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A methodology for the synthesis of highly functionalized 2- and 4-aminoquinoline derivatives

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ABSTRACT

A methodology for the synthesis of 2- and 4-aminoquinoline derivatives, which takes advantage of selective activation of 2- or 4-substituent of 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**, has been developed. Since a procedure for formation of 3-aminoquinolinones from the 4-quinolinone **1** was described previously, the new methodology comprises a general methodology for the selective syntheses of three isomeric 2-, 3- and 4-aminoquinoline derivatives starting with the common 4-quinolinone **1**.

1. Introduction

Quinoline and quinolinone derivatives are important heterocyclic compounds that constitute core structures of many naturally occurring substances that have interesting biological and pharmaceutical properties.[1] In this family, 2- and 4-aminoquinoline derivatives are especially important in that they possess a wide range of pharmaceutical activities including antimalarial,[2] anti-HIV,[3] anti-Alzheimer disease,[4] melanin-concentrating hormone 1 receptor (MCHR) antagonist,[5] and Src kinase inhibitor.[6] Consequently, the development of efficient methods for the synthesis of these heterocyclic compounds has continued to be an important goal. Although some methods are currently available for the preparation of these targets,[1,7] the design of new and simple routes for the preparation of aminoqinolines and aminoquinolones, particularly those that are highly functionalized, remains a significant challenge. In our continuing efforts aimed at the synthesis of 4-quinolinone analogs for biological testing,[8] a need arose for various aminoquinolines. Herein, we report the results of an investigation that led to a new strategy for facile preparation of highly functionalized 2- and 4-aminoquinoline beginning with the common 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** (Fig. 1).

2. Results and discussion

In devising a strategy for the synthesis of 2- and 4-aminoquinoline, we envisioned that selective transformation of 2- and 4-substituent in 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** into good leaving groups would enable subsequent treatment with various amines to afford the corresponding 2- and 4-aminoquinoline. To test this proposal in the context of the synthesis of 4-aminoquinoline **4**, **1** was converted to 4-methanesulfonyloxyquinoline **2** in good yield by reaction with methanesulfonyl chloride under basic conditions (Fig. 2).

Reaction of morpholine with **2** led to the formation of the desired 4-morpholino-quinoline **4** along with 4-quinolinone **1** as side product. The competitive, undesired process leading to **1** likely takes place by attack of the amine at the 4-sulfonyl sulfur atom of **2** instead of the C-4 carbon. Consistent with this explanation is the finding that *N*-methanesulfonyl morpholine was also produced in this reaction. The yields of 4-morpholino-quinoline **4** were highly

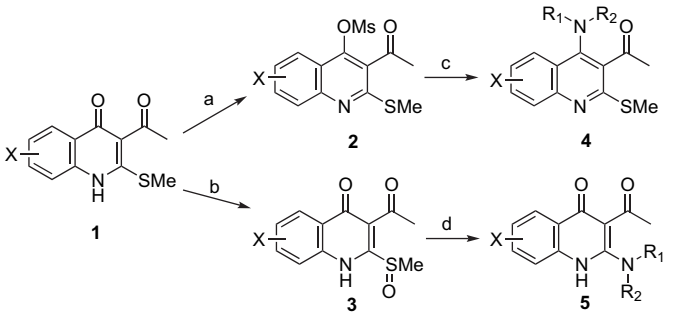

Figure 1. Syntheses of 2-aminoquinolin-4-one **5** and 4-aminoquinoline **4** from 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**. (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (b) H_2O_2, AcOH; (c) R_1R_2NH, base/solvent; (d) R_1R_2NH, THF.

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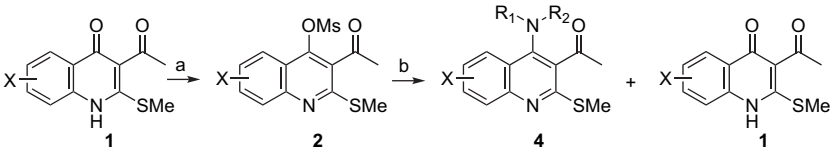


Figure 2. Synthesis of 4-amino-4-quinolinone **4** from 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**. (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt; (b) R_1R_2NH, K_2CO_3, CH_2Cl_2, reflux.

dependent on both the reaction conditions and the nature of substituents in **2**. For example, reaction of morpholine with **2** in the presence of Et_3N in CH_2Cl_2 gave the desired 4-morphorinoquinoline **4** in only 12% yield and undesired 4-quinolinone **1** as major product (70%). In contrast, the yield of **4** increased significantly (91%) when reaction of morpholine with **2** was performed in the presence of K_2CO_3 as base. Also, reactions of **2** with benzylamine and isobutylamine, employing K_2CO_3 as the base, produced the corresponding 4-aminoquinolines **4** as major products. Quinolines **2** containing strong electron withdrawing substituents were highly reactive as exemplified by the observation that reactions of **2d** with amines were completed in 3 h and high yields (Table 1, entries 10 and 11). In contrast to reactions with alkylamines, 4-methanesulfonyloxyquinoline **2a** is unreactive with aromatic amines, such as aniline. 6-Chloro-8-trifluoromethyl-4-methanesulfonyloxyquinoline **2c** bearing electron withdrawing substituents is also resistant to the reaction with aniline under the same reaction condition only producing small amount of undesired **1c** and recovery of most of **2c**. The results of these exploratory studies are summarized in Table 1.

In the next phase of this effort, a route for the synthesis of 2-amino-4-quinolinones **5** from 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** was investigated. For this purpose, 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** was converted to 2-methylsulfinyl-3-acyl-1*H*-quinolin-4-one **3**, the latter is more susceptible to nucleophilic substitution reactions with amines. The requisite sulfoxides **3** were obtained in good yields by oxidation of the corresponding sulfides **1** with hydrogen peroxide in acetic acid (Fig. 3).[9] Treatment of 2-methylsulfinyl-1*H*-quinolin-4-one **3** with various alkylamines at room temperature in THF leads to smooth formation of the corresponding 2-amino-4-quinolinones **5**.[10] We obtained 2-aminoquinolin-4-one **5** from the corresponding **3** with the same substituents of 4-aminoquinoline **4** and amines systematically to show the usefulness of the present method to obtain **4** and **5** selectively from the common starting compound **1** (compare Table 2, entries 1–11 with Table 1, entries 1–11).

