HETEROCYCLES, Vol. 87, No. 12, 2013, pp. -. © The Japan Institute of Heterocyclic Chemistry
Received, 25th September, 2013, Accepted, 18th October, 2013, Published online, 30
DOI: 10.3987/COM-13-12849

A VERSATILE METHOD FOR THE SYNTHESIS OF FLUORINE-CONTAINING CHLOROQUINE ANALOGUES STARTING FROM 7-CHLORO-4-(*N*,*N*-DIMETHYLAMINO)QUINOLINE USING NUCLEOPHILIC *N*-*N*, *N*-*S*, AND *N*-*O* EXCHANGE REACTIONS

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Abstract – A new synthetic method was developed to access fluorine-containing chloroquine analogues which have unique potentials contributing to the discovery of novel anti-microorganisms. (7-Chloro-3-trifluoroacetylquinolin-4-yl)amines (**7**), thiols (**8**), and ethers (**9**) were easily synthesized in high yields by the trifluoroacetylation of 7-chloro-4-(*N*,*N*-dimethylamino)quinoline (**6**) with 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate followed by the nucleophilic *N*-*N*, *N*-*S*, and *N*-*O* exchange reactions.

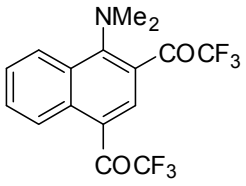
During recent years, we can recognize that the new spread of malaria is one of the serious issues, and it is widely known that an improvement of treatment effect is demanded for controlling the infection since chloroquine which is the classical and standard therapeutic agent has lost effectiveness in a lot of cases caused by the resistant strain such as *Plasmodium falciparum*.[1] The continual studies on the modification of 4- and 7-substituents of chloroquine are also addressed to find out new therapeutic agents intently. In those studies, for instance, it is suggested that the structure for activity against chloroquine-resistant *Plasmodium falciparum* demands the chlorine atom at the 7-position which is the most suitable substituent based on the QSAR analyses.[2] This result seems to be well compatible to the investigation on the activity of chloroquine analogues, which shows that 7-chloro substituent could be irreplaceable with the other substituent in so far as promising an antimalarial activity.[3]

Recently, a lot of methodologies have been reported for the syntheses of various kinds of fluorine-containing heterocycles since these compounds are emphasized on the interest of their versatile

functionalization. Especially, the remarkable biological activities were found quite often in the field of life science.[4-7]

In the course of our investigation on the nucleophilic substitutions at aromatic carbon activated by trifluoroacetyl group, it was found that the *N*-*N*, *N*-*S*, and *N*-*O* exchange occurred by the reactions of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) with amines, thiols, and alcohols, respectively.[8] It meant that the dimethylamino group which did not generally show the elimination reactivity in aromatic systems acted as an excellent leaving group to conduct novel nucleophilic substitutions enhanced by trifluoroacetyl group through its strong electron-withdrawing effect. We have continued to explore the similar approaches and also reported with respect to the reaction of *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**2**), *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)-5-quinolylamine (**3**), and *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**4**) with various nucleophiles to afford the corresponding *N*-*N*, *N*-*S*, and *N*-*O* exchanged quinolines.[9-11]

These situations strongly prompted us to begin a research on the application of these nucleophilic *N*-*N*, *N*-*S*, and *N*-*O* exchange reactions to the syntheses of new fluorine-containing chloroquine analogues which might have new characteristic features as a drug.



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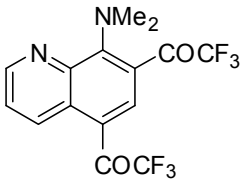

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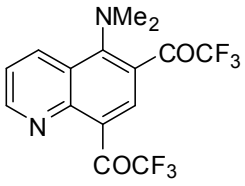

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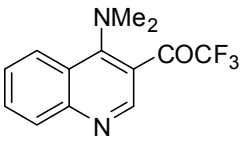

