1,2-Disubstituted 4-Quinolones via Copper-Catalyzed Cyclization of 1-(2-Halophenyl)-2-en-3-amin-1-ones

Roberta Bernini,[a] Sandro Cacchi,*[b] Giancarlo Fabrizi,[b] Alessio Sferrazza[a]

[a] Dipartimento A.B.A.C., Università degli Studi della Tuscia e Consorzio Universitario 'La Chimica per l'Ambiente', Via S. Camillo De Lellis, 01100 Viterbo, Italy

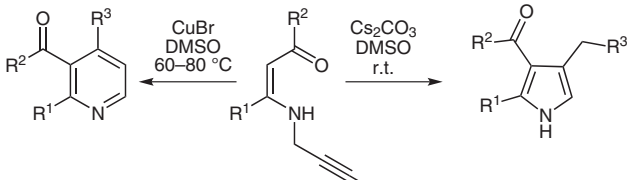
[b] Dipartimento di Chimica e Tecnologie del Farmaco, Università degli Studi 'La Sapienza', P.le A. Moro 5, 00185 Rome, Italy
Fax +39(06)49912780; E-mail: sandro.cacchi@uniroma1.it

Received 28 November 2008

Abstract: 1,2-Disubstituted 4-quinolones have been prepared via copper-catalyzed heterocyclization of 1-(2-bromophenyl)- and 1-(2-chlorophenyl)-2-en-3-amin-1-ones, readily obtained from α,β-ynones and primary amines. The reaction tolerates a variety of useful functionalities including ester, keto, cyano, and chloro substituents. Quinolone derivatives can also be prepared via a sequential process from α,β-ynones and primary amines, omitting the isolation of the 1-(2-halophenyl)-2-en-3-amin-1-one intermediates.

Key words: copper, catalysis, enaminones, 4-quinolones, cyclizations

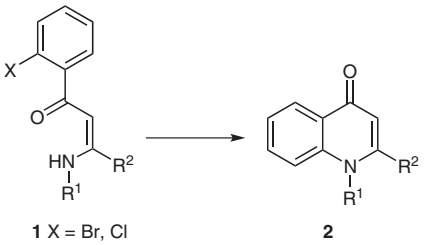
Because of their multifunctional character, 2-en-3-amin-1-ones are useful synthetic intermediates.[1] They have been used in a variety of intra-[2] and intermolecular[3] reactions. A number of transition-metal-promoted[4] and -catalyzed[2g,5] processes have also been described. Recently, we reported on the use of *N*-propargylic 2-en-3-amin-1-ones as common intermediates for the synthesis of polysubstituted pyrroles and pyridines (Scheme 1).[6]



Scheme 1

Following this study, we decided to investigate the potential of 1-(2-halophenyl)-2-en-3-amin-1-ones **1** as building blocks for the construction of the 4-quinolone skeleton **2** according to the intramolecular C–N bond-forming reaction shown in Scheme 2.

4-Quinolone derivatives are abundant in many biologically active compounds.[7] Some of them have been investigated as antiviral[8] and antidiabetic[9] agents. Compounds containing the 3-unsubstituted 2-aryl-4-quinolone motif (structurally similar to flavones with, in addition, a nitrogen group that is available for increasing molecular complexity) have been shown to have positive cardiac effects[10] and exhibit antimitotic,[11] antiplatelet,[12] and antiviral[13] activity. Despite the existence of a variety of synthetic routes for the synthesis of the quinolone scaffold,[14] the utility of 4-quinolone derivatives justifies efforts to develop new and more versatile methods. In this context, the transition-metal-catalyzed cyclization of readily available multifunctional precursors is a promising synthetic strategy.

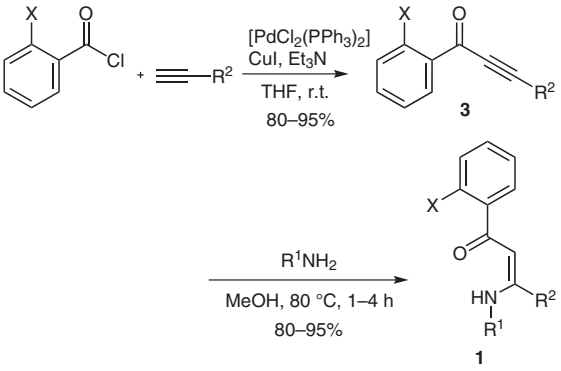


1 X = Br, Cl **2**

Scheme 2

Herein we report a simple approach to the preparation of 1,2-disubstituted 4-quinolones that is based on the copper-catalyzed cyclization of readily available 1-(2-halophenyl)-2-en-3-amin-1-ones **1** (Scheme 2). 1-(2-Bromophenyl)- and 1-(2-chlorophenyl)-2-en-3-amin-1-ones **1** were prepared by conjugate addition of primary amines to α,β-ynones **3**,[5c] obtained by Sonogashira cross-coupling of terminal alkynes with commercially available 2-bromo- and 2-chlorobenzoyl chlorides[15] (Scheme 3).

Compounds **1** were always isolated as single isomers. The *Z* stereochemistry of **1a** ($R^1 = R^2 = Ph$) has been assigned by NOESY experiments, which also showed the presence



3

1

Scheme 3

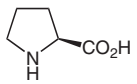
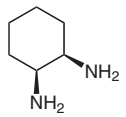
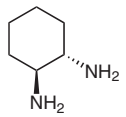
SYNTHESIS 2009, No. 7, pp 1209–1219
Advanced online publication: 06.03.2009
DOI: 10.1055/s-0028-1087990; Art ID: Z26108SS

of an intramolecular hydrogen bond (N–H···O). That of the other 1-(2-halophenyl)-2-en-3-amin-1-ones has been assigned on the basis of these data.

We started our study by examining the conversion of **1a** (**1**, $R^1 = R^2 = Ph$; X = Br) into the corresponding quinolone derivative **2a** (**2**, $R^1 = R^2 = Ph$) (Scheme 2) in the presence of copper(I) iodide[16] and potassium carbonate. The influence of ligands and solvents on the reaction outcome was investigated. Representative optimization experiments are summarized in Table 1. Best results were obtained when the cyclization was carried out in the presence of copper(I) iodide (0.05 equiv), *N*,*N*′-dimethylethylenediamine (DMEDA; 0.05 equiv), and potassium carbonate (2 equiv) in dimethyl sulfoxide at 80 °C (Table 1, entry 8). Compound **2a** was isolated in only 40% yield when the reaction was carried out under the same conditions, but in the absence of copper(I) iodide and *N*,*N*′-dimethylethylenediamine (Table 1, entry 9). There are examples in the literature of cyclizations promoted by the base of related enaminones. However, higher reaction temperatures (110 °C)[14e,h] and/or stronger bases (NaOEt,[14c] *t*-BuOK,[14d] NaH[14f]) are usually required. In addition, fused 4-quinolones[14c,f,h] or quinolone derivatives bearing ethoxycarbonyl or cyano groups at C-3[14e,f,h,i] were prepared. No examples of 3-unsubstituted 4-quinolones have been described.

Using the optimized conditions, we next explored the scope and generality of the process. Our preparative results are summarized in Table 2. A variety of quinolone products **2** containing neutral, electron-rich, and electron-poor aryl substituents could be isolated in high to excellent yields. Alkyl substituents are also tolerated, but our method shows some limitations with them. Indeed, enaminones derived from primary alkylamines require a stron-

Table 1 The Influence of Ligands and Solvents on the Copper-Catalyzed Cyclization of **1a** to Quinolone Derivative **2a**[a,b]

Entry	Ligand	Solvent	Time (h)	Yield[c] (%) of **2a**
1	1,10-phenanthroline	DMF	8	60
2		DMF	48	72[d]
3		DMF	6	69
4		DMF	4	78
5	TMEDA	DMF	4	79
6	DMEDA	DMF	6	82
7	DMEDA	dioxane	12	–[e]
8	DMEDA	DMSO	2.5	93
9	–	DMSO	2.5	40[f]

[a] See Scheme 2; Starting material enaminone **1a** (**1**, $R^1 = R^2 = Ph$; X = Br); product quinolone **2a** (**2**, $R^1 = R^2 = Ph$).
[b] Reagents and conditions: **1a** (0.25 mmol), CuI (0.05 equiv), ligand (0.05 equiv), K_2CO_3 (2 equiv), solvent (2.5 mL), 80 °C.
[c] Yields of isolated products.
[d] Proline (0.1 equiv) was used.
[e] The starting material was recovered in 95% yield.
[f] In the absence of CuI and DMEDA.