Independent of the nature of substituents on the 2-methylsulfinyl-3-acyl-1*H*-quinolin-4-one ring system, substitution reactions with diverse amines take place to provide the corresponding 2-amino-4-quinolinones **5** in good yields. For example, 3-benzoyl-2-methylsulfinyl-1*H*-quinolin-4-ones react with amines to form the corresponding 3-benzoyl-2-amino-1*H*-quinolin-4-ones **5** in good yields (Table 2, entries 15 and 17). Sterically bulky amines such as *tert*-butylamine and *N*-methyl-*N*-phenylamine also smoothly react with **3** affording the corresponding 2-amino-3-acyl-1*H*-quinolin-4-ones **5** (Table 2, entries 13 and 18). The analogous substitution reactions of **3** with aromatic amines take place only slowly at room temperature, but they can be driven to completion when run in refluxing 1,2-dichlorobenzene (Table 2, entries 12 and 13). The results arising from these studies, summarized in Table 2, show that the reactions of 2-methylsulfinyl-3-acyl-1*H*-quinolin-4-ones **3** with amines stand as a versatile and convenient method to prepare 2-amino-3-acyl-1*H*-quinolin-4-ones. Especially important is the fact that this approach to 2-aminoquinolinone synthesis compares favorably with the previously reported method involving condensation of α-benzoylketenedithioacetal with 2-aminobenzoates,[7] which has only limited versatility.

Earlier, we described the preparation of 3-aminoquinolinone **8** by hydrolysis of oxazoloquinoline **7**, which was prepared from the

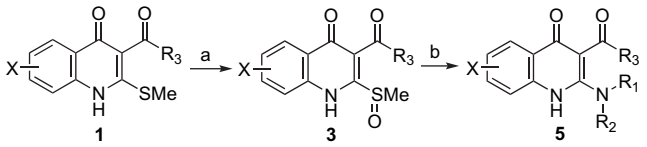
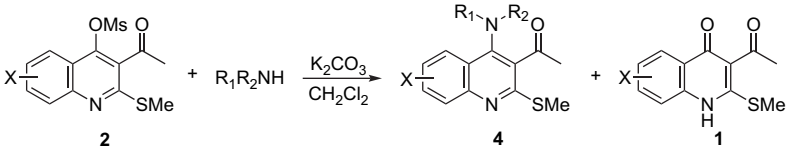


Figure 3. Synthesis of 2-amino-4-quinolinone **5** from 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**. (a) H_2O_2, AcOH (69–98%); (b) R_1R_2NH, THF/rt (for alkylamines) or 1,2-dichlorobenzene/reflux (for aromatic amines) (see Table 2).

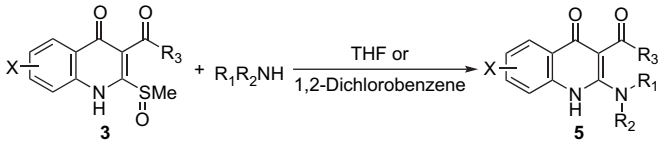
Table 1
Summary of reactions of 4-methanesulfonyloxyquinolines **2** with amines to yield 4-aminoquinolines **4**



Entry	Number	X	R_1R_2NH	Time (day)	Yield (%)[a]	
					4	**1**
1	**4a**	H	$PhCH_2NH_2$	3	51	45
2	**4b**	H	Morpholine	1	91[b]	[c]
3	**4c**	H	$(CH_3)_2CHCH_2NH_2$	3	75	[c]
4	**4d**	6-Cl	$PhCH_2NH_2$	3	47	43
5	**4e**	6-Cl	Morpholine	2	90	[c]
6	**4f**	6-Cl	$(CH_3)_2CHCH_2NH_2$	2	66	4
7	**4g**	6-Cl-8-CF_3	$PhCH_2NH_2$	3	66	25
8	**4h**	6-Cl-8-CF_3	Morpholine	3	66[b]	7
9	**4i**	6-Cl-8-CF_3	$(CH_3)_2CHCH_2NH_2$	3	61[b]	[c]
10	**4j**	5-NO_2-8-Cl	$PhCH_2NH_2$	3 h	95	[c]
11	**4k**	5-NO_2-8-Cl	$(CH_3)_2CHCH_2NH_2$	3 h	90[b]	[c]

[a] Amine (3.0 equiv) was used.
[b] Amine (1.2 equiv) was used.
[c] Trace amount of **1** was obtained.

Table 2
Summary of the reactions of 2-methylsulfinyl-3-acyl-1*H*-quinolin-4-one **3** with amines to form 2-amino-4-quinolinones **5**



3 **5**

Entry	Number	X	R_3	R_1R_2NH	Yield (%)[a]
1	**5a**	H	Me	$PhCH_2NH_2$	85
2	**5b**	H	Me	Morpholine	66
3	**5c**	H	Me	$(CH_3)_2CHCH_2NH_2$	87
4	**5d**	6-Cl	Me	$PhCH_2NH_2$	73
5	**5e**	6-Cl	Me	Morpholine	63
6	**5f**	6-Cl	Me	$(CH_3)_2CHCH_2NH_2$	60
7	**5g**	6-Cl-8-CF_3	Me	$PhCH_2NH_2$	90
8	**5h**	6-Cl-8-CF_3	Me	Morpholine	76
9	**5i**	6-Cl-8-CF_3	Me	$(CH_3)_2CHCH_2NH_2$	75
10	**5j**	5-NO_2-8-Cl	Me	$PhCH_2NH_2$	50
11	**5k**	5-NO_2-8-Cl	Me	$(CH_3)_2CHCH_2NH_2$	50
12	**5m**	H	Me	$PhNH_2$	75[b]
13	**5n**	8-Me	Me	Ph(Me)NH	79[b]
14	**5o**	8-Cl	Et	*i*-$PrNH_2$	82
15	**5p**	H	Ph	*i*-$BuNH_2$	76
16	**5q**	8-Me	Me	Me_2NH	70
17	**5r**	H	Ph	Morpholine	66
18	**5s**	7,8-F_2	Me	*t*-$BuNH_2$	70

[a] Reaction was performed in THF solvent at rt for 24 h.
[b] Reaction was performed in 1,2-dichlorobenzene solvent under reflux for 24 h.

ketoxime **6** of 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** via an indium(III) chloride promoted Beckmann rearrangement.[8] Thus, when combined with our previous work in this area, the current effort rounds out a complete plan for the selective synthesis of the isomeric 2-, 3-, and 4-aminoquinoline derivatives starting from the common 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1** (Fig. 4).