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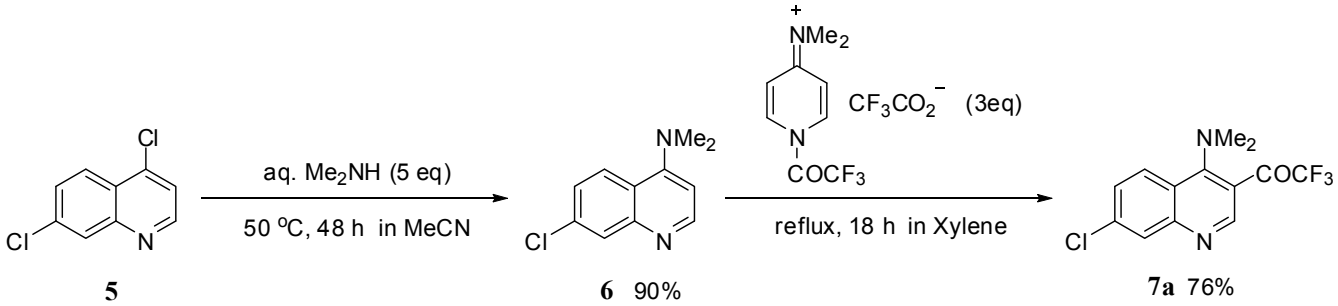
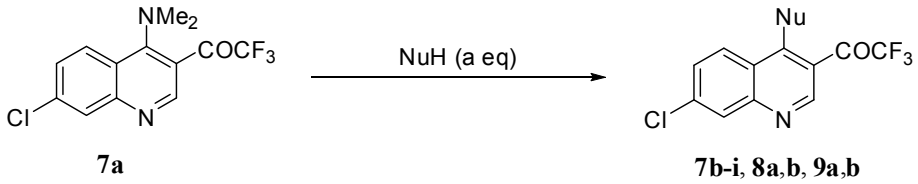
Here we wish to report the synthesis of a new key intermediate 7-chloro-*N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**7a**) which are keeping the chlorine atom at the 7-position as the essential moiety to show drug efficacy, and its nucleophilic *N*-*N*, *N*-*S*, and *N*-*O* exchange reactions at 4-position accessing fluorine-containing chloroquine analogues (**7**-**9**).

Firstly, we examined the trifluoroacetylation of 7-chloro-4-dimethylaminoquinoline (**6**) which was easily afforded by the reaction of 4,7-dichloroquinoline (**5**) with dimethylamine (50% aqueous soln.) in acetonitrile. In the step aimed at selective introduction of trifluoroacetyl group at 3-position, the acylation using 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate[11,12] in refluxing xylene was applied to **6** to afford the desired product (**7a**) in 76% yield (Scheme 1).



Scheme 1

Secondly, we tried the aromatic nucleophilic *N*-*N* exchange reaction of **7a** with amines to access novel 7-chloro-3-trifluoroacetylquinolin-4-amines (**7b**-**i**, Scheme 2, Table 1). Reaction of **7a** with aq. ammonia at 50 °C for 18 h was performed to give the Me_2N-NH_2 exchanged product (**7b**) in 85% yield (Entry 1). The *N*-*N* exchange reactions with simple aliphatic primary amines such as *n*-butyl-, isopropyl-, and *tert*-butylamines were conducted to afford the corresponding *N*-*N* exchanged products cleanly even though the reaction completion in the preparation of **7h** demanded more severe conditions



Scheme 2

Table 1. Synthesis of *N*-*N*, *N*-*S*, and *N*-*O* exchanged quinolines (**7b**-**i**, **8a**,**b**, **9a**,**b**).

Entry	NuH	a (eq)	Solvent	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	NH_3	3[b]	MeCN	50	18	**7b**	85
2	*n*-$BuNH_2$	1	MeCN	rt	8	**7c**	100
3	$Me_2N(CH_2)_3NH_2$	1	MeCN	reflux	8	**7d**	99
4	*i*-$PrNH_2$	3	MeCN	rt	8	**7e**	100
5	$Me(CH_2)_4CH(Me)NH_2$	1	MeCN	reflux	8	**7f**	100
6	$Et_2N(CH_2)_3CH(Me)NH_2$	1	MeCN	reflux	8	**7g**	95
7	*t*-$BuNH_2$	3	MeCN	100[c]	72	**7h**	84
8	*p*-$MeOC_6H_4NH_2$	3	MeCN	reflux	48	**7i**	92
9	$PhCH_2SH$	1	MeCN	reflux	24	**8a**	47
10	*p*-$O_2NC_6H_4SH$	3	toluene	reflux	48	**8b**	63
11	*n*-BuOH	10	xylene	reflux	72	**9a**	96
12	*p*-$MeOC_6H_4OH$	5	xylene	reflux	96	**9b**	68

[a] Isolated yields.
[b] 28% aq. ammonia was used as a nucleophilic agent.
[c] The reaction was carried out in a sealed-tube.