Table 2 Synthesis of 1,2-Disubstituted 4-Quinolones **2** from 1-(2-Bromophenyl)-2-en-3-amin-1-ones **1**[a]

Entry	R^1	R^2	**1** (X = Br)	Time (h)	**2**	Yield[b] (%)
1	Ph	Ph	**1a**	2.5	**2a**	93
2	3-$F_3CC_6H_4$	Ph	**1b**	1.5	**2b**	92
3	4-$MeOC_6H_4$	Ph	**1c**	2	**2c**	89
4	4-AcC_6H_4	Ph	**1d**	1.5	**2d**	87
5	4-chloro-1-naphthyl	Ph	**1e**	2	**2e**	92
6	4-NCC_6H_4	Ph	**1f**	2	**2f**	82
7	2,4-$F_2C_6H_3$	Ph	**1g**	1.5	**2g**	72
8	3,4,5-$(MeO)_3C_6H_2$	Ph	**1h**	2	**2h**	81
9	4-ClC_6H_4	Ph	**1i**	2	**2i**	91
10	*n*-Bu	Ph	**1j**	1	**2j**	86[c]
11	Bn	Ph	**1k**	1	**2k**	53[c]
12	Cy	Ph	**1l**	2	**2l**	36[c]
13	*t*-Bu	Ph	**1m**	5	**2m**	–[c,d]
14	3-$MeOC_6H_4$	4-ClC_6H_4	**1n**	2.5	**2n**	87
15	4-Tol	4-ClC_6H_4	**1o**	1.5	**2o**	85
16	4-FC_6H_4	4-ClC_6H_4	**1p**	2	**2p**	87
17	4-$MeO_2CC_6H_4$	3-$MeOC_6H_4$	**1q**	2.5	**2q**	75
18	3-$F_3CC_6H_4$	3-$MeOC_6H_4$	**1r**	2.5	**2r**	72
19	4-FC_6H_4	3-$MeOC_6H_4$	**1s**	4	**2s**	83
20	4-ClC_6H_4	4-AcC_6H_4	**1t**	2	**2t**	81
21	4-$MeOC_6H_4$	4-AcC_6H_4	**1u**	2.5	**2u**	70
22	Ph	$(CH_2)_4Me$	**1v**	–	**2v**	–[c,e]
23	4-$MeOC_6H_4$	$(CH_2)_4Me$	**1w**	–	**2w**	–[c,f]

[a] See Scheme 2 for structures of **1** (X = Br) and **2**. Reagents and conditions: **1** (0.25 mmol), CuI (0.05 equiv), DMEDA (0.05 equiv), K_2CO_3 (2 equiv), DMSO (2.5 mL), 80 °C.
[b] Yields of isolated products.
[c] *t*-BuONa (2 equiv) was used instead of K_2CO_3.
[d] Starting material **1m** was recovered in 90% yield.
[e] Starting material **1v** was recovered in 92% yield.
[f] Starting material **1w** was recovered in 91% yield.

ger base (Table 2, entries 10–12). In addition, the bulkiness of the alkyl substituent appears to have a detrimental effect on the cyclization process: with the *N*-cyclohexyl derivative **1l**, the desired quinolone was isolated in low yield (Table 2, entry 12), while the starting enone with the *N*-*tert*-butylamino group was recovered in almost quantitative yield (Table 2, entry 13). No quinolone formed from enaminones containing 3-alkyl substituents (Table 2, entries 22 and 23).

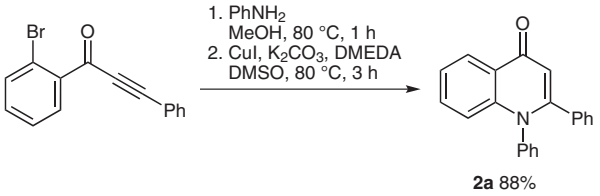
1-(2-Chlorophenyl)-2-en-3-amin-1-ones can also be used for this synthesis under the same conditions. Reaction rates are lower, but yields are equally high to excellent, at least with the examples that we tested (Table 3).

Table 3 Synthesis of 1,2-Disubstituted 4-Quinolones **2** from 1-(2-Chlorophenyl)-2-en-3-amin-1-ones **1**[a]

Entry	R^1	R^2	**1** (X = Cl)	Time (h)	**2**	Yield[b] (%)
1	Ph	Ph	**1x**	6	**2a**	95
2	4-$MeOC_6H_4$	Ph	**1y**	7	**2c**	83
3	4-AcC_6H_4	Ph	**1z**	3	**2d**	83
4	4-ClC_6H_4	Ph	**1za**	3	**2i**	92
5	*n*-Bu	Ph	**1zb**	3	**2j**	89[c]

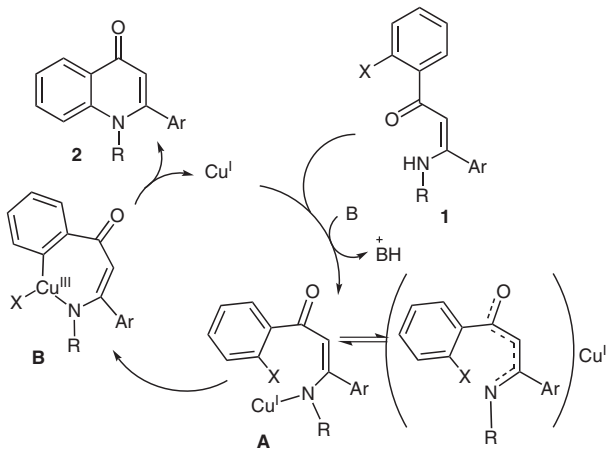
[a] See Scheme 2 for structures of **1** (X = Cl) and **2**. Reagents and conditions: **1** (0.25 mmol), CuI (0.05 equiv), DMEDA (0.05 equiv), K_2CO_3 (2 equiv), DMSO (2.5 mL), 80 °C.
[b] Yields of isolated products.
[c] *t*-BuONa (2 equiv) was used instead of K_2CO_3.

To make this overall approach to 4-quinolones more attractive from a synthetic point of view, we explored their formation through a process that would omit the isolation of the enaminone intermediates. Adding dimethyl sulfoxide and the reagents required for the cyclization step to the crude methanolic mixture resulting from the reaction of the primary amine and the α,β-ynone led to moderate yields. For example, **2a** was isolated in only 47% overall yield when this protocol was used (in comparison with the 87% overall yield in the stepwise process). In addition, no quinolone product was formed when the overall process was carried out with methanol or dimethyl sulfoxide as the sole solvent for the two steps. Control experiments revealed that the cyclization does not proceed in methanol and that the enaminone product is formed in low yields in dimethyl sulfoxide. Finally, we found that excellent results could be obtained if dimethyl sulfoxide, copper(I) iodide, *N*,*N*′-dimethylethylenediamine, and potassium carbonate are added to the crude mixture derived from the reaction of primary amines with α,β-ynones after evaporation of the volatile materials. Under these conditions, **2a** was isolated in 88% overall yield (Scheme 4).



Scheme 4

On the basis of the recently reported tendency of *N*-arylenaminones to coordinate to palladium(II) electrophiles,[17] the lack of reactivity of the bromo substituent at the 4-position under copper-catalyzed conditions,[18] and previous observations on related copper-catalyzed heterocyclizations involving $C_{aromatic}$–X bonds,[19] a plausible mechanism for this quinolone ring formation begins with the initial coordination of nitrogen to copper (Scheme 5). The resulting complex **A** undergoes an oxidative addition of the C–X bond to copper to afford the Cu(III) intermediate **B**. Subsequent reductive elimination releases the product with concomitant regeneration of the Cu(I) species.



Scheme 5

To sum up, an efficient approach to the construction of the 3-unsubstituted 1,2-disubstituted 4-quinolone skeleton from readily available 1-(2-bromophenyl)- and 1-(2-chlorophenyl)-2-en-3-amin-1-ones has been developed. The new method tolerates a variety of useful functionalities including ester, keto, cyano, and chloro substituents. In addition, quinolones can be prepared from α,β-ynones and primary amines by a sequential process that omits the isolation of the 1-(2-halophenyl)-2-en-3-amin-1-one intermediates. Since 3-unsubstituted 1,2-disubstituted 4-quinolones are essentially formed by assembling 2-haloaroyl chlorides, terminal alkynes, and primary amines, a wide variety of quinolone derivatives can be synthesized by this protocol, which could be particularly useful for the preparation of libraries.

Melting points were determined on a Büchi B-545 apparatus and are uncorrected. All the reagents and solvents are commercially available and were used as purchased, without further purification. The 1-(2-halophenyl)-2-en-3-amin-1-ones and 1,2-disustituted 4-quinolones were purified on axially compressed columns, packed with silica gel (25–40 μm, Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and were eluted with *n*-hexane–EtOAc mixtures. ^{1}H NMR (400.13

MHz), ^{13}C NMR (100.6 MHz), and ^{19}F NMR (376.5 MHz) spectra were recorded on a Bruker Avance 400 spectrometer. IR spectra were recorded on a JASCO FT/IR-430 spectrophotometer. Mass spectra were determined on a QP2010 Gas Chromatograph Mass spectrometer (EI) and a Thermo Finnigan LXQ spectrometer (ESI).

1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one; Typical Procedure for the Preparation of an α,β-Ynone 3

A mixture of 2-bromobenzoyl chloride (264 mg, 1.2 mmol), [$PdCl_2(PPh_3)_2$] (14 mg, 0.02 mmol), and Et_3N (167 μL, 1.2 mmol) in anhyd THF (4 mL) was stirred for 10 min under argon at r.t. CuI (7.6 mg, 0.04 mmol) was added and the reaction mixture was stirred for other 10 min before ethynylbenzene (102.2 mg, 1.0 mmol) was added. After 2 h at r.t., the reaction mixture was diluted with EtOAc (50 mL) and washed with 0.1 N HCl (2 × 10 mL) and a sat. NH_4Cl soln (10 mL). The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc, 95:5); this gave 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one.

Yield: 231 mg (81%); orange oil.

IR (KBr): 2931, 2861, 1644 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.72 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.68–7.65 (m, 2 H), 7.52–7.39 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 137.6, 135.0, 133.4, 133.2, 132.8, 131.1, 128.8, 127.5, 121.3, 120.0, 94.3, 88.0.

