+) m/z: 373.0 $[M + H]^+$. Anal. Calcd for $C_{23}H_{17}FN_2O_2$ (372.13) C 74.18, H 4.60, N 7.52; found: C 74.23, H 4.63, N 7.53.

*4-Fluoro-N-(5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-a]quinolin-4-yl)benzamide (**3f**).* The reaction was carried out with **1f** (100 mg, 0.32 mmol) for 3 h according to the general procedure to obtain **3f** (99 mg, 0.31 mmol):

Yield 96%, yellow solid, mp 189−191 220−222 °C, R_f = 0.10 (CH_2Cl_2/AcOEt: 6/4). IR 1657, 1579, 1487, 1293, 1226, 1159, 849, 758, 694, 619 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.69 (s, 1H), 8.35 (d, 1H, J = 8.0 Hz), 7.95 (dd, 2H, J_1 = 8.4 Hz, J_2 = 5.5 Hz), 7.60 (t, 1H, J = 7.7 Hz), 7.32−7.26 (m, 2H), 6.96 (t, 2H, J = 8.5 Hz), 4.25 (t, 2H, J = 7.4 Hz), 3.28 (t, 2H, J = 7.8 Hz), 2.29 (p, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 173.3, 164.7, 164.6 (d, J_{C-F} = 251.8 Hz), 151.8, 137.5, 131.7, 130.1 (d, 2C, J_{C-F} = 9.1 Hz), 130.0, 126.7, 125.0, 123.2, 116.0, 115.5, 115.1 (d, 2C, J_{C-F} = 21.8 Hz), 51.1, 31.7, 21.0. MS ($APCI^+$) m/z: 323.0 $[M + H]^+$. Anal. Calcd for $C_{19}H_{15}FN_2O_2$ (322.11) C 70.80, H 4.69, N 8.69; found: C 70.85, H 4.73, N 8.72.

*N-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)-2-nitrobenzamide (**3g**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 16 h according to the general procedure to obtain **3g** (73 mg, 0.23 mmol):

Yield 64%, yellow solid, mp 148−150 °C °C, R_f = 0.20 (CH_2Cl_2/AcOEt: 8/2). IR 3316, 1689, 1658, 1567, 1525, 1496, 1347, 1323, 1117, 856, 760, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.25 (s, 1H), 9.10 (s, 1H), 8.39 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 8.1 Hz), 7.73−7.65 (m, 3H), 7.55−7.46 (m, 2H), 7.38 (t, 1H, J = 7.4 Hz), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 169.9, 164.3, 146.7, 138.9, 133.6, 133.2, 132.3 (2C), 130.8, 128.6, 126.8, 124.6, 124.1, 123.4, 122.1, 115.4, 41.3. MS ($APCI^+$) m/z: 324.0 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}N_3O_4$ (323.09) C 63.16, H 4.05, N 13.00; found: C 63.18, H 4.09, N 13.02.

*N-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)thiophene-2-carboxamide (**3h**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 1 h according to the general procedure to obtain **3h** (88 mg, 0.31 mmol):

Yield 90%, white solid, mp 215−217 °C, R_f = 0.47 (CH_2Cl_2/AcOEt: 8/2). IR 3279, 1642, 1620, 1565, 1543, 1492, 1474, 1419, 1397, 1316, 1259, 1229, 1163, 1123, 1044, 938, 855, 800, 754, 740, 727, 699, 674. cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.28 (s, 1H), 9.13 (bs, 1H), 8.51 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.73−7.68 (m, 2H), 7.55 (dd, 1H, J_1 = 5.0 Hz, J_2 = 1.0 Hz), 7.48 (d, 1H, J = 8.7 Hz), 7.42 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.1 Hz, J_3 = 0.8 Hz), 7.14 (dd, 1H, J_1 = 4.9 Hz, J_2 = 3.8 Hz), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 169.8, 160.1, 139.0, 138.7, 132.7, 132.1, 130.9, 128.5, 127.9, 126.8, 123.8, 123.4, 122.2, 115.4, 41.3. MS ($APCI^+$) m/z: 285.0 $[M + H]^+$. Anal. Calcd for $C_{15}H_{12}N_2O_2S$ (284.06) C 63.36, H 4.25, N 9.85; found: 63.38, H 4.28, N 9.86.

*2,2-Dimethyl-N-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)chroman-6-carboxamide (**3i**).* The reaction was carried out with **1a** (50 mg, 0.17 mmol) for 5 h according to the general procedure to obtain **3i** (53 mg, 0.14 mmol):

Yield 83%, light solid, mp 188−190 °C, R_f = 0.37 (CH_2Cl_2/AcOEt: 8/2). IR 1653, 1630, 1567, 1536, 1490, 1473, 1403, 1313, 1257, 1155, 1122, 946, 879, 833, 754, 700, 644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.29 (s, 1H), 9.12 (s, 1H), 8.48 (d, 1H, J = 7.4 Hz), 7.71−7.61 (m, 3H), 7.42 (d, 1H, J = 8.7 Hz), 7.36 (t, 1H, J = 7.6 Hz), 6.84 (d, 1H, J = 8.9 Hz), 3.87 (s, 3H), 2.83 (t, 2H, J = 6.7 Hz), 1.82 (t, 2H, J = 6.7 Hz), 1.34 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.0, 165.1, 157.4, 138.6, 132.2, 131.8, 128.9, 126.6 (2C), 125.3, 123.6, 123.0, 122.7, 120.9, 117.4, 115.3, 75.2, 41.1, 32.4, 26.8 (2C), 22.3. MS ($APCI^+$) m/z: 363.1 $[M + H]^+$. Anal. Calcd for $C_{22}H_{22}N_2O_3$ (362.16) C 72.91, H 6.12, N 7.73; found: C 72.95, H 6.17, N 7.80.