(100 ^{o}C, 72 h) than the cases of **7c** and **7e**, which was assumed to be caused by the bulkiness of a nucleophile (Entries 2, 4, and 7). In the cases of 3-(*N*,*N*-dimethylamino)propylamine and more bulky heptan-2-amine, the both reactions proceeded easily in refluxing acetonitrile to yield the *N*-*N* exchanged products (**7d** and **7f**) quantitatively (Entries 3 and 5). For the purpose of the introduction of the same substituent as chloroquine at 4-position of quinoline ring, 5-(*N*,*N*-diethylamino)pentan-2-amine underwent the exchange reaction under the similar conditions as **7d** and **7f** to yield the target compound (**7g**) in 95% as we expected (Entry 6). This type of *N*-*N* exchange reaction was applicable for the reaction with *p*-substituted aniline such as *p*-anisidine, which gave *N*-(*p*-methoxyphenyl)-4-quinolylamine derivative (**7i**) in 92% yield in acetonitrile under reflux conditions with prolonged reaction time (48 h), too (Entry 8).

Next, we attempted the nucleophilic *N*-*S* exchange reactions of **7a** with thiols, which tended to take place less easily than the reactions with amines. The reaction of **7a** with phenylmethanethiol proceeded in refluxing acetonitrile within 24 h to yield the desired 4-(benzylthio)quinoline derivative (**8a**) in 47% yield (Entry 9). *p*-Nitrobenzenethiol, highly electron-deficient aromatic thiol, was also used as the *S*-nucleophile, and the dimethylamino-arylthio exchange consequently took place in refluxing toluene for 48 h to give **8b** in 63% yield (Entry 10).

This exchange reaction was further investigated to be expanded to the *O*-nucleophiles which relatively have less reactivity compared with the corresponding amines and thiols. Contrary to our expectations, the reaction of **7a** with *n*-butanol occurred very cleanly, even though it took 72 h for the reaction completion in refluxing xylene, to give *N*-*O* exchanged product (**9a**) in excellent yield (Entry 11). *p*-Methoxyphenol was also adaptable to the dimethylamino-aryloxy exchange reaction giving aryl 4-quinolyl ether derivative (**9b**) in 68% yield under similar conditions as **9a** (Entry 12).

As presented above, our attempts resulted in success to develop the versatile and simple method for the preparation of various (7-chloro-3-trifluoroacetylquinolin-4-yl)amines, thiols, and ethers which cannot be easily accessed by other synthetic methods.

On the other programs for seeking the potential as the anti-microorganism agent in these compounds, it was verified that the typical chloroquine analogue **7g** having the 5-diethylaminopentan-2-ylamino substituent at the 4-position exhibited good activity to combat the *Plasmodium berghel* of mouse malarial model. In that evaluation of drug efficacy, it was found that the extension of median survival period for malarial infected mouse was performed well with the administration of **7g** giving more than 11.6 days compared with the non-administration group which resulted in 7 days.[13]

As the similar research in the antimalarial field, we have also achieved discovery of lead compounds like **7g** and **9b** having preferable activities as the novel fungicide for the plant protection. The evaluation of these compounds has been tried in comparison with a known fungicide as a control in respect to the

efficacy for plant protection. In the application to *Pseudoperonospora cubensis* (downy mildew of cucumber), we have reached the aim for the creation of new lead compounds by finding **7g** and **9b** which showed almost the same or obviously lower concentration as the value of the half maximal effective concentration of control (**7g**: less than 7.8 ppm, **9b** and oxadixyl: 7.8 ppm).[13] Such character is counted on as for the contribution to the development of new anti-oomycetes since the acquisition of drug-resistance against available phenylamide fungicides (e.g. metalaxyl, oxadixyl, benalaxyl, and so on) has become a serious problem currently.[14]

In summary, we have gotten successful in the development of a versatile and simple method for the synthesis of novel (7-chloro-3-trifluoroacetylquinolin-4-yl)amines (**7**), thiols (**8**), and ethers (**9**). This method could allow us to prepare chloroquine analogues having trifluoroacetyl group with ease. In general, the drug-resistant infection has become an important study subject in the process of seeking new drug against harmful microorganisms, and many challenges are attempted to find out new chemical skeletons having a potential to get over such problem currently.[15,16] Therefore, our methodology would be regarded as a potential tool to provide one of solutions which may enable a creation of new active ingredients performing unique activities against harmful microorganisms.