MS: *m*/*z* (%) = 285 [M$^+$] (25), 199 (21), 157 (35), 115 (38), 105 (100).

Anal. Calcd for $C_{15}H_9BrO$: C, 63.18; H, 3.18. Found: C, 63.09; H, 3.01.

1-(2-Halophenyl)-2-en-3-amin-1-ones 1a–z,za,zb; General Procedure

An oven-dried Schlenk tube was charged with the appropriate 1-(2-halophenyl)-α,β-ynone **3** (1 mmol), the substituted amine (1 mmol), and anhyd MeOH (1 mL). The tube was sealed and stirred at 80 °C for the period of time indicated below for each product **1**. Then the reaction mixture was cooled to r.t., the solvent was evaporated, and the residue was purified by chromatography (silica gel, *n*-hexane–EtOAc).

3-Anilino-1-(2-bromophenyl)-3-phenylprop-2-en-1-one (1a)

Yield: 94% (4 h); mp 118–119 °C; pale yellow solid.

IR (KBr): 3448, 1608, 1587, 1569, 1479, 1325, 758, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.66 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.42–7.31 (m, 6 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 2 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 5.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 161.5, 143.1, 139.3, 135.3, 133.6, 130.6, 129.9, 129.4, 128.8, 128.6, 128.5, 127.3, 124.5, 123.5, 119.6, 100.8.

Anal. Calcd for $C_{21}H_{16}BrNO$: C, 66.68; H, 4.26. Found: C, 66.79; H, 4.21.

(*Z*)-1-(2-Bromophenyl)-3-phenyl-3-[3-(trifluoromethyl)anilino]prop-2-en-1-one (1b)

Yield: 94% (4 h); mp 57–58 °C; pale yellow solid.

IR (KBr): 3435, 1585, 1315, 1271, 1167, 1113, 1068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.65 (s, 1 H), 7.64 (dd, *J* = 8.0, 0.7 Hz, 1 H), 7.56 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.43–7.34 (m, 6 H), 7.29–7.26 (m, 3 H), 7.06 (s, 1 H), 6.99–6.96 (m, 1 H), 5.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 160.7, 142.7, 140.0, 134.7, 133.6, 131.3 (q, J_{CF} = 32 Hz), 130.9, 130.3, 129.4, 129.3, 128.9, 128.4, 127.4, 126.1, 123.6 (q, J_{CF} = 271 Hz), 120.7 (q, J_{CF} = 4 Hz), 119.8 (q, J_{CF} = 4 Hz), 119.5, 101.8.

Anal. Calcd for $C_{22}H_{15}BrF_3NO$: C, 59.31; H, 3.39. Found: C, 59.21; H, 3.21.

(*Z*)-1-(2-Bromophenyl)-3-(4-methoxyanilino)-3-phenylprop-2-en-1-one (1c)

Yield: 94% (1 h); mp 150–151 °C; yellow-orange solid.

IR (KBr): 3433, 1589, 1566, 1512, 1479, 1458, 1321, 1246, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.64 (s, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.55 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.39–7.24 (m, 7 H), 6.80 (d, *J* = 8.9 Hz, 2 H), 6.70 (d, *J* = 8.9 Hz, 2 H), 5.72 (s, 1 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 162.1, 156.8, 143.1, 135.3, 133.5, 132.2, 130.5, 129.8, 129.4, 128.6, 128.5, 127.3, 125.2, 119.6, 114.1, 99.9, 55.4.

Anal. Calcd for $C_{22}H_{18}BrNO_2$: C, 64.72; H, 4.44. Found: C, 64.81; H, 4.31.

(*Z*)-3-(4-Acetylanilino)-1-(2-bromophenyl)-3-phenylprop-2-en-1-one (1d)

Yield: 91% (12 h); mp 154–155 °C; yellow solid.

IR (KBr): 3448, 1676, 1587, 1562, 1317, 1296, 1266, 758, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.58 (s, 1 H), 7.75 (d, *J* = 8.6 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.54 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.45–7.34 (m, 6 H), 7.26 (m, 1 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.86 (s, 1 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 192.5, 160.0, 143.8, 142.6, 135.0, 133.6, 132.6, 131.0, 130.4, 129.4, 128.9, 128.5, 128.3, 127.4, 122.1, 119.5, 102.7, 26.4.

Anal. Calcd for $C_{23}H_{18}BrNO_2$: C, 65.73; H, 4.32. Found: C, 65.65; H, 4.41.

(*Z*)-1-(2-Bromophenyl)-3-[(4-chloro-1-naphthyl)amino]-3-phenylprop-2-en-1-one (1e)

Yield: 95% (3 h); mp 140–141 °C; yellow solid.

IR (KBr): 3448, 1591, 1560, 1479, 1311, 1082, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.09 (s, 1 H), 8.47 (m, 1 H), 8.30 (d, *J* = 7.6 Hz, 1 H), 7.71–7.63 (m, 4 H), 7.41–7.22 (m, 8 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 5.99 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.1, 162.5, 142.7, 135.1, 134.6, 133.5, 131.1, 130.7, 129.9, 129.5, 129.4, 128.7, 128.6, 128.1, 127.6, 127.6, 127.3, 125.3, 125.0, 122.8, 122.4, 119.5, 101.6.

Anal. Calcd for $C_{25}H_{17}BrClNO$: C, 64.89; H, 3.70. Found: C, 64.75; H, 3.51.

(*Z*)-1-(2-Bromophenyl)-3-(4-cyanoanilino)-3-phenylprop-2-en-1-one (1f)

Yield: 85% (9 h); mp 133–134 °C; yellow solid.

IR (KBr): 3433, 2220, 1593, 1516, 1024 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.53 (s, 1 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 7.2 Hz, 1 H), 7.45–7.40 (m, 8 H), 7.28 (m, 1 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 5.90 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 159.4, 143.7, 142.4, 134.6, 133.7, 132.9, 131.1, 130.6, 129.4, 129.1, 128.2, 127.5, 122.5, 119.5, 118.8, 106.7, 103.4.

Anal. Calcd for $C_{22}H_{15}BrN_2O$: C, 65.52; H, 3.75. Found: C, 65.61; H, 3.81

(*Z*)-1-(2-Bromophenyl)-3-(2,4-difluoroanilino)-3-phenylprop-2-en-1-one (1g)
Yield: 100% (6 h); mp 146–147 °C; yellow solid.

IR (KBr): 3448, 1608, 1593, 1568, 1520, 1475, 1315, 1259, 1194, 850, 744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.33 (s, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.55 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.41–7.31 (m, 6 H), 7.26 (dt, *J* = 7.7, 1.6 Hz, 1 H), 6.81 (m, 1 H), 6.72–6.60 (m, 2 H), 5.85 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 161.7, 159.6 (dd, J_{CF} = 250, 11 Hz), 155.5 (dd, J_{CF} = 240, 12 Hz), 142.8, 134.9, 133.6, 130.8, 130.1, 129.4, 128.6, 128.2, 127.4, 126.7 (dd, J_{CF} = 10, 2 Hz), 124.1 (dd, J_{CF} = 12, 4 Hz), 119.5, 111.0 (dd, J_{CF} = 22, 4 Hz), 104.5 (d, J_{CF} = 2.6 Hz), 104.5 (d, J_{CF} = 50 Hz), 101.3.

Anal. Calcd for $C_{21}H_{14}BrF_2NO$: C, 60.89; H, 3.41. Found: C, 60.71; H, 3.28.

(*Z*)-1-(2-Bromophenyl)-3-phenyl-3-(3,4,5-trimethoxyanilino)prop-2-en-1-one (1h)
Yield: 89% (1 h); mp 144–145 °C; yellow solid.

IR (KBr,): 3432, 1569, 1508, 1317, 1235, 1129 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.64 (s, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.54 (d, *J* = 7.1 Hz, 1 H), 7.45–7.40 (m, 6 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 6.04 (s, 2 H), 5.74 (s, 1 H), 3.78 (s, 3 H), 3.58 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 161.2, 153.0, 142.8, 135.5, 134.8, 134.8, 133.5, 130.5, 129.7, 129.2, 128.5, 128.3, 127.2, 119.4, 100.8, 100.4, 60.9, 55.8.

Anal. Calcd for $C_{24}H_{22}BrNO_4$: C, 61.55; H, 4.73. Found: C, 61.51; H, 4.58.

(*Z*)-1-(2-Bromophenyl)-3-(4-chloroanilino)-3-phenylprop-2-en-1-one (1i)
Yield: 98% (3 h); mp 140–141 °C; yellow solid.

IR (KBr) 3435, 1604, 1587, 1558, 1502, 1475, 1309, 1292, 1211, 764, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.58 (s, 1 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.37–7.25 (m, 7 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 6.76 (d, *J* = 7.2 Hz, 2 H), 5.80 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 161.0, 142.8, 138.0, 134.9, 133.6, 130.8, 130.1, 129.8, 129.4, 128.9, 128.8, 128.5, 127.4, 124.6, 119.6, 101.3.

Anal. Calcd for $C_{21}H_{15}BrClNO$: C, 61.11; H, 3.66. Found: C, 61.21; H, 3.61.

(*Z*)-1-(2-Bromophenyl)-3-(butylamino)-3-phenylprop-2-en-1-one (1j)
Yield: 100% (1 h); pale yellow oil.