*N-(1-Benzyl-4-oxo-1,4-dihydroquinolin-3-yl)picolinamide (**3j**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 10 h according to the general procedure to obtain **3j** (74 mg, 0.21 mmol):

Yield 75%, white solid, mp 218−220 °C, R_f = 0.20 (CH_2Cl_2/AcOEt: 9/1). IR 1660, 1628, 1582, 1539, 1492, 1413, 1323, 1212, 997, 745, 687, 621, 595, 545 cm^{-1}.: ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 11.01 (s, 1H), 9.55 (s, 1H), 8.70 (ddd, 1H, J_1 = 4.7 Hz, J_2 = 1.6 Hz, J_3 = 0.9 Hz), 8.57 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.4 Hz), 8.20 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.87 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.54 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 6.9 Hz, J_3 = 1.6 Hz), 7.46 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 4.8 Hz, J_3 = 1.2 Hz), 7.40−7.28 (m, 5H), 7.19−7.17 (m, 2H), 5.45 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.5, 162.6, 149.7, 148.6, 138.4, 137.3, 135.2, 132.8, 132.0, 129.1 (2C), 128.2, 127.1, 126.2, 126.0 (2C), 124.6, 123.2, 122.3, 121.8, 116,1, 57.2. MS ($APCI^+$) m/z: 356.0 $[M + H]^+$. Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.13) C 74.35, H 4.82, N 11.82; found: C 74.38, H 4.86, N 11.84.

*N-(1-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)acetamide (**3k**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 1 h according to the general procedure to obtain **3k** (71 mg, 0.33 mmol):

Yield 94%, beige solid, mp 219−221 °C, R_f = 0.20 (CH_2Cl_2/MeOH: 95/5). IR 3278, 1673, 1626, 1567, 1543, 1494, 1471, 1403, 1372, 1323, 1249, 1221, 1163, 1118, 1049, 911, 793, 743, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.15 (s, 1H), 8.49−8.46 (m, 2H), 7.68 (t, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 8.7 Hz), 7.38 (t, 1H, J = 7.5 Hz), 3.87 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 169.8, 168.8, 138.7, 132.5, 131.9, 126.8, 124.0, 123.1, 122.5, 115.3, 41.1, 24.3. MS ($APCI^+$) m/z: 217.0 $[M + H]^+$. Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.09) C 66.65, H 5.59, N 12.96; found: C 66.67, H 5.60, N 12.96.

*N-(2-(4-Methoxyphenyl)-1-methyl-4-oxo-1,4-dihydroquinolin-3-yl) acetamide (**3l**).* The reaction was carried out with **1d** (100 mg, 0.26 mmol) for 7 h according to the general procedure to obtain **3l** (46 mg, 0.14 mmol):

Yield 56%, brown solid, mp 231−233 °C, R_f = 0.20 (CH_2Cl_2/MeOH: 9/1). IR 3234, 1685, 1589, 1569, 1494, 1471, 1431, 1365,

1290, 1246, 1172, 1113, 1030, 926, 872, 842, 823, 761, 723, 643 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.46 (d, 1H, J = 7.6 Hz), 7.82 (s, 1H), 7.64 (t, 1H J = 7.4 Hz), 7.46 (d, 1H J = 8.5 Hz), 7.38 (t, 1H, J = 7.1 Hz), 7.33 (d, 2H, J = 8.3 Hz), 6.99 (d, 2H, J = 8.3 Hz), 3.85 (s, 3H), 3.50 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.2, 170.1, 160.1, 153.0, 140.9, 132.2, 130.1 (2C), 126.7, 126.2, 125.5, 123.6, 118.7, 116.0, 113.8 (2C), 55.3, 37.5, 22.9. MS (APCI$^+$) m/z: 323.0 $[M + H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.13) C 70.79, H 5.63, N 8.69; found: C 70.83, H 5.67, N 8.72.

*1-Benzyl-3-(2-oxopyrrolidin-1-yl)quinolin-4(1H)-one (**3m**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 1 h according to the general procedure to obtain **3m** (79 mg, 0.25 mmol):

Yield 89%, white solid, mp 259−261 °C, R_f = 0.25 (CH_2Cl_2/MeOH: 95/5). IR 1685, 1593, 1491, 1411, 1371, 1325, 1222, 766, 748, 702, 652, 622 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.10 (s, 1H), 7.54 (ddd, 1H, J_1 = 8.8 Hz, J_2 = 7.1 Hz, J_3 = 1.6 Hz), 7.37−7.30 (m, 5H), 7.19 (d, 2H, J = 8.1 Hz), 5.36 (s, 2H), 4.05 (t, 2H, J = 7.1 Hz), 2.55 (t, 2H, J = 8.1 Hz), 2.19 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 175.6, 173.5, 142.5, 139.0, 134.8, 132.1, 129.2 (2C), 128.3, 127.6, 127.1, 126.2 (2C), 123.8, 119.9, 116.1, 56.9, 48.7, 31.1, 18.6. MS (APCI$^+$) m/z: 319 $[M + H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (318.14) C 75.45, H 5.70, N 8.80; found: C 75.47, H 5.72, N 8.81.

*1-Heptyl-3-(2-oxoazetidin-1-yl)quinolin-4(1H)-one (**3n**).* The reaction was carried out with **1e** (100 mg, 0.27 mmol) for 1 h according to the general procedure to obtain **3n** (83 mg, 0.26 mmol):

Yield 97%, white solid, mp 95−97 °C, R_f = 0.10 (CH_2Cl_2/AcOEt: 9/1). IR 2925, 2859, 1735, 1621, 1581, 1547, 1497, 1466, 1430, 1392, 1365, 1314, 1223, 1173, 1039, 899, 845, 803, 756, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.50 (s, 1H), 8.42 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.61 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz), 7.40 (d, 1H, J = 8.6 Hz), 7.31 (ddd, 1H, J_1 = 7.9 Hz, J_2 = 7.1 Hz, J_3 = 0.8 Hz), 4.15 (t, 2H, J = 4.4 Hz), 4.09 (t, 2H, J = 7.5 Hz), 3.10 (t, 2H, J = 4.4 Hz), 1.87−1.77 (m, 2H), 1.34−1.25 (m, 8H), 0.84 (t, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 171.0, 166.1, 137.8, 134.5, 131.7, 126.8 (2C), 123.1, 120.6, 115.3, 53.5, 42.4, 38.4, 31.5, 28.9, 28.7, 26.5, 22.4, 13.9. MS (APCI$^+$) m/z: 313.0 $[M + H]^+$. Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.18) C 73.05, H 7.74, N 8.97; found: C 73.08, H 7.77, N 8.99.