EXPERIMENTAL

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker AVANCE500 spectrometer (^{1}H at 500 MHz, ^{13}C at 126 MHz) and a JEOL PMX 60SI spectrometer (^{1}H at 60 MHz) using TMS as an internal standard. IR spectra were taken with PerkinElmer Spectrum ONE spectrophotometer. Microanalyses were taken with a YANACO CHN-Coder MT-5 analyzer.

Synthesis of 7-Chloro-*N*,*N*-dimethylquinolin-4-amine (6).

To a solution of 4,7-dichloroquinoline (1.98 g, 10.0 mmol) in MeCN (40 mL) was added 50% aq. dimethylamine (4.51 g, 50.0 mmol) and the mixture was stirred at 50 °C for 48 h. The reaction mixture was washed with 10% aq. Na_2CO_3 (50 mL) and H_2O (50 mL), extracted with CH_2Cl_2 (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **6** (1.85 g, 90%). **6**: ^{1}H NMR ($CDCl_3$): δ 8.51 (1H, d, J = 5.0 Hz, 2-H), 7.98 (1H, d, J = 2.0 Hz, 8-H), 7.86 (1H, d, J = 9.0 Hz, 5-H), 7.18 (1H, dd, J = 2.0, 9.0 Hz, 6-H), 6.52 (1H, d, J = 5.0 Hz, 3-H), 2.84 (6H, s, $N(CH_3)_2$).

Synthesis of 1-(7-chloro-4-dimethylaminoquinolin-3-yl)-2,2,2-trifluoroethanone (7a).

To a solution of DMAP (3.30 g, 27.0 mmol) in xylene (18 mL) was added dropwise trifluoroacetic anhydride (5.68 g, 27.0 mmol) to generate 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate in situ. After vigorously stirring for 1 h, **6** (1.86 g, 9.0 mmol) was added and subsequently refluxed for 18 h. The evaporated residual reaction mixture was washed with 10% aq. Na_2CO_3 (50 mL) and H_2O (50

mL), extracted with CH_2Cl_2 (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel column using *n*-hexane/EtOAc (4/1) as eluent to give 1-(7-chloro-4-dimethylaminoquinolin-3-yl)-2,2,2-trifluoroethanone (**7a**) (2.08 g, 76%). **7a**: mp 107-108 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, q, *J* = 2.0 Hz, 2-H), 8.15 (1H, d, *J* = 9.0 Hz, 5-H), 8.06 (1H, d, *J* = 2.0 Hz, 8-H), 7.45 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 3.15 (6H, s, $N(CH_3)_2$); IR (KBr): 1698, 1167, 1137 cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClF_3N_2O$: C, 51.59; H, 3.33; N, 9.26. Found: C, 51.46; H, 3.49; N, 9.27.

General procedure for the *N*-*N* exchange reactions of 7a with amines.

To a solution of **7a** (154 mg, 0.5 mmol) in MeCN (4 mL) was added amines (0.5 mmol for **7c**, **d**, **f**, and **g**; 1.5 mmol for **7b**, **e**, **h**, and **i**) and the mixture was stirred under respective conditions (see Table 1). The sole case applying sealed tube reaction was for the synthesis of **7h**. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane/EtOAc (3/1) as eluent to give *N*-*N* exchanged products, **7b-i**.

1-(4-Amino-7-chloroquinolin-3-yl)-2,2,2-trifluoroethanone (7b): mp 225-226 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.02-6.88 (2H, br, NH_2), 8.88 (1H, q, *J* = 2.0 Hz, 2-H), 8.09 (1H, d, *J* = 9.0 Hz, 5-H), 7.87 (1H, d, *J* = 2.0 Hz, 8-H), 7.50 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H); IR(KBr): 3331, 1641, 1175, 1132 cm^{-1}. Anal. Calcd for $C_{11}H_6ClF_3N_2O$: C, 48.11; H, 2.20; N, 10.20. Found: C, 48.13; H, 2.50; N, 9.88.