In summary, a facile method has been developed for the synthesis of 2- and 4-aminoquinoline derivatives beginning with the common 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**. The procedures involve initial selective activation of 2- or 4-substituent present in **1** and subsequent reaction with amines. Since a procedure to produce 3-aminoquinolinones from 4-quinolinone **1** has been described earlier,[8] the chemistry reported above completes the development of sequences for the selective synthesis of isomeric 2-, 3-, and 4-aminoquinoline derivatives starting with the common 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**.

3. Experimental section

3.1. General

Flash column chromatography was performed on silica gel (230–400 mesh, Merck). THF was refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was distilled from calcium hydride. All other reagent grade chemicals were obtained from commercial sources and used as-received. 2-Methylsulfanyl-3-acyl-1*H*-quinolin-4-ones were prepared by using the literature procedure.[9]

3.2. A representative procedure for the synthesis of 2-methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinolines (2)

To a solution of 2-methylsulfanyl-3-acetyl-1*H*-quinolin-4-one (**1a**) (800 mg, 3.43 mmol) and Et_3N (714 μL, 5.14 mmol) in dry CH_2Cl_2 (10 mL) was added slowly methanesulfonyl chloride (319 μL, 4.12 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then at ambient temperature for 4.5 h. The reaction was quenched with H_2O and extracted with diethyl ether twice. The combined organic layer was washed successively with saturated aq $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a residue, which was subjected to flash chromatography on silica gel (*n*-hexane/ ethyl acetate=3/1) to afford the desired product **2a** (830 mg, 78%) as a white solid.

*3.2.1. 2-Methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinoline (**2a**)*

Yield: 78%; white needle; mp: 117–119 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, J=8.7 Hz, 1H), 7.99 (d, J=8.4 Hz, 1H), 7.76 (t, J=7.1 Hz, 1H), 7.56 (t, J=7.1 Hz, 1H), 3.32 (s, 3H), 2.74 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.19, 156.40, 149.50, 148.40, 131.58, 127.97, 127.09, 126.76, 123.43, 120.53, 39.36, 31.90, 13.75; MS (EI): m/z 311 (M^+), 296 (40), 232 (100), 218 (67), 217 (21), 202 (44), 199 (27), 198 (38), 172 (20), 130 (21), 114 (21); HRMS (EI): m/z calcd for $C_{13}H_{13}NO_4S_2$ 311.0286, found 311.0286.

*3.2.2. 6-Chloro-2-methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinoline (**2b**)*

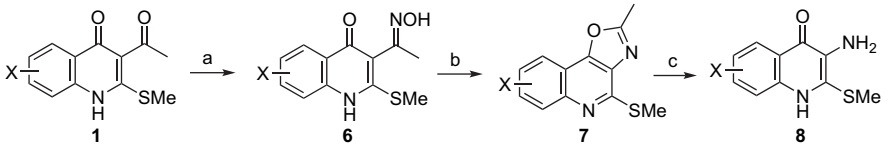
Yield: 86%; white solid; mp: 175–177 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H), 7.92 (d, J=9.0 Hz, 1H), 7.68 (d, J=9.0 Hz, 1H), 3.33 (s, 3H), 2.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.77, 156.98, 147.82, 147.28, 132.74, 132.48, 129.51, 127.87, 122.45, 121.39, 39.44, 31.80, 13.76; MS (EI): m/z 345 (13), 330 (25), 266 (100), 252 (54), 251 (31), 236 (37), 232 (45), 148 (14); HRMS (EI): m/z calcd for $C_{13}H_{12}ClNO_4S_2$ 344.9896, found 344.9894.

*3.2.3. 6-Chloro-8-trifluoromethyl-2-methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinoline (**2c**)*

Yield: 90%; white solid; mp: 228–229 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (s, 1H), 8.03 (s, 1H), 3.36 (s, 3H), 2.73 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.14, 159.01, 147.07, 143.82, 131.44, 130.96, 130.89, 128.52, 126.74, 122.39, 39.54, 31.66, 13.95; MS m/z 413 (7), 398 (20), 334 (100), 314 (41), 300 (46), 284 (34), 272 (14), 181 (12), 143 (11), 79 (12); HRMS (EI): m/z calcd for $C_{14}H_{11}ClF_3NO_4S_2$ 412.9770, found 412.9759.

*3.2.4. 5-Nitro-8-chloro-2-methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinoline (**2d**)*

Yield: 69%; yellow solid; mp: 160–162 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, J=8.7 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H), 3.27 (s, 3H), 2.78 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 197.57, 161.63, 145.03, 137.75, 130.82, 129.72, 122.34, 38.27, 31.53, 14.32; MS m/z 390 (M^+), 311 (100), 297 (17), 235 (16), 232 (15), 79 (13); HRMS (EI): m/z calcd for $C_{13}H_{11}ClN_2O_6S_2$ 389.9749, found 389.9748.



1 **6** **7** **8**

Figure 4. Synthesis of 3-amino-4-quinolinone **8** from 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one **1**.[8] (a) NH_2OH, EtOH; (b) $InCl_3$, CH_3CN; (c) 5% HCl, reflux.

3.3. Preparation of 2-methylsulfanyl-3-acetyl-4-aminoquinolines (4): a representative procedure for amination of 2-methylsulfanyl-3-acetyl-4-methanesulfonyloxyquinoline (2)

To a mixture of **2a** (310 mg, 1 mmol) and potassium carbonate (400 mg, 3.9 mmol) in 30 mL of methylene chloride was added morpholine (100 μL, 1.2 mmol). The reaction mixture was stirred at reflux until the starting material was totally consumed (1 day). The reaction was quenched with H_2O and extracted with methylene chloride three times. The methylene chloride extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo giving a residue, which was subjected to flash chromatography on silica gel using a gradient elution of *n*-hexane/ethyl acetate (10/1) to give product **4b** (260 mg, 90%).

*3.3.1. 2-Methylsulfanyl-3-acetyl-4-benzylamino-quinoline (**4a**)*

Yield: 51%; white solid; mp: 141–143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, J=7.8 Hz, 2H), 7.65–7.60 (m, 1H), 7.36–7.26 (m, 6H), 6.59 (br s, 1H), 4.57 (d, J=5.4 Hz, 2H), 2.69 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.79, 157.21, 150. 45, 148.24, 138.38, 130.57, 129.02, 128.75, 128.01, 127.66, 124.25, 122.85, 118.66, 117.59, 53.06, 32.23, 13.89; MS m/z 322 (M^+), 218 (100), 171 (42), 89 (30); HRMS (EI): m/z calcd for $C_{19}H_{18}N_2OS$ 322.1140, found 322.1158.