*4-Methyl-N-(1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzenesulfonamide (**3o**).* The reaction was carried out with **1a** (100 mg, 0.35 mmol) for 48 h according to the general procedure to obtain **3o** (61 mg, 0.18 mmol):

Yield 53%, white solid, mp 260−262 °C, R_f = 0.17 (CH_2Cl_2/AcOEt: 8/2). IR 1715, 1627, 1580, 1447, 1389, 1306, 1196, 1155, 1116, 1091, 993, 816, 768, 718, 673, 617, 581, 568, 552. cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.33 (d, 1H, J = 8.2 Hz), 8.15 (s, 1H), 7.71−7.66 (m, 3H) 7.46−7.35 (m, 3H), 7.17 (d, 2H, J = 7.8 Hz), 3.89 (s, 3H) 2.31 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 170.9, 142.5, 140.9, 139.2, 137.6, 131.9, 129.0 (2C), 126.7 (2C), 125.5, 125.2, 123.4, 117.7, 116.7, 40.3, 20.8. MS (APCI$^+$) m/z: 329.0 $[M + H]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_3S$ (328.09) C 62.18, H 4.91, N 8.53; found: C 62.19, H 4.94, N 8.54.

*N-(1-Heptyl-4-oxo-1,4-dihydroquinolin-3-yl)methanesulfonamide (**3p**).* The reaction was carried out with **1e** (100 mg, 0.27 mmol) for 60 h according to the general procedure to obtain **3p** (60 mg, 0.18 mmol, 65%) as a brown solid:

Yield 65%, brown solid, mp 143−145 °C, R_f = 0.15 (CH_2Cl_2/AcOEt: 8/2). IR 2920, 2851, 1621, 1580, 1545, 1498, 1449, 1406, 1323, 1281, 1225, 1151, 996, 799, 758, 706, 650, 615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.48 (d, 1H, J = 8.1 Hz), 8.05 (s, 1H), 7.71 (t, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 8.7 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.29 (bs, 1H), 4.19 (t, 2H, J = 7.4 Hz), 2.92 (s, 3H), 1.89−1.85 (m, 2H), 1.36−1.23 (m, 8H), 0.85 (t, 3H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 172.0, 138.6, 138.2, 132.4, 127.1, 125.7, 123.9, 119.1, 115.6, 53.8, 39.0, 31.5, 28.9, 28.7, 26.5, 22.4, 13.9. MS (APCI$^+$) m/z: 337.0 $[M + H]^+$. Anal. Calcd for $C_{17}H_{24}N_2O_3S$ (336.15) C 60.69, H 7.19, N 8.33; found: C 60.71, H 7.22, N 8.35.

*3-(1H-Indol-1-yl)-1-méthylquinolin-4(1H)-one (**4a**).* The reaction was carried out with **1a** (50 mg, 0.17 mmol) for 14 h according to the general procedure to obtain **4a** (47 mg, 0.17 mmol):

Yield 98%, yellow solid, mp 166−168 °C, R_f = 0.52 (CH_2Cl_2/AcOEt: 8/2). IR 1585, 1555, 1509, 1453, 1364, 1305, 1268, 1238, 1213, 1122, 1066, 945, 837, 735, 699, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.3 Hz), 7.77 (s, 1H), 7.77−7.70 (m, 1H), 7.63−7.60 (m, 1H), 7.46−7.41 (m, 2H), 7.23−7.18 (m, 2H), 7.10−7.07 (m, 2H), 6.60 (d, 1H, J = 3.0 Hz), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.2, 141.7, 139.8, 137.0, 132.4, 129.3, 128.5, 127.4, 127.3, 124.1, 121.8, 121.1, 120.7, 119.8, 115.5, 110.3, 102.7, 40.6. MS (APCI$^+$) m/z: 275.0 $[M + H]^+$. Anal. Calcd for $C_{18}H_{14}N_2O$ (274.11) C 78.81, H 5.14, N 10.21; found: C 78.83, H 5.19, N 10.22.

*1-Heptyl-3-(3-methyl-1H-indol-1-yl)quinolin-4(1H)-one (**4b**).* The reaction was carried out with **1e** (100 mg, 0.27 mmol) for 14 h according to the general procedure to obtain **4b** (98 mg, 0.26 mmol):

Yield 97%, beige solid, mp 108−110 °C, R_f = 0.80 (CH_2Cl_2/AcOEt: 9/1). IR 2927, 1591, 1555, 1494, 1455, 1396, 1230, 914, 765, 742, 705, 654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.56 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.4 Hz), 7.82 (s, 1H), 7.70 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 = 1.4 Hz), 7.60−7.56 (m, 1H), 7.49 (d, 1H, J = 8.6 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.22−7.09 (m, 4H), 4.06 (t, 2H, J = 7.2 Hz), 2.36 (s, 3H), 1.88−1.83 (m, 2H), 1.36−1.31 (m, 8H), 0.91 (t, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 173.1, 140.7, 138.7, 137.1, 132.1, 129.0, 127.6, 127.5, 126.8, 123.7, 121.7, 121.1, 119.1, 118.8, 115.4, 111.6, 109.9, 53.2, 31.5, 28.8, 28.7, 26.6, 22.4, 13.9, 9.5. MS (APCI$^+$) m/z: 373.0 $[M + H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O$ (372.22) C 80.61, H 7.58, N 7.52; found: C 80.63, H 7.62, N 7.56.