1-(4-Butylamino-7-chloroquinolin-3-yl)-2,2,2-trifluoroethanone (7c): mp 98-99 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 10.85-10.37(1H, br, NH), 8.77 (1H, q, *J* = 2.0 Hz, 2-H), 8.12 (1H, d, *J* = 9.0 Hz, 5-H), 7.78 (1H, d, *J* = 2.0 Hz, 8-H), 7.25 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.00 - 3.70 (2H, m, NCH_2), 2.11-0.71 (7H, m, $CH_2CH_2CH_3$); IR (KBr): 3258, 1633, 1168, 1146 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClF_3N_2O$: C, 54.47; H, 4.27; N, 8.47. Found: C, 54.42; H, 4.23; N, 8.55.

1-[7-Chloro-4-(3-dimethylaminopropylamino)quinolin-3-yl]-2,2,2-trifluoroethanone (7d): mp 89-90 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 10.70-10.53 (1H, br, NH), 8.81 (1H, q, *J* = 2.0 Hz, 2-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H), 7.80 (1H, d, *J* = 2.0 Hz, 8-H), 7.27 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.01-3.71 (2H, m, NCH_2), 2.30 (6H, s, $N(CH_3)_2$), 2.63-1.70 (4H, m, $(CH_2)_2N$); IR (KBr): 3269, 1646, 1174, 1130 cm^{-1}. Anal. Calcd for $C_{16}H_{17}ClF_3N_3O$: C, 53.41; H, 4.76; N, 11.68. Found: C, 53.22; H, 4.67; N, 11.60.

1-(7-Chloro-4-isopropylaminoquinolin-3-yl)-2,2,2-trifluoroethanone (7e): mp 119-120 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 10.96-10.49 (1H, br, NH), 8.86 (1H, br s, 2-H), 8.06 (1H, d, *J* = 9.0 Hz, 5-H), 7.83 (1H, d, *J* = 2.0 Hz, 8-H), 7.28 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.80-4.20 (1H, m, CH), 1.49 (6H, d, *J* = 6.0 Hz, CH_3); IR (KBr): 3359, 1647, 1172, 1140 cm^{-1}. Anal. Calcd for $C_{14}H_{12}ClF_3N_2O$: C, 53.09; H, 3.82; N, 8.85. Found: C, 52.91; H, 4.05; N, 8.80.

1-[7-Chloro-4-(heptan-2-ylamino)quinolin-3-yl]-2,2,2-trifluoroethanone (7f): bp 180 °C/3 mmHg (oven temperature); ^{1}H NMR ($CDCl_3$): δ 10.63 (1H, d, *J* = 8.0 Hz, NH), 8.88 (1H, q, *J* = 2.0 Hz, 2-H), 8.10 (1H, d, *J* = 9.0 Hz, 5-H), 7.88 (1H, d, *J* = 2.0 Hz, 8-H), 7.33 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.67-4.03 (1H, m, NCH), 2.03-0.80 (14H, m); IR (neat): 3269, 1647, 1173, 1144 cm^{-1}. Anal. Calcd for $C_{18}H_{20}ClF_3N_2O$: C, 57.99; H, 5.41; N, 7.51. Found: C, 58.01; H, 5.22; N, 7.60.

1-[7-Chloro-4-(5-diethylaminopentan-2-ylamino)quinolin-3-yl]-2,2,2-trifluoroethanone (7g): bp 175 °C / 3 mmHg (oven temperature); ^{1}H NMR ($CDCl_3$): δ 10.90-10.47 (1H, br, NH), 8.90 (1H, q, *J* = 2.0 Hz, 2-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H), 7.92 (1H, d, *J* = 2.0 Hz, 8-H), 7.37 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.77-4.16 (1H, m, NCH), 2.67-2.30 (6H, m, $(CH_3C\underline{H_2})_2NC\underline{H_2}$), 1.73-1.45 (7H, m, $(CH_3)C(CH_2)_2$), 0.97 (6H, t, *J* = 7.0 Hz, $(C\underline{H_3}CH_2)_2N$): IR (neat): 3286, 1646, 1173, 1143 cm^{-1}. Anal. Calcd for $C_{20}H_{25}ClF_3N_3O$: C, 57.76; H, 6.06; N, 10.10. Found: C, 58.05; H, 5.90; N, 9.97.