*3.3.2. 2-Methylsulfanyl-3-acetyl-4-morpholino-quinoline (**4b**)*

Yield: 91%; white solid; mp: 151–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, J=8.7 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.65 (t, J=7.1 Hz, 1H), 7.43 (t, J=7.1 Hz, 1H), 3.87 (t, J=4.5 Hz, 4H), 3.02 (t, J=4.5 Hz, 4H), 2.68 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 204.29, 155.82, 150.92, 149.56, 130.31, 130.19, 129.13, 125.38, 124.30, 123.60, 67.75, 52.36, 33.18, 31.13, 13.57; MS m/z 302 (M^+), 287 (100), 251 (59), 229 (38), 202 (32), 128 (48), 127 (38); HRMS (EI): m/z calcd for $C_{16}H_{18}N_2O_2S$ 302.1089, found 302.1070.

*3.3.3. 2-Methylsulfanyl-3-acetyl-4-isobutylamino-quinoline (**4c**)*

Yield: 75%; light brown solid; mp: 65–66 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (d, J=8.7 Hz, 1H), 7.82 (d, J=8.1 Hz, 1H), 7.61 (t, J=8.1 Hz, 1H), 7.32 (t, J=8.3 Hz, 1H), 7.24 (br s, 1H), 3.32 (t, J=5.9 Hz, 2H), 2.70 (s, 3H), 2.66 (s, 3H), 1.95–1.86 (m, 1H), 1.00 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.23, 157.94, 152.05, 148.29, 130.59, 128.64, 123.70, 123.28, 118.39, 115.21, 56.62, 32.32, 30.06, 20.12, 14.02; MS m/z 288 (M^+), 271 (58), 245 (20), 149 (48), 81 (53); HRMS (EI): m/z calcd for $C_{16}H_{20}N_2OS$ 288.1296, found 288.1269.

*3.3.4. 6-Chloro-2-methylsulfanyl-3-acetyl-4-benzylamino-quinoline (**4d**)*

Yield: 47%; white solid; mp: 125–127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 1H), 7.79 (d, J=9.0 Hz, 1H), 7.55 (d, J=9.0 Hz, 1H), 7.37–7.32 (m, 3H), 7.26–7.24 (m, 2H), 6.39 (t, J=5.4 Hz, 1H, –NH–), 4.53 (d, J=5.7 Hz, 2H), 2.66 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.63, 157.59, 149.21, 146.67, 138.05, 131.12, 130.26, 129.83, 129.08, 128.15, 127.73, 122.23, 119.57, 118.37, 52.99, 32.20, 13.84; MS m/z 356 (M^+), 341 (72), 323 (17), 265 (9), 163 (10), 106 (10), 91 (100), 65 (15); HRMS (EI): m/z calcd for $C_{19}H_{17}ClN_2OS$ 356.0750, found 356.0531.

*3.3.5. 6-Chloro-2-methylsulfanyl-3-acetyl-4-morpholino-quinoline (**4e**)*

Yield: 90%; white solid; mp: 135–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, 1H), 7.88 (d, J=9.0 Hz, 1H), 7.58 (d, J=9.0 Hz, 1H), 3.88 (t, J=4.4 Hz, 4H), 3.26 (t, J=4.4 Hz, 4H), 2.66 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.61, 156.23, 149.81, 147.64, 130.94, 130.71, 130.60, 130.41, 124.19, 123.16, 67.64, 52.06, 32.94, 13.36; MS m/z 336 (M^+), (27), 321 (100), 285 (29), 263 (27), 163 (24), 128 (27); HRMS (EI): m/z calcd for $C_{16}H_{17}ClN_2O_2S$ 336.0699, found 336.0687.

*3.3.6. 6-Chloro-2-methylsulfanyl-3-acetyl-4-isobutylamino-quinoline (**4f**)*

Yield: 66%; light brown solid; mp: 101–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1H), 7.75 (d, J=8.7 Hz, 1H), 7.53 (d, J=8.7 Hz, 1H), 7.08 (br s, 1H), 3.30 (dd, J=5.4, 0.9 Hz, 1H), 2.70 (s, 3H), 2.65 (s, 3H), 1.95–1.84 (m, 1H), 1.00 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.18, 158.36, 150.94, 146.74, 131.13, 130.17, 129.15, 122.62, 119.64, 115.74, 56.48, 32.36, 30.07, 21.13, 14.02; MS m/z 322 (M^+), 322 (19), 307 (100), 279 (42), 264 (30), 251 (24), 233 (17), 163 (11); HRMS (EI): m/z calcd for $C_{16}H_{19}ClN_2O_2S$ 322.0907, found 322.0900.

*3.3.7. 6-Chloro-8-trifluoromethyl-2-methylsulfanyl-3-acetyl-4-benzylamino-quinoline (**4g**)*

Yield: 66%; white solid; mp: 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.91 (s, 1H), 7.38–7.35 (m, 3H), 7.27–7.24 (m, 2H), 6.86 (br s, 1H), 4.55 (d, J=5.7 Hz, 2H), 2.68 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.08, 159.58, 149.74, 143.22, 137.70, 129.78, 129.70, 129.19, 128.32, 128.17, 127.66, 126.84, 120.40, 118.27, 53.22, 32.20, 14.07; MS m/z 424 (M^+), 409 (52), 391 (12), 106 (9), 91 (100), 65 (19); HRMS (EI): m/z calcd for $C_{20}H_{16}ClF_3N_2OS$ 424.0624, found 424.0482.

*3.3.8. 6-Chloro-8-trifluoromethyl-2-methylsulfanyl-3-acetyl-4-morpholino-quinoline (**4h**)*

Yield: 66%; light yellow solid; mp: 157–160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (s, 1H), 7.94 (s, 1H), 3.89 (t, J=4.4 Hz, 4H), 3.23 (t, J=4.2 Hz, 4H), 2.68 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.00, 158.25, 149.81, 143.83, 130.77, 129.61, 129.36, 129.28, 127.33, 125.04, 67.34, 52.20, 32.95, 30.92, 13.54; MS m/z 404 (M^+), 389 (100), 369 (27), 355 (67), 327 (41), 311 (28), 211 (28); HRMS (EI): m/z calcd for $C_{17}H_{16}ClF_3N_2O_2S$ 404.0573, found 404.0553.