IR (neat): 3060, 2958, 2929, 2871, 1567, 1484, 1330, 754, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.21 (br s, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.50–7.41 (m, 6 H), 7.30 (t, *J* = 8.3 Hz, 1 H), 7.18 (dt, *J* = 7.4, 1.3 Hz, 1 H), 5.37 (s, 1 H), 3.25 (q, *J* = 6.5 Hz, 2 H), 1.58 (m, 2 H), 1.38 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1, 166.9, 143.5, 135.3, 133.3, 130.0, 129.6, 129.3, 128.5, 127.8, 127.1, 119.6, 97.0, 44.7, 32.8, 19.9, 13.7.

Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63. Found: C, 63.51; H, 5.51.

(*Z*)-3-(Benzylamino)-1-(2-bromophenyl)-3-phenylprop-2-en-1-one (1k)
Yield: 96% (1 h); pale yellow wax.

IR (neat): 3423, 3027, 1589, 1560, 1483, 1334, 758, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.52 (s, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.52 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.46–7.43 (m, 5 H), 7.38–7.27 (m, 6 H), 7.21 (t, *J* = 8.3 Hz, 1 H), 5.51 (s, 1 H), 4.48 (d, *J* = 6.4 Hz, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 166.7, 143.2, 138.1, 134.9, 133.3, 130.1, 129.7, 129.2, 128.7, 128.5, 127.8, 127.5, 127.1, 126.9, 119.5, 97.8, 48.5

Anal. Calcd for $C_{22}H_{18}BrNO$: C, 67.36; H, 4.62. Found: C, 67.29; H, 4.51.

(*Z*)-1-(2-Bromophenyl)-3-(cyclohexylamino)-3-phenylprop-2-en-1-one (1l)
Yield: 95% (5 h); pale yellow wax.

IR (neat): 3448, 2927, 2852, 1568, 1485, 1333, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.21 (d, *J* = 8.6 Hz, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.51–7.42 (m, 6 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 5.34 (s, 1 H), 3.35 (m, 1 H), 1.86 (m, 2 H), 1.75 (m, 2 H), 1.47 (m, 2 H), 1.22 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 165.8, 143.5, 135.7, 133.3, 130.0, 129.5, 129.3, 128.5, 127.6, 127.1, 119.6, 97.3, 53.1, 34.3, 25.3, 24.5.

Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77. Found: C, 65.70; H, 5.82.

(*Z*)-1-(2-Bromophenyl)-3-(*tert*-butylamino)-3-phenylprop-2-en-1-one (1m)
Yield: 66% (5 h); pale yellow wax.

IR (neat): 3413, 2966, 1589, 1344, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.51 (s, 1 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.48 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.41 (m, 5 H), 7.28 (m, 1 H), 7.17 (dt, *J* = 7.7, 1.5 Hz, 1 H), 5.22 (s, 1 H), 1.26 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 166.9, 143.5, 137.2, 133.3, 130.0, 129.0, 128.2, 127.9, 127.1, 119.5, 99.1, 54.4, 31.8.

Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63. Found: C, 63.80; H, 5.52.

(*Z*)-1-(2-Bromophenyl)-3-(4-chlorophenyl)-3-(3-methoxyanilino)prop-2-en-1-one (1n)
Yield: 92% (2 h); mp 84–85 °C; yellow solid.

IR (KBr): 3448, 1595, 1558, 1313, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.51 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.54 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.40–7.25 (m, 6 H), 7.08 (m, 1 H), 6.62 (dd, *J* = 15.0, 2.2 Hz, 1 H), 6.41 (m, 2 H), 5.74 (s, 1 H), 3.67 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 160.0, 159.9, 142.8, 140.2, 136.0, 133.9, 133.6, 130.7, 129.8, 129.6, 129.3, 128.9, 127.4, 119.5, 116.0, 110.8, 109.1, 101.0, 55.2.

Anal. Calcd for $C_{22}H_{17}BrClNO_2$: C, 59.68; H, 3.87. Found: C, 59.79; H, 3.99.

(*Z*)-1-(2-Bromophenyl)-3-(4-chlorophenyl)-3-(4-toluidino)prop-2-en-1-one (1o)
Yield: 99% (2 h); mp 148–149 °C; pale yellow solid.

IR (KBr): 3448, 1591, 1554, 1477, 1319, 1205, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.54 (s, 1 H), 7.63 (dd, *J* = 8.5, 0.8 Hz, 1 H), 7.54 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.40–7.24 (m, 6 H),

6.99 (d, J = 8.1 Hz, 2 H), 6.74 (d, J = 8.2 Hz, 2 H), 5.71 (s, 1 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6, 160.3, 143.0, 136.4, 135.9, 134.6, 133.9, 133.5, 130.6, 129.9, 129.6, 129.3, 128.9, 127.3, 123.7, 119.5, 110.4, 20.9.

Anal. Calcd for $C_{22}H_{17}BrClNO$: C, 61.92; H, 4.02. Found: C, 61.79; H, 3.92.

(*Z*)-1-(2-Bromophenyl)-3-(4-chlorophenyl)-3-(4-fluoroanilino)prop-2-en-1-one (1p)
Yield: 87% (3 h); mp 138–139 °C; pale yellow solid.

IR (KBr): 3448, 1579, 1558, 1512, 1477, 1321, 1203, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.51 (s, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.54 (d, J = 7.5 Hz, 1 H), 7.38 (t, J = 7.4 Hz, 1 H), 7.31–7.25 (m, 5 H), 6.91–6.80 (m, 4 H), 5.75 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 160.2, 159.9 (d, J_{CF} = 244 Hz), 142.7, 136.1, 135.1, 133.6, 133.5, 130.8, 129.9, 129.3, 129.0, 127.4, 125.4 (d, J_{CF} = 8 Hz), 119.5, 115.8 (d, J_{CF} = 23 Hz), 100.7.

Anal. Calcd for $C_{21}H_{14}BrClFNO$: C, 58.56; H, 3.28. Found: C, 58.39; H, 3.42.

(*Z*)-1-(2-Bromophenyl)-3-[4-(methoxycarbonyl)anilino]-3-(3-methoxyphenyl)prop-2-en-1-one (1q)
Yield: 82% (24 h); mp 132–133 °C; pale yellow solid.

IR (KBr): 3423, 1714, 1593, 1282, 1242, 1180, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.56 (s, 1 H), 7.84 (d, J = 8.6 Hz, 2 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.54 (dd, J = 7.6, 1.5 Hz, 1 H), 7.38 (t, J = 6.8 Hz, 1 H), 7.29–7.25 (m, 2 H), 6.99–6.94 (m, 3 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.87 (s, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 166.6, 160.0, 159.8, 143.7, 142.6, 136.3, 133.6, 130.9, 130.5, 130.0, 129.4, 127.4, 125.4, 122.0, 120.7, 119.5, 115.9, 113.7, 102.3, 55.4, 52.0.

Anal. Calcd for $C_{24}H_{20}BrNO_4$: C, 61.81; H, 4.32. Found: C, 61.89; H, 4.22.

(*Z*)-1-(2-Bromophenyl)-3-(3-methoxyphenyl)-3-[3-(trifluoromethyl)anilino]prop-2-en-1-one (1r)
Yield: 88% (2 h); pale yellow viscous oil.

IR (neat): 3443, 1574, 1454, 1313, 1238, 1124, 1070 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.62 (s, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.29–7.25 (m, 4 H), 7.10 (s, 1 H), 6.99–6.92 (m, 4 H), 5.87 (s, 1 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 160.5, 159.8, 142.6, 140.0, 136.0, 133.6, 131.3 (q, J_{CF} = 32 Hz), 130.9, 130.0, 129.4, 129.3, 127.4, 126.0, 123.7 (q, J_{CF} = 271 Hz), 120.7, 119.7, 119.7, 119.5, 116.0, 113.8, 101.7, 55.4.

Anal. Calcd for $C_{23}H_{17}BrF_3NO_2$: C, 58.00; H, 3.60. Found: C, 58.19; H, 3.42.

(*Z*)-1-(2-Bromophenyl)-3-(3-fluoroanilino)-3-(3-methoxyphenyl)prop-2-en-1-one (1s)
Yield: 91% (2 h); mp 112–113 °C; pale yellow solid.

IR (KBr): 3434, 1569, 1512, 1333, 1246, 1205, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.57 (s, 1 H), 7.64 (d, J = 7.9 Hz, 1 H), 7.55 (d, J = 7.6 Hz, 1 H), 7.37 (t, J = 7.4 Hz, 1 H), 7.28–7.22 (m, 2 H), 6.95–6.82 (m, 7 H), 5.78 (s, 1 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 161.5, 159.8 (d, J_{CF} = 244 Hz), 159.6, 142.9, 136.3, 135.4 (d, J_{CF} = 3 Hz), 133.6, 130.7, 129.8, 129.4, 127.3, 125.2 (d, J_{CF} = 8 Hz), 120.9, 119.6, 115.7 (d, J_{CF} = 5 Hz), 115.6, 113.9, 100.5, 55.3.

Anal. Calcd for $C_{22}H_{17}BrFNO_2$: C, 61.99; H, 4.02. Found: C, 62.11; H, 3.81.

(*Z*)-3-(3-Acetylphenyl)-1-(2-bromophenyl)-3-(4-chloroanilino)prop-2-en-1-one (1t)
Yield: 88% (2 h); mp 170–171 °C; yellow solid.