*1-Heptyl-3-(5-methyl-1H-indol-1-yl)quinolin-4(1H)-one (**4c**).* The reaction was carried out with **1e** (100 mg, 0.27 mmol) for 14 h according to the general procedure to obtain **4c** (96 mg, 0.26 mmol):

Yield 95%, white solid, mp 132−134 °C, R_f = 0.78 (CH_2Cl_2/AcOEt: 8/2). IR 2923, 1592, 1487, 1383, 1222, 907, 843, 756, 722, 704, 654, 592, 579, 567, 543 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.56 (d, 1H, J = 8.0 Hz), 7.83 (s, 1H), 7.71 (t, 1H, J = 7.4 Hz), 7.50 (d, 1H, J = 8.7 Hz), 7.43−7.39 (m, 2H), 7.29 (d, 1H, J = 3.2 Hz), 7.13 (d, 1H, J = 8.3 Hz), 6.96 (d, 1H, J = 8.5 Hz), 6.56 (d, 1H, J = 3.1 Hz), 4.09 (t, 2H, J = 7.2 Hz), 2.44 (s, 3H), 1.89−1.82 (m, 2H), 1.35−1.30 (m, 8H), 0.90 (t, 3H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.0, 140.7, 138.8, 135.3, 132.2, 129.4, 129.0, 128.8, 127.7, 127.6, 123.8, 123.4, 121.2, 120.4, 115.4, 109.7, 102.2, 53.4, 31.5, 28.8, 28.7, 26.7, 22.4, 21.3, 13.9. MS (APCI$^+$) m/z: 373.0 $[M + H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O$ (372.22) C 80.61, H 7.58, N 7.52; found: C 80.63, H 7.65, N 7.56.

*4-(5-Methoxy-1H-indol-1-yl)-2,3-dihydropyrrolo[1,2-a]quinolin-5(1H)-one (**4d**).* The reaction was carried out with **1g** (100 mg, 0.38 mmol) for 48 h according to the general procedure to obtain **4d** (95 mg, 0.29 mmol):

Yield 76%, white solid, mp 128−130 °C, R_f = 0.35 (CH_2Cl_2/AcOEt: 8/2). IR 1620, 1588, 1550, 1503, 1470, 1446, 1390, 1342, 1288, 1263, 1232, 1161, 1070, 1026, 821, 757, 706, 617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.47 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.0 Hz), 7.68 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 = 1.5 Hz), 7.42−7.35 (m, 2H), 7.12−7.10 (m, 2H), 6.90 (d, 1H, J = 8.8 Hz), 6.76 (dd, 1H, J_1= 8.8 Hz, J_2 = 2.4 Hz), 6.57 (d, 1H, J = 3.1 Hz), 4.35−4.27 (m, 2H), 3.82 (s, 3H), 2.92 (t, 2H, J = 7.7 Hz), 2.25 (p, 2H, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.9, 154.2, 154.1, 138.1, 132.1, 131.8, 129.7, 128.7, 127.3, 126.6, 123.8, 117.1, 115.7, 111.8, 110.8, 102.6, 102.4, 55.8, 51.1, 30.1, 20.8. MS (APCI$^+$) m/z: 331.0 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O_2$ (330.14) C 76.34, H 5.49, N 8.48; found: C 76.36, H 5.53, N 8.51.

*4-(5-Chloro-1H-indol-1-yl)-2,3-dihydropyrrolo[1,2-a]quinolin-5(1H)-one (**4e**).* The reaction was carried out with **1f** (100 mg, 0.32 mmol) for 36 h according to the general procedure to obtain **4e** (44 mg, 0.13 mmol):

Yield 41%, rose solid, mp 210−212 °C, R_f = 0.50 (CH_2Cl_2/AcOEt: 8/2). IR 1589, 1552, 1502, 1450, 1385, 1325, 1286, 1215, 1021, 907, 870, 797, 753, 721, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.47 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.4 Hz), 7.71 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz), 7.59 (d, 1H, J = 2.0 Hz), 7.44−7.37 (m, 2H), 7.15 (d, 1H, J = 3.2 Hz), 7.04 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.0 Hz), 6.91 (d, 1H, J = 8.7 Hz), 6.58 (d, 1H, J = 3.1 Hz), 4.38−4.32 (m, 2H), 2.95−2.88 (m, 2H), 2.34−2.24 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.8, 154.2, 138.1, 135.0, 132.3, 130.5, 129.4, 127.3, 126.6, 125.3, 124.0, 122.0, 120.1, 116.5, 115.7, 111.2, 102.4, 51.1, 30.1, 20.8. MS (APCI$^+$) m/z: 335.0 ([M + H]$^+$, ^{35}Cl), 337.0 ([M + H]$^+$, ^{37}Cl). Anal. Calcd for $C_{20}H_{15}ClN_2O$ (334.09) C 71.75, H 4.52, N 8.37; found: C 71.77, H 4.63, N 8.40.

*1-Methyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)quinolin-4(1H)-one (**4f**).* The reaction was carried out with **1a** (50 mg, 0.17 mmol) for 96 h according to the general procedure to obtain **4f** (42 mg, 0.15 mmol):

Yield 87%, ochre solid, mp 179−181 °C, R_f = 0.40 (CH_2Cl_2/MeOH: 95/5). IR 1587, 1552, 1511, 1422, 1331, 1214, 752, 662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.54 (d, 1H, J = 8.1 Hz), 8.31 (s, 1H), 8.26 (d, 1H, J = 3.2 Hz), 7.94 (d, 1H, J = 7.1 Hz), 7.76 (d, 1H, J = 3.6 Hz), 7.71 (dt, 1H, J_1 = 8.4 Hz, J_2 = 1.2 Hz), 7.45−7.40 (m, 2H), 7.08 (dd, 1H, J_1 = 7.5 Hz, J_2 = 4.8 Hz), 6.60 (d, 1H, J = 3.4 Hz), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.0, 147.8, 142.7, 141.8, 139.6, 132.3, 130.3, 128.8, 127.4, 127.2, 124.0, 120.9, 119.3, 116.4, 115.4, 100.4, 41.1. MS (APCI$^+$) m/z: 276.0 [M + H]$^+$. Anal. Calcd for $C_{17}H_{13}N_3O$ (275.11) C 74.17, H 4.76, N 15.26; found: C 74.20, H 4.79, N 15.28.