*3.3.9. 6-Chloro-8-trifluoromethyl-2-methylsulfanyl-3-acetyl-4-isobutylamino-quinoline (**4i**)*

Yield: 61%; white solid; mp: 135–137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.89 (s, 1H), 7.72 (br s, 1H), 3.33 (t, J=5.9 Hz, 2H), 2.74 (s, 3H), 2.66 (s, 3H), 1.96–1.89 (m, 1H), 1.01 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 202.62, 160.40, 151.68, 143.37, 129.76, 129.68, 127.40, 127.34, 120.04, 115.47, 56.83, 32.45, 30.14, 20.08, 14.24; MS m/z 390 (M^+), 375 (100), 357 (18), 347 (29), 329 (23), 299 (18), 281 (11), 210 (8); HRMS (EI): m/z calcd for $C_{17}H_{18}ClF_3N_2OS$ 390.0780, found 390.0769.

*3.3.10. 5-Nitro-8-chloro-2-methylsulfanyl-3-acetyl-4-benzylamino-quinoline (**4j**)*

Yield: 95%; yellow solid; mp: 128–130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, J=8.1 Hz, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.32–7.27 (m, 3H), 7.04–7.01 (m, 2H), 4.26 (d, J=5.7 Hz, 2H), 2.78 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 202.20, 161.46, 150.93, 147.17, 144.94, 138.20, 137.06, 128.99, 128.92, 128.24, 127.61, 120.55, 111.36, 53.30, 31.98, 14.41; MS m/z 401 (M^+), 386 (10), 106 (6), 91 (100), 65 (7); HRMS (EI): m/z calcd for $C_{19}H_{16}ClN_3O_3S$ 401.0601, found 401.0589.

*3.3.11. 5-Nitro-8-chloro-2-methylsulfanyl-3-acetyl-4-isobutylamino-quinoline (**4k**)*

Yield: 90%; yellow solid; mp: 120–123 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (br s, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.76 (d, J=8.1 Hz, 1H), 2.98 (t, J=5.9 Hz, 2H), 2.76 (s, 3H), 2.74 (s, 3H), 1.78–1.67 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.63, 162.07, 153.24, 147.29, 144.98, 138.34, 128.87, 120.12, 115.65, 110.22, 55.81, 32.57, 30.02, 19.80, 14.67; MS m/z 367 (M^+), 352 (57), 324 (80), 292 (33), 280 (89), 263 (100), 250 (42), 236 (24), 163 (26); HRMS (EI): m/z calcd for $C_{16}H_{18}ClN_3O_3S$ 367.0757, found 367.0749.

3.4. Preparation of 2-methylsulfinyl-3-acyl-1*H*-quinolin-4-ones (3): a representative procedure for oxidation of 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-ones (1)

To a well stirred suspension of 2-methylsulfanyl-3-acyl-1*H*-quinolin-4-one (**1a**) (1.17 g, 5 mmol) in acetic acid (30 mL) was added hydrogen peroxide (35%, 1.1 mL, 12.5 mmol). Stirring was continued for 24 h at room temperature. The reaction mixture was poured into ice-water and precipitated solid was collected by filtration. The solid product was washed with water several times and dried. The solid was pure enough to use in next step or can be purified by recrystallization (EtOH) or chromatography on silica gel.

*3.4.1. 2-Methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3a**)*

Yield: 98%; mp: 228–229 °C; TLC R_f 0.07 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (br s, 1H), 8.46 (d, J=7.8 Hz, 1H), 7.76 (t, J=8.1 Hz, 1H), 7.55 (m, 2H), 3.01 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.964, 176.654, 141.192, 137.115, 133.576, 127.759, 127.213, 126.543, 118.516, 114.535, 43.685, 31.413; MS (EI): m/z 249 (M^+), 232, 218, 191, 158, 130, 114, 89; HRMS (EI): m/z calcd for $C_{12}H_{11}NO_3S$ 249.0460, found 249.0475.

*3.4.2. 6-Chloro-2-methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3b**)*

Yield: 88%; mp: 241–243 °C; TLC R_f 0.36 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.65 (br s, 1H), 8.42 (d, J=2.1 Hz, 1H), 7.70 (dd, J=8.7, 2.4 Hz, 1H), 7.55 (d, J=9.0 Hz, 1H), 3.02 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.996, 175.667, 161.567, 135.735, 134.163, 133.070, 129.094, 127.054, 120.309, 114.850, 45.639, 31.137; MS (EI): m/z 283 (M^+), 266, 252, 222, 192, 88, 75, 55; HRMS (EI): m/z calcd for $C_{12}H_{10}ClNO_3S$ 283.007, found 283.0069.

*3.4.3. 6-Chloro-8-trifluoromethyl-2-methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3c**)*

Yield: 89%; mp: 202–203 °C; TLC R_f 0.63 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.21 (br s, 1H), 8.63 (d, J=2.7 Hz, 1H), 8.00 (d, J=2.4 Hz, 1H), 3.01 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.285, 174.385, 162.345, 132.549, 131.884, 131.519, 131.452, 131.141, 130.181, 124.399, 115.096, 43.549, 31.403; MS (EI): m/z 351 (M^+), 334, 320, 293, 90, 268, 143, 84, 64; HRMS (EI): m/z calcd for $C_{13}H_9ClF_3NO_3S$ 350.9944, found 350.9927.

*3.4.4. 5-Nitro-8-chloro-2-methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3d**)*

Yield: 69%; mp: 263–264 °C; TLC R_f 0.37 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.30 (br s, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.43 (d, J=8.1 Hz, 1H), 3.04 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.334, 173.060, 162.522, 148.098, 135.240, 133.069, 126.252, 120.269, 120.200, 116.101, 43.734, 31.600; MS (EI): m/z 328 (M^+), 311, 297, 270, 251, 229, 109, 74; HRMS (EI): m/z calcd for $C_{12}H_9ClN_2O_5S$ 327.9921, found 327.9927.

*3.4.5. 8-Methyl-2-methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3e**)*

Yield: 80%; mp: 208–210 °C; TLC R_f 0.38 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.79 (br s, 1H), 8.31 (d, J=8.1 Hz, 1H), 7.58 (d, J=7.2 Hz, 1H), 7.43 (t, J=8.1 Hz, 1H), 3.03 (s, 3H), 2.83 (s, 3H), 2.65 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.343, 178.737, 160.629, 135.976, 134.575, 128.060, 126.805, 126.392, 125.327, 114.415, 43.863, 31.607, 17.713; MS (EI): m/z 263 (M^+), 246, 232, 200, 182, 113, 98, 69, 56; HRMS (EI): m/z calcd for $C_{13}H_{13}NO_3S$ 263.0616, found 263.0613.