IR (KBr): 3435, 1591, 1554, 1327, 1261, 1217 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.48 (s, 1 H), 7.91 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.53 (dd, J = 7.6, 1.5 Hz, 1 H), 7.47 (d, J = 8.2 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 7.26 (dt, J = 7.9, 1.7 Hz, 1 H), 7.11 (d, J = 8.7 Hz, 2 H), 6.74 (d, J = 8.7 Hz, 2 H), 5.80 (s, 1 H), 2.60 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 192.2, 159.5, 142.5, 139.5, 138.0, 137.6, 133.6, 131.0, 130.2, 129.4, 129.1, 128.8, 128.7, 127.4, 124.6, 119.5, 101.6, 26.7.

Anal. Calcd for $C_{23}H_{17}BrClNO_2$: C, 60.75; H, 3.77. Found: C, 60.59; H, 3.52.

(*Z*)-3-(3-Acetylphenyl)-1-(2-bromophenyl)-3-(4-methoxyanilino)prop-2-en-1-one (1u)
Yield: 92% (1 h); mp 157–158 °C; yellow-orange solid.

IR (KBr): 3448, 1684, 1597, 1556, 1510, 1323, 1248 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.54 (s, 1 H), 7.87 (d, J = 7.9 Hz, 2 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.53 (dd, J = 7.8, 1.3 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 2 H), 7.35 (t, J = 7.2 Hz, 2 H), 7.24 (t, J = 7.3 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 2 H), 6.68 (d, J = 8.1 Hz, 2 H), 5.71 (s, 1H), 3.71 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 191.6, 160.6, 157.1, 142.9, 140.0, 137.7, 133.6, 131.8, 130.7, 129.4, 128.9, 128.4, 127.4, 125.3, 119.5, 114.2, 100.1, 55.4, 26.7.

Anal. Calcd for $C_{24}H_{20}BrNO_3$: C, 64.01; H, 4.48. Found: C, 63.89; H, 4.52.

(*Z*)-3-Anilino-1-(2-bromophenyl)oct-2-en-1-one (1v)
Yield: 82% (2 h); yellow oil.

IR (neat): 2956, 2929, 1591, 1491, 1294, 1108, 1026, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.83 (br s, 1 H), 7.61 (d, J = 6.3 Hz, 1 H), 7.50 (dd, J = 7.6, 1.4 Hz, 1 H), 7.42–7.04 (m, 3 H), 7.29–7.21 (m, 4 H), 5.55 (s, 1 H), 2.40 (t, J = 7.8 Hz, 2 H), 1.55 (m, 2 H), 1.25 (m, 4 H), 0.85 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 167.3, 143.4, 138.3, 133.4, 130.2, 129.3, 129.2, 127.2, 126.4, 125.6, 119.5, 96.8, 32.1, 31.4, 27.8, 22.2, 13.9.

Anal. Calcd for $C_{20}H_{22}BrNO$: C, 64.52; H, 5.96. Found: C, 64.41; H, 5.91.

(*Z*)-1-(2-Bromophenyl)-3-(4-methoxyanilino)oct-2-en-1-one (1w)
Yield: 87% (1 h); yellow oil.

IR (neat): 2956, 2931, 1595, 1566, 1514, 1248, 1034, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.65 (br s, 1 H), 7.60 (d, J = 7.9 Hz, 1 H), 7.50 (dd, J = 7.8, 1.5 Hz, 1 H), 7.35 (t, J = 7.4 Hz, 1 H), 7.21 (dt, J = 7.7, 1.6 Hz, 1 H), 7.14 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 5.50 (s, 1 H), 3.84 (s, 3 H), 2.32 (t, J = 7.7 Hz, 2 H), 1.51 (m, 2 H), 1.24 (m, 4 H), 0.84 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 168.1, 158.2, 143.5, 133.4, 131.0, 130.1, 129.2, 127.3, 127.2, 119.5, 114.4, 96.2, 55.5, 32.0, 31.4, 27.7, 22.2, 13.9.

Anal. Calcd for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01. Found: C, 62.61; H, 5.91.

(*Z*)-3-Anilino-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (1x)
Yield: 93% (2 h); mp 124–125 °C; yellow solid.

IR (KBr): 3435, 1591, 1558, 1479, 1313, 1211, 1036, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.72 (s, 1 H), 7.62 (m, 1 H), 7.46–7.21 (m, 8 H), 7.16 (t, *J* = 7.8 Hz, 2 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 6.85 (d, *J* = 7.9 Hz, 2 H), 5.84 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 161.4, 141.0, 139.3, 135.3, 131.1, 130.6, 129.9, 129.5, 128.9, 128.6, 128.5, 126.8, 124.5, 123.5, 101.1.

Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.65; H, 4.83. Found: C, 75.59; H, 4.61.

(*Z*)-1-(2-Chlorophenyl)-3-(4-methoxyanilino)-3-phenylprop-2-en-1-one (1y)
Yield: 92% (1 h); mp 136–137 °C; yellow-orange solid.

IR (KBr): 3423, 1604, 1570, 1508, 1483, 1331, 1213, 1032, 762 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.71 (s, 1 H), 7.60 (m, 1 H), 7.44–7.29 (m, 8 H), 6.80 (d, *J* = 8.9 Hz, 2 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 5.77 (s, 1 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.3, 162.0, 156.8, 141.1, 135.4, 132.2, 131.0, 130.4, 130.3, 129.8, 129.5, 129.5, 128.6, 128.5, 126.8, 125.1, 114.1, 100.1, 55.4.

Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 76.62; H, 4.99. Found: C, 76.71; H, 5.10.

(*Z*)-3-(4-Acetylanilino)-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (1z)
Yield: 75% (12 h); mp 157–158 °C; yellow-brown solid.

IR (KBr): 3448, 1676, 1589, 1566, 1319, 1268 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.63 (s, 1 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.59 (m, 1 H), 7.42–7.28 (m, 8 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 5.91 (s, 1 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 191.5, 159.9, 143.9, 140.5, 135.0, 132.6, 131.1, 130.9, 130.5, 130.3, 129.5, 129.4, 128.9, 128.3, 126.9, 122.0, 102.9, 26.4.

Anal. Calcd for $C_{23}H_{18}ClNO_2$: C, 73.50; H, 4.83. Found: C, 73.68; H, 4.71.

(*Z*)-3-(4-Chloroanilino)-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (1za)
Yield: 87% (4 h); mp 124–125 °C; yellow solid.

IR (KBr): 3448, 1604, 1589, 1552, 1500, 1309, 1211, 1080, 1039, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 12.63 (s, 1 H), 7.60 (m, 1 H), 7.45–7.33 (m, 8 H), 7.11 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 5.85 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 161.0, 140.8, 138.0, 135.0, 131.1, 130.7, 130.4, 130.1, 129.8, 129.5, 128.9, 128.8, 128.5, 126.8, 124.5, 101.5.

Anal. Calcd for $C_{21}H_{15}Cl_2NO$: C, 68.49; H, 4.11. Found: C, 68.29; H, 4.01.

(*Z*)-3-(Butylamino)-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (1zb)
Yield: 92% (2 h); pale yellow oil.

IR (neat): 3060, 2958, 2931, 2871, 1567, 1484, 1331, 1089, 1035, 756, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.26 (br s, 1 H), 7.53 (d, *J* = 7.7 Hz, 1 H), 7.45–7.37 (m, 6 H), 7.26 (dd, *J* = 7.7, 1.3 Hz, 1 H), 5.43 (s, 1 H), 3.25 (q, *J* = 6.5 Hz, 2 H), 1.58 (m, 2 H), 1.38 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1, 166.9, 141.4, 135.3, 130.9, 130.1, 129.9, 129.6, 129.4, 128.5, 127.7, 126.6, 97.3, 44.6, 32.8, 19.9, 13.7.

Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42. Found: C, 72.80; H, 6.33.

1,2-Disubstituted 4-Quinolones 2a–i,n–u; General Procedure
An oven-dried Schlenk tube was charged with the appropriate 1-(2-halophenyl)-2-en-3-amin-1-one **1** (1 equiv), CuI (5 mol%), DMEDA (5 mol%), K_2CO_3 (2 equiv), and DMSO (0.1 M). The tube was sealed and stirred at 80 °C for the period of time indicated below (and in Tables 2 and 3) for each product **2**. The reaction mixture was cooled to r.t., diluted with Et_2O (50 mL) and washed with 1 N HCl (2 × 10 mL) (except for **2h**) and a sat. NaCl soln (10 mL). The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc).

1,2-Diphenyl-4-quinolone (2a)
Yield: 93% (2.5 h) from **1a**; 95% (6 h) from **1x**; mp 280–281 °C; white-brownish solid.

IR (KBr): 1627, 1596, 1490, 1477, 1458, 1402, 1314, 1135, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 7.4 Hz, 1 H), 7.48 (d, *J* = 7.5 Hz, 1 H), 7.39–7.35 (m, 4 H), 7.20–7.16 (m, 7 H), 6.91 (d, *J* = 8.6 Hz, 1 H), 6.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 154.0, 142.6, 139.2, 135.7, 131.9, 130.0, 129.6, 129.2, 129.0, 128.6, 127.9, 126.3, 126.1, 123.8, 118.1, 112.6.

MS (EI, 70 eV): *m*/*z* (%) = 297 (100), 269 (96), 51 (57), 102 (51), 77 (50).

Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08. Found: C, 84.69; H, 4.99.

2-Phenyl-1-[3-(trifluoromethyl)phenyl]-4-quinolone (2b)
Yield: 92% (1.5 h); mp 235–236 °C; white solid.

IR (KBr): 3042, 1629, 1329, 1116, 752, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 7.9 Hz, 1 H), 7.59 (m, 1 H), 7.55–7.48 (m, 2 H), 7.45–7.36 (m, 3 H), 7.21–7.14 (m, 5 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 6.44 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 153.6, 142.3, 139.9, 135.2, 133.6, 132.3 (q, J_{CF} = 33 Hz), 132.2, 130.4, 129.1, 128.9, 128.2, 127.3 (q, J_{CF} = 4 Hz), 126.6, 126.1, 125.6 (q, J_{CF} = 4 Hz), 124.1, 123.2 (q, J_{CF} = 271 Hz), 117.5, 112.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.92.

MS (EI, 70 eV): *m*/*z* (%) = 365 (100), 337 (94).

Anal. Calcd for $C_{22}H_{14}F_3NO$: C, 72.32; H, 3.86. Found: C, 72.19; H, 3.95.

1-(4-Methoxyphenyl)-2-phenyl-4-quinolone (2c)
Yield: 89% (2 h) from **1c**; 83% (7 h) from **1y**; mp 201–202 °C (Lit.[20] 202–204 °C); white solid.

IR (KBr): 1625, 1507, 1458, 1405, 1251, 1027, 838, 758, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.44 (t, *J* = 7.1 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.21–7.16 (m, 5 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.42 (s, 1 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 159.5, 154.4, 143.0, 135.9, 131.9, 131.8, 131.0, 129.2, 128.6, 128.0, 126.2, 123.7, 118.2, 114.7, 112.5, 55.5.

MS (EI, 70 eV): *m*/*z* (%) = 327 (89), 299 (49), 102 (100).

Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23. Found: C, 80.80; H, 5.19.

1-(4-Acetylphenyl)-2-phenyl-4-quinolone (2d)
Yield: 87% (1.5 h) from **1d**; 83% (3 h) from **1z**; mp 221–222 °C; white solid.

IR (KBr): 1683, 1628, 1597, 1462, 1400, 1262, 763, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.20–7.15 (m, 5 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.41 (s, 1 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 177.8, 153.5, 143.3, 142.2, 137.1, 135.3, 132.1, 130.5, 129.6, 129.1, 129.0, 128.1, 126.4, 126.1, 124.0, 117.7, 112.8, 26.7.

MS (EI, 70 eV): *m*/*z* (%) = 339 (100), 327 (73), 311 (59), 102 (79).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05. Found: C, 81.29; H, 4.99.

1-(4-Chloro-1-naphthyl)-2-phenyl-4-quinolone (2e)
Yield: 92% (2 h); mp 239–240 °C; white solid.

IR (KBr): 1617, 1595, 1478, 1459, 1410, 1383, 1319, 1278, 1136, 762, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (m, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.52 (m, 2 H), 7.43 (m, 1 H), 7.36–7.29 (m, 3 H), 7.10–6.99 (m, 5 H), 6.43 (m, 1 H), 6.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 154.7, 142.6, 135.3, 134.7, 133.6, 132.3, 132.2, 131.4, 129.0, 128.8, 128.6, 128.4, 128.1, 127.8, 126.4, 126.1, 125.6, 125.4, 124.1, 123.2, 118.1, 113.0.

MS (EI, 70 eV): *m*/*z* (%) = 381 (100), 353 (49), 327 (20), 102 (59).

Anal. Calcd for $C_{25}H_{16}ClNO$: C, 78.63; H, 4.22. Found: C, 78.75; H, 4.29.

1-(4-Cyanophenyl)-2-phenyl-4-quinolone (2f)
Yield: 82% (2 h); mp 255–256 °C; white solid.

IR (KBr): 3038, 2234, 1628, 1600, 1508, 1481, 1466, 1413, 1318, 768, 748, 737, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.49 (t, *J* = 8.3 Hz, 1 H), 7.36 (m, 3 H), 7.28–7.21 (m, 3 H), 7.15 (m, 2 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 6.40 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 153.2, 143.3, 142.0, 135.0, 133.5, 132.3, 131.3, 129.2, 129.1, 128.4, 126.7, 126.1, 124.3, 117.5, 117.3, 113.2, 113.1.

MS (EI, 70 eV): *m*/*z* (%) = 322 (100), 294 (88).

Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38. Found: C, 81.79; H, 4.22.

1-(2,4-Difluorophenyl)-2-phenyl-4-quinolone (2g)
Yield: 72% (1.5 h); mp 187–188 °C; white solid.

IR (KBr): 1683, 1628, 1597, 1462, 1400, 1262, 763, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.51 (d, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.29–7.17 (m, 6 H), 6.91–6.83 (m, 3 H), 6.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 163.3 (dd, J_{CF} = 252, 11 Hz), 158.7 (dd, J_{CF} = 251, 11 Hz), 154.0, 142.1, 135.0, 132.5 (d, J_{CF} = 10 Hz), 132.3, 129.1, 128.4, 128.1, 126.5, 126.0, 124.0, 123.4 (dd, J_{CF} = 13, 4 Hz), 116.8, 112.8, 112.3 (dd, J_{CF} = 22, 4 Hz), 105.2 (dd, J_{CF} = 26, 23 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.3, –113.4.

MS (EI, 70 eV): *m*/*z* (%) = 339 (100), 327 (88), 331 (56), 299 (32).

Anal. Calcd for $C_{21}H_{13}F_2NO$: C, 75.67; H, 3.93. Found: C, 75.75; H, 3.99.

2-Phenyl-1-(3,4,5-trimethoxyphenyl)-4-quinolone (2h)
Yield: 81% (2 h); mp 222–223 °C; white solid.

IR (KBr): 1626, 1598, 1503, 1464, 1421, 1265, 1239, 1125, 753, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.26–7.19 (m, 5 H), 7.05 (d, *J* = 8.6 Hz, 1 H), 6.38 (s, 3 H), 3.81 (s, 3 H), 3.69 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 153.9, 153.7, 142.5, 138.5, 135.9, 134.4, 131.9, 128.9, 128.7, 127.9, 126.3, 126.1, 123.8, 118.1, 112.6, 107.8, 61.1, 56.5.

MS (EI, 70 eV): *m*/*z* (%) = 387 (100).

Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46. Found: C, 74.21; H, 5.23.

1-(4-Chlorophenyl)-2-phenyl-4-quinolone (2i)
Yield: 91% (2 h) from **1i**; 92% (3 h) from **1za**; mp 206–207 °C; white solid.

IR (KBr): 3044, 1267, 1599, 1487, 1466, 1413, 1318, 840, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 7.4 Hz, 1 H), 7.47 (dt, *J* = 7.1, 1.5 Hz, 1 H), 7.37–7.33 (m, 3 H), 7.23–7.11 (m, 7 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 6.40 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 153.8, 143.3, 142.5, 137.8, 135.4, 135.0, 132.1, 131.4, 129.9, 129.2, 128.9, 128.2, 126.4, 126.1, 124.0, 117.8, 112.8.

MS (EI, 70 eV): *m*/*z* (%) = 373 (100), 345 (67), 330 (41).

Anal. Calcd for $C_{21}H_{14}ClNO$: C, 76.02; H, 4.25. Found: C, 76.09; H, 4.32.

2-(4-Chlorophenyl)-1-(3-methoxyphenyl)-4-quinolone (2n)
Yield: 87% (2.5 h); mp 211–212 °C; white solid.

IR (KBr): 1631, 1597, 1480, 1418, 1251, 852, 828, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.48 (dt, *J* = 7.1, 1.4 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.30 (t, *J* = 8.1 Hz, 1 H), 7.21–7.14 (m, 4 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 6.90 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.78 (dd, *J* = 8.3, 1.0 Hz, 1 H), 6.69 (m, 1 H), 6.37 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 160.6, 152.6, 142.5, 139.9, 134.9, 134.2, 132.1, 130.4, 128.3, 126.3, 126.1, 124.0, 122.2, 118.1, 115.8, 114.8, 112.7, 55.6.

MS (EI, 70 eV): *m*/*z* (%) = 395 (100), 367 (63).

Anal. Calcd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46. Found: C, 74.88; H, 4.32.

2-(4-Chlorophenyl)-1-(4-tolyl)-4-quinolone (2o)
Yield: 85% (1.5 h); mp 211–212 °C; white solid.

IR (KBr): 3035, 1629, 1514, 1480, 1420, 1319, 1094, 828, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.45 (dt, *J* = 7.8, 1.5 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 7.19–7.11 (m, 6 H), 7.02 (d, *J* = 8.2 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 1 H), 6.37 (s, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 152.9, 142.8, 139.3, 136.3, 134.8, 134.3, 132.0, 130.6, 130.5, 129.6, 128.3, 126.2, 126.1, 123.9, 118.2, 112.6, 21.3.

MS (EI, 70 eV): *m*/*z* (%) = 345 (100), 317 (79), 281 (13).

Anal. Calcd for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66. Found: C, 76.29; H, 4.77.

2-(4-Chlorophenyl)-1-(4-fluorophenyl)-4-quinolone (2p)
Yield: 87% (2 h); mp 252–253 °C; white solid.