*1-Benzyl-3-(1H-indazol-1-yl)quinolin-4(1H)-one (**4g**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 14 h according to the general procedure to obtain **4g** (84 mg, 0.24 mmol):

Yield 86%, brown solid, mp 145−147 °C, R_f = 0.20 (CH_2Cl_2/AcOEt: 8/2). IR 2926, 1615, 1590, 1489, 1464, 1423, 1378, 1300, 1199, 1025, 909, 853, 762, 728, 695, 654, 623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.59 (d, 1H, J = 8.0 Hz), 8.17 (bs, 2H), 7.74 (d, 1H, J = 8.1 Hz), 7.60−7.55 (m, 1H), 7.47−7.29 (m, 7H), 7.20−7.17 (m, 3H), 5.36 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 171.9, 142.1, 139.1, 135.4, 134.5 (2C), 132.4, 129.2 (2C), 128.3, 127.5, 126.6, 126.1 (2C), 124.2, 122.8, 121.1, 120.7, 116.3, 112.0, 56.8, one C mising. MS (APCI$^+$) m/z: 352.0 [M + H]$^+$. Anal. Calcd for $C_{23}H_{17}N_3O$ (351.14) C 78.61, H 4.88, N 11.96; found: C 78.65, H 4.90, N 11.98.

*1-Benzyl-3-(1H-pyrrol-1-yl)quinolin-4(1H)-one (**4i**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 14 h according to the general procedure to obtain **4i** (69 mg, 0.23 mmol):

Yield 83%, violet solid, mp 180−182 °C, R_f = 0.40 (CH_2Cl_2/AcOEt: 9/1). IR 1589, 1486, 1355, 1260, 1107, 1066, 835, 756, 724, 700, 658, 635 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.55 (d, 1H, J = 8.2 Hz), 7.85 (s, 1H), 7.57 (t, 1H, J = 8.6 Hz), 7.39−7.32 (m, 5H), 7.17 (d, 2H, J = 7.9 Hz), 7.07 (t, 2H, J = 2.1 Hz), 6.30 (t, 2H, J = 2.1 Hz), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.4, 138.9, 138.0, 134.7, 132.2, 129.2 (2C), 128.4, 127.4 (2C), 126.1 (2C), 123.8, 123.7, 121.5, 116.0, 109.0 (2C), 56.5, one C mising. MS (APCI$^+$) m/z: 301.0 [M + H]$^+$. Anal. Calcd for $C_{20}H_{16}N_2O$ (300.13) C 79.98, H 5.37, N 9.33; found: C 79.99, H 5.40, N 9.36.

*1-Benzyl-3-(1H-imidazol-1-yl)quinolin-4(1H)-one (**4j**).* The reaction was carried out with **1c** (100 mg, 0.28 mmol) for 84 h according to the general procedure to obtain **4j** (57 mg, 0.19 mmol):

Yield 68%, light yellow solid, mp 215−217 °C, R_f = 0.43 (CH_2Cl_2/MeOH: 9/1). IR 3059, 1634, 1575, 1556, 1510, 1489, 1467, 1451, 1381, 1310, 1260, 1233, 1165, 1148, 1110, 1064, 1032, 975, 940, 905, 841, 813, 754, 728, 692, 657, 617, 608 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.51 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.96 (s, 1H), 7.88 (s, 1H), 7.61 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz), 7.43−7.26 (m, 6H), 7.19−7.13 (m, 3H), 5.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 171.9, 139.2, 138.3, 137.3, 134.3, 132.7, 129.3 (2C), 128.9, 128.6, 127.3 (2C), 126.2 (2C), 124.4, 120.2, 119.9, 116.2, 56.6. MS (APCI$^+$) m/z: 302.0 [M + H]$^+$. Anal. Calcd for $C_{19}H_{15}N_3O$ (301.12) C, 75.73; H 5.02, N 13.94; found: C, 75.76; H 5.09, N 13.96.

*4-Methoxy-N-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)benzamide (**6a**).* The reaction was carried out with **5a** (50 mg, 0.21 mmol) for 2 h according to the general procedure to obtain **6a** (63 mg, 0.21 mmol):

Yield: 98%; mp 181−183 °C; R_f = 0.74 (CH2Cl2/EtOAc: 8:2); IR (neat): 3375, 1669, 1638, 1619, 1598, 1576, 1527, 1494, 1465, 1421, 1377, 1327, 1296, 1255, 1217, 1177, 1115, 1023, 965, 947, 907, 858, 838, 800, 777, 752, 739, 716, 692, 621, 598, 559 cm^{-1}. 1H NMR (300 MHz, CDCl3): δ 9.24 (s, 1H), 8.78 (s, 1H), 7.85 (d, 2H, J = 9.0 Hz), 7.55 (dd, 1H, J_1 = 7.8, J_2 = 1.5 Hz), 7.40 (td, 1H, J_1 = 8.7, J_2 = 1.5 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.19 (td, 1H, J_1 = 8.1, J_2 = 1.2 Hz), 6.69 (d, 2H, J = 9.0 Hz), 3.79 (s, 3H), 3.74 (s, 3H). 13C NMR (75 MHz, CDCl3): δ 165.3 (CO), 162.7, 158.2 (CO), 135.5, 129.1 (2CH), 128.9, 128.8, 127.9, 126.5, 123.1, 121.2, 120.1, 114.5 (2CH), 114.0, 55.5 (OCH3), 30.3 (CH3); m/z MS (ES+) 331.0 (M + Na^+); Anal. Calcd for $C_{18}H_{16}N_2O_3$ (308.12): C 70.12, H 5.23 N, 9.09; found: C 70.14, H 5.26 N, 9.10.