*3.4.6. 8-Chloro-2-methylsulfinyl-3-propionyl-1H-quinolin-4-one (**3f**)*

Yield: 78%; mp: 186–187 °C; TLC R_f 0.67 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.18 (br s, 1H), 8.36 (d, J=8.1 Hz, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.46 (t, J=8.1 Hz, 1H), 3.46–3.17 (m, 2H), 3.04 (s, 3H), 1.81 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.077, 176.205, 161.983, 134.309, 133.241, 129.319, 126.523, 126.179, 123.730, 114.778, 44.040, 36.909, 8.008; MS (EI): m/z 297 (M^+), 280, 264, 253, 225, 206, 179, 148, 114, 75; HRMS (EI): m/z calcd for $C_{13}H_{12}ClNO_3S$ 297.0226, found 297.0213.

*3.4.7. 7,8-Difluoro-2-methylsulfinyl-3-acetyl-1H-quinolin-4-one (**3g**)*

Yield: 80%; mp: 187–189 °C; TLC R_f 0.14 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 8.21 (m, 1H), 7.33 (m, 1H), 3.02 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.74, 175.23, 162.19, 153.55, 153.48, 151.51, 151.44, 141.01, 140.89, 138.99, 138.87, 128.70, 128.67, 128.62, 128.59, 124.88, 123.60, 123.56, 123.53, 123.50, 115.68, 115.53, 115.27, 43.75, 31.56 (because of coupling with fluorine atoms, more peaks appeared than the actual numbers of carbon atom); MS (EI): m/z 285 (M^+), 268, 254, 239, 224, 194, 180, 166, 150, 125, 112, 57; HRMS (EI): m/z calcd for $C_{12}H_9F_2NO_3S$ 285.0271, found 285.0991.

*3.4.8. 2-Methylsulfinyl-3-benzoyl-1H-quinolin-4-one (**3h**)*

Yield: 83%; mp: 239–240 °C; TLC R_f 0.34 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (br s, 1H), 8.39 (d, J=8.1 Hz, 1H), 7.76 (m, 3H), 7.52 (m, 5H), 3.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.98, 175.70, 159.81, 138.23, 137.56, 133.65, 132.74, 129.04, 128.08, 127.57, 127.34, 126.30, 118.40, 44.42, 30.91; MS (EI): m/z 311 (M^+), 296, 264, 248, 220, 202, 190, 165, 105, 77, 57; HRMS (EI): m/z calcd for $C_{17}H_{13}NO_3S$ 311.0616, found 311.0610.

3.5. Preparation of 2-amino-3-acyl-1*H*-quinolin-4-one (5)

*A representative procedure for amination of 2-methylsulfinyl-3-acyl-1H-quinolin-4-one (**3**) with alkylamines*. A solution of 2-methylsulfinyl-3-acetyl-1*H*-quinolin-4-one (**3a**) (1.2 g, 4.9 mmol) and benzylamine (0.53 g, 4.9 mmol) in 20 mL of anhydrous THF was stirred at room temperature for 24 h and concentrated in vacuo giving a residue, which was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated, in vacuo giving a residue, which was subjected to flash chromatography on silica gel with *n*-hexane/ethyl acetate to give pure product **5a** (1.2 g, 85%).

*A representative procedure for amination of 2-methylsulfinyl-3-acyl-1H-quinolin-4-one (**3**) with aromatic amine*. A solution of 2-methylsulfinyl-3-acetyl-1*H*-quinolin-4-one (**3a**) (1.0 g, 4 mmol) and aniline (483 μL, 4 mmol) in 20 mL of anhydrous 1,2-dichlorobenzene was stirred at reflux for 24 h and concentrated in vacuo to give a residue, which was dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo giving a residue, which was subjected to flash chromatography on silica gel with *n*-hexane/ethyl acetate to give pure product **5m** (0.84 g, 75%).

*3.5.1. 2-Benzylamino-3-acetyl-1H-quinolin-4-one (**5a**)*

Yield: 85%; mp: 213–215 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.00 (br s, 1H), 8.26 (d, J=7.8 Hz, 1H), 7.75 (br s, 1H), 7.45–7.34 (m, 6H), 7.23 (t, J=7.4 Hz, 1H), 6.90 (d, J=8.1 Hz, 1H), 4.64 (d, J=5.5 Hz, 2H), 2.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.37, 177.14, 156.29, 136.18, 135.31, 132.21, 129.59, 128.67, 127.01, 126.86, 124.28, 123.88, 115.41, 101.78, 45.35, 33.47; MS (EI): m/z 292 (M^+), 277 (29), 201 (36), 172 (45), 106 (73), 91 (100); HRMS (EI): m/z calcd for $C_{18}H_{16}N_2O_2$ 292.1212, found 292.1213.

*3.5.2. 2-Morpholino-3-acetyl-1H-quinolin-4-one (**5b**)*

Yield: 66%; mp: 200–202 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.84 (s, 1H), 8.18 (d, J=8.2 Hz, 1H), 7.68 (m, 2H), 7.33 (m, 1H), 3.87 (m, 4H), 3.41 (m, 4H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.27, 168.58, 159.64, 148.73, 133.11, 127.22, 123.98, 123.76, 117.72, 105.10, 66.50,

51.75, 28.11; MS (EI): *m*/*z* 272 (M^+), 257, 227, 215, 197, 172, 145, 86, 58; HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1191.

*3.5.3. 2-Isobutylamino-3-acetyl-1H-quinolin-4-one (**5c**)*

Yield: 87%; mp: 203–205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.65 (br s, 1H), 8.41 (br s, 1H), 8.2 (d, *J*=8.0 Hz, 1H), 7.51–7.47 (m, 1H), 7.25–7.22 (m, 2H), 3.19 (t, *J*=5.8 Hz, 2H), 2.80 (s, 3H), 2.06–2.02 (m, 1H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.08, 177.35, 155.97, 132.33, 126.86, 124.10, 123.66, 115.62, 101.52, 48.74, 33.54, 30.97, 28.01, 20.31; MS (EI): *m*/*z* 258 (M^+), 243 (33), 215 (100), 202 (30), 197 (35), 187 (29); HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1363.