IR (KBr): 1630, 1510, 1480, 1419, 1230, 1159, 1092, 1021, 840, 819, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.48 (dt, *J* = 7.2, 1.4 Hz, 1 H), 7.34 (t, *J* = 7.7 Hz, 1 H), 7.21–7.07 (m, 8 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 6.35 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 162.3 (d, J_{CF} = 250 Hz), 152.7, 142.7, 135.1, 135.0 (d, J_{CF} = 4 Hz), 134.0, 132.2, 131.8 (d, J_{CF} = 8 Hz), 130.5, 128.5, 126.4, 126.1, 124.1, 117.8, 117.0 (d, J_{CF} = 23 Hz), 112.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –110.3.

MS (EI, 70 eV): *m*/*z* (%) = 349 (100), 321 (88), 285 (23).

Anal. Calcd for $C_{21}H_{13}ClFNO$: C, 72.11; H, 3.75. Found: C, 71.99; H, 3.58.

2-(3-Methoxyphenyl)-1-[(4-methoxycarbonyl)phenyl]-4-quinolone (2q)
Yield: 75% (2.5 h); mp 218–219 °C; white solid.

IR (KBr): 2953, 1726, 1626, 1598, 1464, 1408, 1280, 1115, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 7.9 Hz, 1 H), 8.05 (d, *J* = 8.3 Hz, 2 H), 7.46 (t, *J* = 8.2 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.09 (t, *J* = 7.9 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 6.76–6.72 (m, 3 H), 6.34 (s, 1 H), 3.92 (s, 3 H), 3.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 165.8, 159.1, 153.3, 143.2, 142.2, 136.5, 132.1, 130.9, 130.6, 130.2, 129.3, 126.5, 126.1, 124.0, 121.7, 117.7, 114.9, 114.6, 112.8, 55.3, 52.5.

MS (EI, 70 eV): *m*/*z* (%) = 385 (51), 357 (27), 59 (100).

Anal. Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97. Found: C, 74.88; H, 4.78.

2-(3-Methoxyphenyl)-1-[3-(trifluoromethyl)phenyl)]-4-quinolone (2r)
Yield: 72% (2.5 h); mp 245–246 °C; white solid.

IR (KBr): 3059, 1631, 1599, 1496, 1466, 1408, 1323, 1167, 1120, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 8.0 Hz, 1 H), 7.62 (m, 1 H), 7.56–7.48 (m, 3 H), 7.41–7.36 (m, 2 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 6.74 (t, *J* = 8.4 Hz, 2 H), 6.67 (s, 1 H), 6.45 (s, 1 H), 3.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 159.1, 153.4, 142.3, 139.9, 136.3, 133.5, 132.3, 132.2 (q, J_{CF} = 33 Hz), 130.4, 129.4, 127.3 (q, J_{CF} = 3 Hz), 126.6, 126.2, 125.8 (q, J_{CF} = 3 Hz), 124.1, 123.2 (q, J_{CF} = 271 Hz), 121.6, 117.5, 115.0, 114.5, 112.8, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.9.

MS (EI, 70 eV): *m*/*z* (%) = 395 (100), 367 (55).

Anal. Calcd for $C_{23}H_{16}F_3NO_2$: C, 69.87; H, 4.08. Found: C, 69.69; H, 3.99.

1-(4-Fluorophenyl)-2-(3-methoxyphenyl)-4-quinolone (2s)
Yield: 83% (4 h); mp 188–189 °C; white solid.

IR (KBr): 3042, 1631, 1597, 1509, 1465, 1403, 1219, 1039, 849, 808, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.48 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 7.20–7.05 (m, 5 H), 6.88 (d, *J* = 8.6 Hz, 1 H), 6.78–6.71 (m, 3 H), 6.41 (s, 1 H), 3.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 162.2 (d, J_{CF} = 249 Hz), 159.0, 153.8, 142.7, 136.7, 135.2 (d, J_{CF} = 4 Hz), 132.0, 131.8 (d, J_{CF} = 9 Hz), 129.2, 126.4, 126.2, 123.9, 121.7, 117.8, 116.7 (d, J_{CF} = 23 Hz), 115.0, 114.4, 112.6, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –110.9.

MS (EI, 70 eV): *m*/*z* (%) = 345 (100), 317 (67).

Anal. Calcd for $C_{22}H_{16}FNO_2$: C, 76.51; H, 4.67. Found: C, 76.39; H, 4.80.

2-(4-Acetylphenyl)-1-(4-chlorophenyl)-4-quinolone (2t)
Yield: 81% (2 h); mp 248–249 °C; white solid.

IR (KBr): 3056, 1690, 1625, 1598, 1490, 1410, 1266, 1017, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ: = 8.42 (d, *J* = 7.5 Hz, 1 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 7.0 Hz, 1 H), 7.36–7.23 (m, 5 H), 7.16 (d, *J* = 7.5 Hz, 2 H), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.35 (s, 1 H), 2.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 177.6, 152.5, 142.4, 139.8, 137.4, 137.0, 135.3, 132.3, 131.3, 130.2, 129.5, 128.1, 126.4, 126.1, 124.2, 117.8, 112.7, 26.6.

MS (EI, 70 eV): *m*/*z* (%) = 373 (100), 345 (53), 330 (41).

Anal. Calcd for $C_{23}H_{16}ClNO_2$: C, 73.90; H, 4.31. Found: C, 73.77; H, 4.09.

2-(4-Acetylphenyl)-1-(4-methoxyphenyl)-4-quinolone (2u)
Yield: 70% (2.5 h); mp 236–237 °C.

IR (KBr): 1683, 1624, 1599, 1511, 1462, 1413, 1258, 833, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 7.7 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 7.47 (t, *J* = 7.1 Hz, 1 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 7.7 Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.37 (s, 1 H), 3.78 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 177.6, 159.6, 153.1, 142.9, 140.2, 136.7, 132.0, 131.3, 130.8, 129.4, 127.8, 126.1, 126.1, 123.9, 118.0, 114.8, 112.3, 55.4, 26.5.

MS (EI, 70 eV): *m*/*z* (%) = 369 (100), 341 (40).

Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18. Found: C, 77.87; H, 5.00.

1,2-Disubstituted 4-Quinolones 2j–l; General Procedure
An oven-dried Schlenk tube was charged with the appropriate 1-(2-halophenyl)-2-en-3-amin-1-one **1** (1 equiv), CuI (5 mol%), DMEDA (5 mol%), *t*-BuONa (2 equiv), and DMSO (0.1 M). The tube was sealed and stirred at 80 °C for the period of time indicated below (and in Tables 2 and 3) for each product **2**. The reaction mixture was cooled to r.t., diluted with Et_2O, and washed with a sat. NaCl soln. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc).

1-Butyl-2-phenyl-4-quinolone (2j)
Yield: 86% (1 h) from **1j**; 89% (3 h) from **1zb**; mp 72–73 °C; pale brown crystals.

IR (KBr): 2963, 2933, 2874, 1626, 1594, 1483, 1462, 1415, 1302, 1173, 763, 706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.69 (dt, *J* = 7.7, 1.2 Hz, 1 H), 7.55 (m, 1 H), 7.50–7.48 (m, 3 H), 7.31–7.48 (m, 3 H), 6.24 (s, 1 H), 4.02 (t, *J* = 7.7 Hz, 2 H), 1.66 (m, 2 H), 1.16 (m, 2 H), 0.75 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 154.6, 140.7, 136.1, 132.2, 129.4, 128.7, 128.3, 127.4, 127.1, 123.5, 116.3, 112.9, 48.0, 30.8, 19.7, 13.4.

MS (EI, 70 eV): *m*/*z* (%) = 277 (56), 234 (100).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90. Found: C, 82.10; H, 6.97.

1-Benzyl-2-phenyl-4-quinolone (2k)
Yield: 53% (1 h); mp 118–119 °C; white crystals.

IR (KBr): 1626, 1599, 1484, 1416, 1312, 1269, 737, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 7.8 Hz, 1 H), 7.54 (t, *J* = 7.1 Hz, 1 H), 7.47–7.25 (m, 10 H), 7.01 (d, *J* = 7.2 Hz, 3 H), 6.37 (s, 1 H), 5.30 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7, 155.1, 141.2, 136.4, 135.7, 132.4, 129.7, 129.1, 128.7, 128.2, 127.7, 127.3, 126.9, 125.5, 123.8, 117.3, 113.2, 52.2.

MS (EI, 70 eV): *m*/*z* (%) = 311 (56), 91 (100).

Anal. Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50. Found: C, 84.90; H, 5.69.

1-Cyclohexyl-2-phenyl-4-quinolone (2l)
Yield: 36% (2 h); mp 199–200 °C; white crystals.

IR (KBr): 2936, 2852, 1626, 1598, 1484, 1400, 1260, 1169, 764, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.64 (t, *J* = 7.1, 1.7 Hz, 1 H), 7.51 (m, 3 H), 7.42–7.37 (m, 3 H), 6.23 (s, 1 H), 4.17 (m, 1 H), 2.44 (m, 2 H), 1.86 (m, 4 H), 1.63 (m, 1 H), 1.22–1.00 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 155.7, 141.1, 137.4, 130.9, 129.4, 128.8, 128.2, 127.7, 127.2, 123.3, 118.9, 113.4, 63.5, 31.1, 26.5, 25.2.

MS (EI, 70 eV): *m*/*z* (%) = 303 (100), 221 (67).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98. Found: C, 83.00; H, 6.79.