*Ethyl 2-(2-Oxo-3-(thiophene-2-carboxamido)quinolin-1(2H)-yl) acetate (**6b**).* The reaction was carried out with **5b** (100 mg, 0.32 mmol) for 12 h according to the general procedure to obtain **6b** (85 mg, 0.24 mmol):

Yield 74%, white solid, mp 160−162 °C, R_f = 0.76 (CH_2Cl_2). IR 1753, 1633, 1599, 1526, 1492, 1416, 1372, 1200, 1023, 727, 640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.11 (s, 1H), 8.84 (s, 1H), 7.67 (d, 1H, J = 3.7 Hz), 7.63 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.56 (d, 1H, J = 4.9 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.27 (t, 1H, J = 7.5 Hz), 7.14−7.11 (m, 2H), 5.15 (s, 2H), 4.25 (q, 2H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.5, 160.2, 157.9, 138.8, 134.8, 131.4, 129.0, 128.9, 128.7, 127.9, 127.1, 123.4, 121.3, 121.0, 113.2, 61.9, 44.6, 14.0. MS (APCI$^+$) m/z: 357.0 [M + H]$^+$. Anal. Calcd for $C_{18}H_{16}N_2O_4S$ (356.08) C 60.66, H 4.53, N 7.86; found: C 60.68, H 4.59, N 7.90.

*3-(1H-Indol-1-yl)-1-methylquinolin-2(1H)-one (**6c**).* The reaction was carried out with **5a** (100 mg, 0.42 mmol) for 12 h according to the general procedure to obtain **6c** (63 mg, 0.23 mmol):

Yield 54%, orange solid, mp 193−195 °C, R_f = 0.75 (CH_2Cl_2). IR 1641, 1594, 1449, 1322, 1232, 946, 731, 705, 649 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.77 (s, 1H), 7.56 (d, 1H, J = 7.6 Hz), 7.52−7.43 (m, 3H), 7.33−7.29 (m, 2H), 7.19 (t, 1H, J = 7.5 Hz), 7.13−7.03 (m, 2H), 6.58 (d, 1H, J = 3.3 Hz), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 159.1, 138.5, 136.3, 131.9, 130.4, 129.3, 129.1, 128.9, 128.6, 122.7, 122.1, 121.0, 120.4, 119.6, 114.1, 110.6, 103.5, 30.2. MS (APCI$^+$) m/z: 275.0 [M + H]$^+$. Anal. Calcd for $C_{18}H_{14}N_2O$ (274.11) C 78.81, H 5.14, N 10.21; found: C 78.86, H 5.16, N 10.26.

*N-(6-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4-fluoro-benzamide (**6d**).* The reaction was carried out with **5c** (50 mg, 0.16 mmol) for 3 h according to the general procedure to obtain **6d** (38 mg, 0.10 mmol):

Yield 65%, white solid, mp 228−230 °C, R_f = 0.57 (CH_2Cl_2/*c*-hexane: 8/2). IR 3366, 1672, 1638, 1614, 1593, 1532, 1504, 1487, 1426, 1365, 1204, 1165, 1098, 920, 874, 855, 809, 754, 656, 617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.25 (s, 1H), 8.69 (s, 1H), 7.91−7.87 (m, 2H), 7.68 (d, 1H, J = 2.1 Hz), 7.50 (dd, 1H, J_1 = 8.9 Hz, J_2 = 2.1 Hz), 7.19−7.08 (m, 3H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.2 (d, 1C, J_{C-F} = 253.4 Hz), 164.7, 157.8, 134.5, 131.4, 130.6, 130.1 (d, 1C, J_{C-F} = 2.7 Hz), 129.7, 129.6, 128.5, 122.7, 119.0, 116.2, 116.1, 115.8, 115.6, 30.5. MS (APCI$^+$) m/z: 375.0 ([M + H]$^+$, ^{79}Br), 377.0 ([M + H]$^+$, ^{81}Br). Anal. Calcd for $C_{17}H_{12}BrFN_2O_2$ (374.01) C 54.42, H 3.22, N 7.47; found: C 54.43, H 3.26, N 7.47.

*N-(5-Bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-methoxy-benzamide (**6e**).* The reaction was carried out with **5e** (100 mg, 0.37 mmol) for 3 h according to the general procedure to obtain **6e** (86 mg, 0.25 mmol):

Yield 68%, white solid, mp 163−165 °C, R_f = 0.50 (Et_2O). IR 1644, 1598, 1500, 1349, 1221, 1173, 1027, 756, 613 cm^{-1}. ^1H NMR (300

MHz, $CDCl_3$, δ, ppm): 9.09 (s, 1H), 8.59 (s, 1H), 7.85 (d, 2H, J = 8.6 Hz), 7.12 (s, 1H), 6.94 (d, 2H, J = 8.6 Hz), 3.83 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.1, 162.7, 156.5, 129.8 (2C), 129.0 (2C), 125.9, 124.3, 113.9 (2C), 99.2, 55.4, 37.7. MS (APCI$^+$) m/z: 337.0 ([M + H]$^+$, ^{79}Br), 339.0 ([M + H]$^+$, ^{81}Br). Anal. Calcd for $C_{14}H_{13}BrN_2O_3$ (336.01) C 49.87, H 3.89, N 8.31; found: C 49.89, H 3.93, N 8.35.

*5-Bromo-1-methyl-3-(2-oxoazetidin-1-yl)pyridin-2(1H)-one (**6f**).* The reaction was carried out with **5e** (100 mg, 0.37 mmol) for 12 h according to the general procedure to obtain **6f** (55 mg, 0.21 mmol):

Yield 57%, white solid, mp 241−243 °C, R_f = 0.30 (Et_2O). IR 3079, 1729, 1641, 1584, 1391, 1320, 1081, 882, 726, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.03 (d, 1H, J = 2.5 Hz), 7.13 (d, 1H, J = 2.5 Hz), 4.12 (t, 2H, J = 4.6 Hz), 3.48 (s, 3H), 3.08 (t, 2H, J = 4.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 166.6, 156.1, 131.9, 128.7, 127.4, 97.8, 43.0, 38.5, 37.6. MS (ESI$^+$) m/z: 279.0 ([M + Na]$^+$, ^{79}Br), 281.0 ([M + Na]$^+$, ^{81}Br). Anal. Calcd for $C_9H_9BrN_2O_2$ (255.98) C 42.05 H 3.53; N 10.90; found: C 42.09 H 3.59; N 10.92.