*3.5.4. 2-Benzylamino-6-chloro-3-acetyl-1H-quinolin-4-one (**5d**)*

Yield: 73%; mp: 231–232 °C; TLC R_f 0.45 (hexane/EtOAc=1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.00 (br s, 1H), 8.22 (s, 1H), 7.65 (br s, 1H), 7.40 (m, 6H), 6.84 (d, *J*=8.4 Hz, 1H), 4.64 (d, *J*=5.7 Hz, 2H), 2.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.45, 175.96, 156.36, 135.23, 134.73, 132.40, 129.87, 129.80, 128.92, 126.98, 126.80, 125.63, 117.10, 101.85, 45.55, 33.54, 29.87; MS (EI): *m*/*z* 326 (M^+), 311, 283, 235, 206, 179, 106, 91, 65; HRMS (EI): *m*/*z* calcd for $C_{18}H_{15}ClN_2O_2$ 326.0822, found 326.0818.

*3.5.5. 2-Morphorino-6-chloro-3-acetyl-1H-quinolin-4-one (**5e**)*

Yield: 63%; mp: 220–222 °C; TLC R_f 0.26 (hexane/EtOAc=1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.71 (s, 1H), 8.13 (s, 1H), 7.61 (m, 2H), 3.85 (t, *J*=4.8 Hz, 4H), 3.41 (t, *J*=4.8 Hz, 4H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.55, 167.66, 159.82, 147.29, 133.76, 129.42, 128.93, 123.13, 118.54, 106.38, 66.59, 51.83, 28.23; MS (EI): *m*/*z* 306 (M^+), 291, 289, 261, 249, 233, 206, 179, 164, 86, 58; HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}ClN_2O_3$ 306.0771, found 306.0386.

*3.5.6. 2-Isobutylamino-6-chloro-3-acetyl-1H-quinolin-4-one (**5f**)*

Yield: 60%; mp: 254–255 °C; TLC R_f 0.43 (hexane/EtOAc=1/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.67 (br s, 1H), 8.22 (d, *J*=2.3 Hz, 1H), 8.04 (br s, 1H), 7.43 (d, *J*=8.5 Hz, 1H), 7.14 (d, *J*=8.5 Hz, 1H), 3.17 (t, *J*=6.3 Hz, 2H), 2.77 (s, 3H), 2.05 (m, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.21, 176.02, 155.93, 135.01, 132.43, 129.68, 126.79, 125.55, 117.11, 101.58, 48.87, 33.53, 28.15, 20.47; MS (EI): *m*/*z* 292 (M^+), 263 (100), 245 (23), 235 (32); HRMS (EI): *m*/*z* calcd for $C_{15}H_{17}ClN_2O_2$ 292.0979, found 292.1278.

*3.5.7. 2-Benzylamino-6-chloro-8-trifluoromethyl-3-acetyl-1H-quinolin-4-one (**5g**)*

Yield: 90%; mp: 167–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.16 (br s, 1H), 8.48 (s, 1H), 7.76 (br s, 1H), 7.68 (s, 1H), 7.45–7.36 (m, 5H), 4.65 (d, *J*=5.7 Hz, 2H), 2.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.48, 174.39, 156.26, 134.14, 131.98, 131.46, 129.83, 129.76, 129.28, 129.16, 127.43, 126.95, 101.74, 45.54, 33.56; MS (EI): *m*/*z* 394 (M^+), 379 (21), 303 (7), 105 (49), 91 (95), 65 (24); HRMS (EI): *m*/*z* calcd for $C_{19}H_{14}N_2O_2F_3Cl$ 394.0696, found 394.0701.

*3.5.8. 2-Morphorino-6-chloro-8-trifluoromethyl-3-acetyl-1H-quinolin-4-one (**5h**)*

Yield: 76%; mp: 150–152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.69 (s, 1H, –NH–), 8.29 (s, 1H), 7.93 (s, 1H), 3.82 (t, *J*=2.4 Hz, 4H), 3.54 (t, *J*=2.4 Hz, 4H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 204.28, 167.42, 159.11, 144.06, 132.01, 132.06, 127.68, 127.28, 119.19, 106.10, 66.49, 51.62, 31.12, 27.95; MS (EI): *m*/*z* 374 (M^+), 361 (40), 359 (100), 339 (17), 331 (12), 317 (15), 86 (43); HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}N_2O_3F_3Cl$ 374.0645, found 374.06521.

*3.5.9. 2-Isobutylamino-6-chloro-8-trifluoromethyl-3-acetyl-1H-quinolin-4-one (**5i**)*

Yield: 75%; mp: 119–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.76 (br s, 1H), 8.49 (s, 1H), 7.79 (br s, 1H), 7.76 (s, 1H), 3.15 (t, *J*=6.0 Hz, 2H), 2.76 (s, 3H), 2.11–2.04 (m, 1H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.26, 174.35, 155.68, 132.05, 131.60, 129.81, 129.76, 129.17, 127.34, 101.34, 48.59, 33.46, 28.33, 20.43; MS (EI): *m*/*z* 360 (M^+), 345 (76), 317 (100), 297 (70), 279 (21), 72 (31); HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2O_2F_3Cl$ 360.0852, found 360.0849.

*3.5.10. 2-Benzylamino-5-nitro-8-chloro-3-acetyl-1H-quinolin-4-one (**5j**)*

Yield: 50%; mp: 260–261 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.13 (br s, 1H), 7.97 (br s, 1H), 7.54 (d, *J*=13.5 Hz, 1H), 7.46–7.39 (m, 5H), 7.10 (d, *J*=13.5 Hz, 1H), 4.70 (d, *J*=9.0 Hz, 2H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.49, 155.88, 134.39, 133.99, 131.49, 129.96, 129.34, 127.36, 122.21, 117.74, 101.89, 45.94, 33.46; MS (EI): *m*/*z* 371 (M^+), 353 (8), 323 (7), 247 (4), 206 (6), 91 (100), 65 (11); HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}ClN_3O_4$ 371.0673, found 371.0693.

*3.5.11. 2-Isobutylamino-5-nitro-8-chloro-3-acetyl-1H-quinolin-4-one (**5k**)*

Yield: 50%; mp: 203–210 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.75 (br s, 1H), 7.99 (br s, 1H), 7.63 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J*=8.4 Hz, 1H), 3.23 (t, *J*=5.9 Hz, 2H), 2.68 (s, 3H), 2.15–2.10 (m, 1H), 1.14 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 201.29, 172.81, 155.21, 133.93, 131.49, 121.98, 117.66, 101.42, 48.79, 33.34, 31.12, 28.32, 20.54; MS (EI): *m*/*z* 337 (M^+), 294 (34), 276 (66), 247 (100), 219 (36), 129 (33), 114 (35), 57 (57); HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_3O_4Cl$ 337.0827, found 337.0817.