Acknowledgment

The work was carried out in the framework of FIRB 2003 supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica and by the University 'La Sapienza'.

References

(1) For recent reviews, see: (a) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463. (b) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.

(2) For some recent references, see: (a) Tietcheu, C.; Garcia, C.; Gardette, D.; Dugat, D.; Gramain, J.-C. *J. Heterocycl. Chem.* **2002**, *39*, 965. (b) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081. (c) Bellur, E.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 2151. (d) Cruz, M. C.; Jiménez, F.; Delgado, F.; Tamariz, J. *Synlett* **2006**, 749. (e) Ursic, U.; Bevk, D.; Pirc, S.; Pezdirc, L.; Stanovnik, B.; Svete, J. *Synthesis* **2006**, 2376. (f) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046. (g) Yan, S.; Wu, H.; Wu, N.; Jiang, Y. *Synlett* **2007**, 2699.

(3) For some recent references, see: (a) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Synth. Catal.* **2006**, *348*, 2571. (b) Hu, H.-Y.; Liu, Y.; Ye, M.; Xu, J.-H. *Synlett* **2006**, 1913. (c) Nishiwaki, N.; Nishimoto, T.; Tamura, M.; Ariga, M. *Synlett* **2006**, 1437. (d) Pešková, M.; Šimůnek, P.; Bertolasi, V.; Macháček, V.; Lyčka, A. *Organometallics* **2006**, *25*, 2025. (e) Tu, S.; Jiang, B.; Jia, R.-H.; Zhang, J.-Y.; Zhang, Y.; Yao, C.-S.; Shi, F. *Org. Biomol. Chem.* **2006**, *4*, 3664. (f) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345. (g) Tu, S.; Li, C.; Li, G.; Cao, L.; Shao, Q.; Zhou, D.; Jiang, B.; Zhou, J.; Xia, M. *J. Comb. Chem.* **2007**, *9*, 1144. (h) Cheng, X.-M.; Liu, X.-M. *J. Comb. Chem.* **2007**, *9*, 906. (i) Cunha, S.; Damasceno, F.; Ferrari, J. *Tetrahedron Lett.* **2007**, *48*, 5795. (j) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593.

(4) (a) Osuka, A.; Mori, Y.; Suzuki, H. *Chem. Lett.* **1982**, 2031. (b) Yang, S. C.; Wang Huey, M.; Kuo, C. S.; Chen, L. C. *Heterocycles* **1991**, *32*, 2399. (c) Gravestock, D.; Dovey, M. C. *Synthesis* **2003**, 523. (d) Gravestock, D.; Dovey, M. C. *Synthesis* **2003**, 1470.

(5) For some selected palladium-catalyzed reactions, see: (a) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938. (b) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927. (c) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215. (d) Michael, J. P.; Chang, S.-F.; Wilson, C. *Tetrahedron Lett.* **1993**, *34*, 8365. (e) Koerber-Plé, K.; Massiot, G. *Synlett* **1994**, 759. (f) Chen, L.-C.; Yang, S.-C.; Wang, H.-M. *Synthesis* **1995**, 385. (g) Latham, E. J.; Stanfoth, S. P. *Chem. Commun.* **1996**, 2253. (h) Latham, E. J.; Stanfoth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2059. (i) Blache, Y.; Sinibaldi-Troin, M.-E.; Voldoire, A.; Chavignon, O.; Gramain, J.-C.; Teulade, J.-C.; Chapat, J.-P. *J. Org. Chem.* **1997**, *62*, 8553. (j) Edmonson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109. (k) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2002**, *4*, 191. (l) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011. (m) Sorensen, U. S.; Pombo-Villar, E. *Helv. Chim. Acta* **2004**, *87*, 82. (n) Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Dommisse, R. A.; Lemière, G. L. F.; Košmrlj, J.; Mátyus, P. *Tetrahedron* **2004**, *60*, 2283. For copper-catalyzed reactions, see ref. 2g. For gold-catalyzed reactions see: (o) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715. For silver-catalyzed reactions, see: (p) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Tetrahedron Lett.* **2004**, *45*, 6787.

(6) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629.

(7) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles and Health,* In *Heterocycles in Life and Society*; John Wiley: Chichester UK, **1997**, 135–164.

(8) Nakamura, S.; Kozuka, M.; Bastow, K. F.; Tokuda, H.; Nishino, H.; Suzuki, M.; Tatsuzaki, J.; Natschke, S. L. M.; Kuo, S.-C.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 4396.

(9) Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831.

(10) Osawa, T.; Ohta, H.; Akimoto, K.; Harada, K.; Soga, H.; Jinno, Y. EP 343574, **1989**; *Chem. Abstr.* **1990**, *112*, 235197.

(11) (a) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932. (b) Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.;

Lawson, M. A.; Dumontet, C.; Boumendjel, A. *J. Med. Chem.* **2004**, *47*, 4964. (c) Hradil, P.; Krejcí, P.; Hlavác, J.; Wiedermannová, I.; Lycka, A.; Bertolasi, V. *J. Heterocycl. Chem.* **2004**, *41*, 375. (d) Lai, Y.-Y.; Hung, L.-J.; Lee, K.-H.; Xiao, Z.; Bastow, K. F.; Yamori, T.; Kuo, S.-C. *Bioorg. Med. Chem.* **2005**, *13*, 265. (e) Ferlin, M. G.; Chiarelotto, G.; Gasparotto, V.; Via, L. D.; Pezzi, V.; Barzon, L.; Palu, G.; Castagliuolo, I. *J. Med. Chem.* **2005**, *48*, 3417. (f) Gasparotto, V.; Castagliuolo, I.; Chiarelotto, G.; Pezzi, V.; Montanaro, D.; Brun, P.; Palu, G.; Viola, G.; Ferlin, M. G. *J. Med. Chem.* **2006**, *49*, 1910.

(12) Huang, L.-J.; Hsieh, M.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C. *Bioorg. Med. Chem.* **1998**, *6*, 1657.

(13) (a) Llinàs-Brunet, M.; Bailey, M. D.; Ghiro, E.; Gorys, V.; Halmos, T.; Poirier, M.; Rancourt, J.; Goudreau, N. *J. Med. Chem.* **2004**, *47*, 6584. (b) Wu, F. X. H.; Nakajima, S.; Or, Y. S.; Lu, Z.-H.; Sun, Y.; Miao, Z.; Wang, Z. WO 2005010029, **2005**; *Chem. Abstr.* **2005**, *142*, 198355. (c) Frutos, R. P.; Haddad, N.; Houpis, I. N.; Johnson, M.; Smith-Keenan, L. L.; Fuchs, V.; Yee, N. K.; Farina, V.; Faucher, A.-M.; Brochu, C.; Haché, B.; Duceppe, J.-S.; Beaulieu, P. *Synthesis* **2006**, 2563.

(14) For recent reviews, see: (a) Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, M. M. *Curr. Org. Chem.* **2005**, *9*, 141. (b) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559. For other selected references, see: (c) Glushkov, R. G.; Marchenko, N. B.; Padeiskaya, E. N.; Shipilova, L. D. *Khim.-Farm. Zh.* **1990**, *24*, 24. (d) White, L. A.; Storr, R. C. *Tetrahedron* **1996**, *52*, 3117. (e) Clemencin-Le Guillou, C.; Remuzon, P.; Bouzard, D.; Quirion, J.-C.; Giorgi-Renault, S.; Husson, H.-P. *Tetrahedron* **1998**, *54*, 83. (f) Liu, Y.; Yu, C.-Y.; Wang, M.-X. *ARKIVOC* **2003**, *(ii)*, 146. (g) Ding, D.; Li, X.; Wang, X.; Du, Y.; Shen, J. *Tetrahedron Lett.* **2006**, *47*, 6997. (h) Park, C.-H.; Lee, J.; Jung, H. Y.; Kim, M. J.; Lim, S. H.; Yeo, H. T.; Choi, E. C.; Yoon, E. J.; Kim, K. W.; Cha, J. H.; Kim, S.-H.; Chang, D.-J.; Kwon, D.-Y.; Li, F.; Suh, Y.-G. *Bioorg. Med. Chem.* **2007**, *15*, 6517. (i) Al-Hiari, Y. M.; Al-Mazari, I. S.; Shakya, A. K.; Darwish, R. M.; Abu-Dahab, R. *Molecules* **2007**, *12*, 1240. (j) Zewge, D.; Chen, C.-y.; Deer, C.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2007**, *72*, 4276. (k) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968.

(15) Karpov, A. S.; Muller, T. J. J. *Org. Lett.* **2003**, *5*, 3451.

(16) In general, the use of copper catalysts proved superior to that of palladium catalysts in this reaction. For example, **2a** was isolated in only 25% yield when **1a** was subjected to $Pd_2(dba)_3$ (0.025 equiv), P(*o*-Tol)$_3$ (0.1 equiv), and Cs_2CO_3 (2 equiv) in toluene at 80 °C for 8 hours.

(17) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708.

(18) The enaminone derivative containing a 4-bromophenyl substituent (instead of the 2-halophenyl group in **1**), and with R^1 = *n*-Bu, R^2 = Ph was recovered essentially unchanged after 8 hours when it was subjected to standard cyclization conditions.

(19) (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802.

(20) Bell, M. R.; Zalay, A. W.; Oesterlin, R.; Schane, P.; Potts, G. O. *J. Med. Chem.* **1970**, *13*, 664.