*6-Bromo-1-methyl-3-(1H-pyrrol-1-yl)quinolin-2(1H)-one (**6g**).* The reaction was carried out with **5c** (50 mg, 0.16 mmol) for 18 h according to the general procedure to obtain **6g** (20 mg, 0.07 mmol):

Yield 42%, white solid, mp 168−170 °C, R_f = 0.60 (CH_2Cl_2). IR 1650, 1587, 1476, 1422, 1308, 1254, 1099, 902, 816, 723, 666, 620 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.73 (d, 1H, J = 1.9 Hz), 7.65 (dd, 1H, J_1 = 9.0 Hz, J_2 = 1.9 Hz), 7.54 (s, 1H), 7.30−7.27 (m, 3H), 6.37−7.36 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 158.0, 136.7, 132.5, 131.5, 130.5, 125.9, 121.4, 121.3 (2C), 115.7, 115.5, 110.2 (2C), 30.3. MS (APCI$^+$) m/z: 303.0 ([M + H]$^+$, ^{79}Br), 305.0 ([M + H]$^+$, ^{81}Br). Anal. Calcd for $C_{14}H_{11}BrN_2O$ (302.01) C 55.47, H 3.66, N 9.24; found: C 55.50, H 3.69, N 9.29.

*4-Methoxy-N-(2-oxo-2H-chromen-3-yl)benzamide (**6h**).* The reaction was carried out with **5d** (100 mg, 0.44 mmol) for 1.5 h according to the general procedure to obtain **6h** (54 mg, 0.18 mmol, 41%) as a white solid:

Yield 41%, white solid, mp 177−179 °C, R_f = 0.48 (CH_2Cl_2). IR 3401, 1712, 1667, 1604, 1578, 1507, 1446, 1359, 1296, 1246, 1190, 1112, 1063, 925, 910, 859, 842, 754, 691, 643, 606, 568 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.77 (s, 1H), 8.69 (bs,1H), 7.82 (d, 2H, J = 8.8 Hz), 7.47 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.38 (td, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.30 −7.18 (m, 2H), 6.92 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.6, 163.1, 159.1, 149.8, 129.6, 129.2 (2C), 127.9, 125.7, 125.2, 124.3, 123.0, 120.0, 116.4, 114.2 (2C), 55.5. MS (ESI$^+$) m/z: 318.0 [M + Na]$^+$. Anal. Calcd for $C_{17}H_{13}NO_4$ (295.08) C 69.15, H 4.44, N 4.74; found: C 69.19, H 4.49, N 4.79.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*samir.messaoudi@u-psud.fr, mouad.alami@u-psud.fr

■ ACKNOWLEDGMENT

The Centre National de Recherche Scientifique [CNRS] is gratefully acknowledged for financial support of this research. We thank the European Union [EU] within the EST network BIOMEDCHEM [MEST-CT-2005-020580] for a Ph.D. grant (to Davide Audisio) and for financial support. Region Ile-de-France is also acknowledged for support. Thanks also to E. Morvan for her help in the NMR experiments and A. Solgadi for performing mass spectra analysis (SAMM platform, Châtenay-Malabry).

■ REFERENCES

(1) (a) Andersen, K.; Perregaard, J.; Arnt, J.; Bay Nielsen, J.; Begtrup, M. *J. Med. Chem.* **1992**, *35*, 4823. (b) Frontana-Uribe, B. A.; Moinet, C.; Toupet, L. *Eur. J. Org. Chem.* **1999**, 419.(c) Le, R. A.; Harpey, C. FR2911143, 2008. (d) Huger, F. P.; Smith, C. P.; Kongsamut, S.; Tang, L. US Patent 5,776,955, 1998. (e) Effland, R. C.; Klein, J. T.; Davis, L.; Olson, G. E. EP0402752, 1990. (f) Gurkan, A. S.; Karabay, A.; Buyukbingol, Z.; Adejare, A.; Buyukbingol, E. *Arch. Pharm. Chem. Life Sci.* **2005**, *338*, 67. (g) Itoh, T.; Miyazaki, M.; Maeta, H.; Matsuya, Y.; Nagata, K.; Ohsawa, A. *Bioorg. Med. Chem.* **2000**, *8*, 1983. (h) Santos, F. d. C.; Abreu, P.; Castro, H. C.; Paixao, I. C. P. P.; Cirne-Santos, C. C.; Giongo, V.; Barbosa, J. E.; Simonetti, B. R.; Garrido, V.; Bou-Habib, D. C.; Silva, D. d. O.; Batalha, P. N.; Temerozo, J. R.; Souza, T. M.; Nogueira, C. M.; Cunha, A. C.; Rodrigues, C. R.; Ferreira, V. F.; de Souza, M. C. B. V. *Bioorg. Med. Chem.* **2009**, *17*, 5476–5481. (i) Senthilkumar, P.; Dinakaran, M.; Yogeeswari, P.; Sriram, D.; China, A.; Nagaraja, V. *Eur. J. Med. Chem.* **2009**, *44*, 345–358. (j) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559–592. (k) Van Bambeke, F.; Michot, J. M.; Van Eldere, J.; Tulkens, P. M. *Clin. Microbiol. Infect.* **2005**, *11*, 256–280. (l) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358–1363. (m) Ziegler, C. B.; Bitha, P.; Kuck, N. A.; Fenton, T. J.; Petersen, P. J.; Lin, Y. I. *J. Med. Chem.* **1990**, *33*, 142–146. (n) Ma, X.; Zhou, W.; Brun, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 986–989. (o) Hu, G. Q.; Zhang, Z. Q.; Xie, S. Q.; Huang, W. L. *Chin. Chem. Lett.* **2010**, *21*, 661–663. (p) Wang, H.; You, Q. D.; Li, Z. Y.; Zou, Y. Q. *Chin. Chem. Lett.* **2008**, *19*, 1395–1397. (q) Anderson, V. E.; Osheroff, N. *Curr. Pharm. Des.* **2001**, *7*, 337–353. (r) Sissi, C.; Palumbo, M. *Curr. Med. Chem.* **2003**, *3*, 439–450. (s) Yang, F. V.; Shipe, W. D.; Bunda, J. L.; Nolt, M. B.; Wisnoski, D. D.; Zhao, Z.; Barrow, J. C.; Ray, W. J.; Ma, L.; Wittmann, M.; Seager, M. A.; Koeplinger, K. A.; Hartman, G. D.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 531–536.