*3.5.12. 2-Phenylamino-3-acetyl-1H-quinolin-4-one (**5m**)*

Yield: 75%; mp: 210–211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.11 (br s, 1H), 8.31 (d, *J*=8.0 Hz, 1H), 7.70 (br s, 1H), 7.70–7.55 (m, 2H), 7.54–7.42 (m, 2H), 7.38–7.35 (m, 2H), 7.30–7.25 (m, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.73, 177.31, 154.36, 135.81, 134.50, 132.34, 130.76, 128.15, 127.12, 126.31, 124.40, 101.50, 33.39; MS *m*/*z* 278 (M^+), 263, 235, 205, 187, 120, 77, 65; HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}N_2O_2$ 278.1055, found 278.1048.

*3.5.13. 2-(N-Methyl-N-phenylamino)-8-methyl-3-acetyl-1H-quinolin-4-one (**5n**)*

Yield: 79%; mp: 229–230 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.02 (br s, 1H), 8.17 (d, *J*=7.8 Hz, 1H), 7.86 (br s, 1H), 7.60–7.55 (m, 2H), 7.47–7.41 (m, 3H), 7.31 (d, *J*=7.2 Hz, 1H), 7.16 (t, *J*=7.8 Hz, 1H), 2.89 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.84, 177.65, 153.98, 134.66, 134.375, 133.33, 130.79, 128.15, 125.92, 125.11, 123.41, 122.25, 101.26, 33.37, 30.94, 15.58; MS (EI): *m*/*z* 292 (M^+), 277, 249, 201, 77; HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}N_2O_2$ 292.1212, found 292.1209.

*3.5.14. 2-Isopropylamino-8-chloro-3-propionyl-1H-quinolin-4-one (**5o**)*

Yield: 82%; mp: 167–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.69 (br d, *J*=6.3 Hz, 1H), 8.22 (d, *J*=8.0 Hz, 1H), 7.96 (br s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.21 (t, *J*=8.1 Hz, 1H), 3.89–3.82 (m, 1H), 3.27 (q, *J*=7.2 Hz, 2H), 1.49 (s, 3H), 1.46 (s, 3H), 1.17 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.72, 176.30, 154.72, 132.93, 131.55, 126.20, 125.82, 123.72, 119.68, 100.73, 43.47, 37.85, 22.84, 9.03; MS (EI): *m*/*z* 292 (M^+), 227, 263, 249, 221, 194, 179, 50; HRMS (EI): *m*/*z* calcd for $C_{15}H_{17}ClN_2O_2$ 292.0979, found 292.0206.

*3.5.15. 2-Isobutylamino-3-benzoyl-1H-quinolin-4-one (**5p**)*

Yield: 76%; mp: 301–303 °C; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 10.61 (t, *J*=4.8 Hz, 1H), 9.85 (s, 1H), 8.12 (d, *J*=7.5 Hz, 1H), 7.51–7.44 (m, 4H), 7.37–7.30 (m, 3H), 7.20–7.15 (m, 1H), 3.30 (dd, *J*=6.6, 5.4 Hz, 2H), 2.06–2.02 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6) δ 198.06, 176.61, 156.13, 143.72, 138.13, 131.83, 129.47, 127.62, 127.06, 126.37, 124.22, 122.96, 116.50, 100.47, 49.13, 28.13, 20.30; MS (EI): *m*/*z* 320 (M^+), 305, 227, 263, 249, 235, 199, 187, 120, 91, 66; HRMS (EI): *m*/*z* calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1499.

*3.5.16. 2-Dimethylamino-8-methyl-3-acetyl-1H-quinolin-4-one (**5q**)*

Yield: 70%; mp: 130–131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.72 (br s, 1H), 7.99 (d, J=7.2 Hz, 1H), 7.51 (d, J=7.2 Hz, 1H), 7.16 (t, J=7.4 Hz, 1H), 3.03 (s, 6H), 2.66 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.856, 168.672, 148.249, 135.422, 133.345, 122.677, 121.779, 117.587, 42.483, 31.135, 27.846, 17.767; MS (EI): m/z 244 (M^+), 229, 211, 201, 186, 159, 130, 103, 77; HRMS (EI): m/z calcd for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1208.

*3.5.17. 2-Morphorino-3-benzoyl-1H-quinolin-4-one (**5r**)*

Yield: 66%; mp: 315–317 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.68 (s, 1H), 8.20 (d, J=8.4 Hz, 1H), 7.74–7.68 (m, 4H), 7.57 (d, J=7.2 Hz, 1H), 7.44 (d, J=7.2 Hz, 2H), 7.35–7.30 (m, 1H), 3.24 (m, 4H), 3.12 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.22, 168.34, 158.86, 149.37, 137.67, 133.13, 133.04, 129.87, 127.99, 126.99, 123.88, 123.29, 117.26, 102.70, 65.79, 50.04; MS (EI): m/z 334 (M^+), 333, 316, 289, 275, 257, 248, 220, 213, 201, 145, 91, 77; HRMS (EI): m/z calcd for $C_{20}H_{18}N_2O_3$ 334.1317, found 334.1314.

*3.5.18. 2-tert-Butylamino-3-acetyl-7,8-difluoro-1H-quinolin-4-one (**5s**)*

Yield: 70%; mp: 227–228 °C; TLC R_f 0.71 (hexane/EtOAc=3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (br s, 1H), 8.03 (m, 1H), 7.77 (br s, 1H), 7.05 (q, J=7.2 Hz, 1H), 2.75 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.08, 175.51, 155.27, 152.80, 152.72, 150.79, 150.71, 137.14, 137.01, 126.99, 126.96, 126.89, 123.08, 123.05, 123.02, 122.98, 121.26, 111.88, 111.74, 101.43, 51.77, 33.48, 30.30 (because of coupling with fluorine atoms, more peaks appeared than the actual numbers of carbon atom); MS (EI): m/z 294 (M^+), 279, 261, 237, 223, 196, 119, 86, 57; HRMS (EI): m/z calcd for $C_{15}H_{16}F_2N_2O_2$ 294.1180, found 294.1176.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.014.

References and notes

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10. We depicted the structure of **5** as 2-amino-1*H*-quinolin-4-one based on the structure of **1** as 2-ethylsulfanyl-1*H*-quinolin-4-one, which was unambiguously determined by X-ray analysis (Ref. 9b). But some of **5** (**5b**, **5e**, **5h**, **5j**, **5q**, **5r**) seem to exist as 2-amino-quinolin-4-ol **10**, since they show only one carbonyl carbon (204–198 ppm) in ^{13}C NMR spectra.