(2) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605–618.

(3) Stern, E; Muccioli, G. G.; Bosier, B.; Hamtiaux, L.; Millet, R.; Poupaert, J. H.; Hénichart, J. P.; Depreux, P.; Goossens, J. F.; Lambert, D. M. *J. Med. Chem.* **2007**, *50*, 5471–5484.

(4) Kumar, D. V.; Rai, R. WO 2007/005779 A2.

(5) (a) Al-Qawasmeh, R. A.; Zahra, J. A.; Khanfar, M. A.; AL-Hiari, Y. M.; El-Abadelah, M. M.; Voelter, W. *Lett. Org. Chem.* **2009**, *6*, 511–514. (b) Radl, S.; Chan, K.-K. *J. Heterocycl. Chem.* **1994**, *31*, 437–440.

(6) Hradil, Pavel.; Grepl, M.; Hlavac, J.; Soural, M.; Malofi, M.; Bertolasi, V. *J. Org. Chem.* **2006**, *71*, 819–822.

(7) (a) Messaoudi, S.; Tréguier, B.; Hamze, A.; Provot, O.; Peyrat, J.-F.; De Losada, J. R.; Liu, J.-M.; Bignon, J.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *J. Med. Chem.* **2009**, *52*, 4538–4542. (b) Hamze, A.; Giraud, A.; Messaoudi, S.; Provot, O.; Peyrat, J.-F.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2009**, *4*, 1912–1924. (c) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; De Losada, J. R.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami *ChemMedChem* **2011**, *6*, 488–497.

(8) (a) Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Anticancer Agents Med. Chem.* **2008**, *8*, 761–782. (b) Janin, Y. L. *Drug Discovery Today* **2010**, *15*, 342–353.

(9) Audisio, D.; Messaoudi, S.; Brion, J.-B.; Alami, M. *Eur. J. Org. Chem.* **2010**, 1046–1051.

(10) (a) Audisio, D.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, A *Tetrahedron Lett.* **2007**, *48*, 6928–6932. (b) Messaoudi, S.; Audisio, D.; Brion, J.-D.; Alami, A. *Tetrahedron* **2007**, *63*, 10202–10210. (c) Messaoudi, S.; Brion, J.-D.; Alami, M. *Adv. Synth. Catal.* **2010**, *352*, 1677–1687. (d) Messaoudi, S.; Brion, J.-D.; Alami, M. *Tetrahedron. Lett.* **2011**, *52*, 2687–2691.

(11) (a) Le Bras, G.; Radanyi, C.; Peyrat, J.-F.; Brion, J.-D.; Alami, M.; Marsaud, V.; Stella, B.; Renoir, J.-M. *J. Med. Chem.* **2007**, *50*, 6189–6200. (b) Radanyi, C.; Le Bras, G.; Messaoudi, S.; Bouclier, C.; Peyrat, J.-F.; Brion, J.-D.; Marsaud, V.; Renoir, J.-M.; Alami, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2495–2498. (c) Radanyi, C.; Le Bras, G.; Marsaud, V.; Peyrat, J.-F.; Messaoudi, S.; Catelli, M. G.; Brion, J.-D.; Alami, M.; Renoir, J.-M. *Cancer Lett.* **2008**, *274*, 88–94. (d) Radanyi, C.; Le Bras, G.; Bouclier, C.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M; Renoir, J.-M. *Biochem. Bioph. Res. Commun.* **2009**, *379*, 514–518. (e) Audisio, D.; Messaoudi, S.; Ijjaali, I.; Dubus, E.; Petitet, F.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Eur. J. Med. Chem.* **2010**, *45*, 2000–2009. (f) Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279–7283. (g) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2009**, *7*, 4271–4278. (h) Sahnoun, S.; Messaoudi, S.; Brion, J.-B.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6097–6102. (i) Sahnoun, S.; Messaoudi, S.; Brion, J.-B.; Alami, M. *Chem.Cat.Chem.* **2011**, *3*, 893–897. (j) Audisio, D; Messaoudi, S.; Cegielkowski, L.; Peyrat, J.-F.; Brion, J.-D.; Methy-Gonnot, D.; Radanyi, C.; Renoir, J.-M.; Alami, M. *Chem.Med.Chem.* **2011**, *6*, 804–815.

(12) For recent reviews on copper-catalyzed cross couplings, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (o) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. For selected samples, see:(f) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (g) Klapars, A.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (h) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688. (i) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987–4990. (j) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317. (k) Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Yoshifuji, F. *Chem. Commun.* **2004**, 1994–1995. (l) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (m) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455. (n) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351–4354.

(13) For selected references on the preparation of 3-halo-4(1*H*)-quinolones, see: (a) Renault, J.; Mailliet, P.; Renault, S.; Berlot, J. *Synthesis* **1977**, *12*, 865–866. (b) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243–246. (c) Mphahlele, M. J.; Nwamadi, M. S.; Mabeta, P. *J. Heterocycl. Chem.* **2006**, *43*, 255–260. (d) Tois, J.; Vahermo, M.; Koskinen, A. *Tetrahedron Lett.* **2005**, *46*, 735–737. (e) Zhao, T.; Xu, B. *Org. Lett.* **2010**, *12*, 212–215. (f) Cross, R. M.; Manetsch, R. *J. Org. Chem.* **2010**, *75*, 8654–8657.

(14) No reaction occurred when 3-iodo-4-quinolinones **1a** was treated with *N*-methyl benzamide under our optimized conditions described above, only starting material was recovered unchanged.

(15) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 276.

(16) Antilla, J. K.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.

(17) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609–2612.

(18) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968–7973.

(19) Bekaert, A.; Barberan, O.; Kaloun, E. B.; Danan, A.; Brion, J.-D.; Lemoine, P.; Viossat, B. *Z. Kristallogr.* **2001**, *216*, 1–2.