1-(4-*tert*-butylamino-7-chloroquinolin-3-yl)-2,2,2-trifluoroethanone (7h): mp 142-143 °C (*n*-hexane/ EtOAc); ^{1}H NMR ($CDCl_3$): δ 10.47-10.17 (1H, br, NH), 8.85 (1H, q, *J* = 2.0 Hz, 2-H), 8.13 (1H, d, *J* = 9.0 Hz, 5-H), 7.87 (1H, d, *J* = 2.0 Hz, 8-H), 7.33 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 1.55 (9H, s, $(CH_3)_3$); IR (KBr): 3305, 1656, 1168, 1138 cm^{-1}. Anal. Calcd for $C_{15}H_{14}ClF_3N_2O$: C, 54.47; H, 4.27; N, 8.47. Found: C, 54.43; H, 4.25; N, 8.52.

1-[7-Chloro-4-(*p*-methoxyphenyl)aminoquinolin-3-yl]-2,2,2-trifluoroethanone (7i): mp 135-136 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 11.90-11.63 (1H, br, NH), 9.03 (1H, q, *J* = 2.0 Hz, 2-H), 7.87 (1H, d, *J* = 2.0 Hz, 8-H), 7.47 (1H, d, *J* = 9.0 Hz, 5-H), 7.25-6.82 (5H, m, 6-H / C_6H_4), 3.85 (3H, s, CH_3O); IR (KBr): 3202, 1648, 1174, 1130 cm^{-1}. Anal. Calcd for $C_{18}H_{12}ClF_3N_2O_2$: C, 56.78; H, 3.18; N, 7.36. Found: C, 56.62; H, 3.45; N, 7.25.

A typical procedure for the *N*-*S* exchange reactions of 8a with thiols.

To a solution of **7a** (121 mg, 0.4 mmol) in MeCN (3 mL) was added benzyl mercaptan (50 mg, 0.4 mmol) and the mixture was refluxed for 24 h. The solvent was removed under reduced pressure and the crude mixture was chromatographed on silica gel column using *n*-hexane/EtOAc (39/1) as eluent to give *N*-*S* exchanged products (**8a**, 72mg, 47%).

The similar procedure gave **8b** by the reaction of **8a** with 3 molar equivalents of *p*-nitrothiophenol in toluene under reflux condition for 48 h.

1-(4-Benzylthio-7-chloroquinolin-3-yl)-2,2,2-trifluoroethanone (8a): mp 102-103 °C (*n*-hexane/ EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.93 (1H, s, 2-H), 8.43 (1H, d, *J* = 9.0 Hz, 5-H), 8.17 (1H, d, *J* = 2.0 Hz, 8-H), 7.58 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 7.35-6.90 (5H, m, C_6H_5), 4.07 (2H, s, SCH_2); IR (KBr): 1737, 1215, 1150 cm^{-1}. Anal. Calcd for $C_{18}H_{11}ClF_3NOS$: C, 56.62; H, 2.90; N, 3.67. Found: C, 57.02; H, 3.18; N, 3.56.

1-[7-Chloro-4-(*p*-nitrophenylthio)quinolin-3-yl]-2,2,2-trifluoroethanone (8b): bp 200 °C/3 mmHg (oven temperature); ^{1}H NMR ($CDCl_3$): δ 9.16 (1H, s, 2-H), 8.43-7.17 (7H, m, 5-H/6-H/8-H/C_6H_4); IR (neat): 1737, 1211, 1155 cm^{-1}. Anal. Calcd for $C_{17}H_8ClF_3N_2O_3S$: C, 49.47; H, 1.95; N, 6.79. Found: C, 49.46; H, 1.94; N, 6.71.

A typical procedure for the *N-O* exchange reactions of 7a with alcohols.

To a solution of **7a** (121 mg, 0.4 mmol) in xylene (3 mL) was added *n*-butanol (296 mg, 4.0 mmol) and the mixture was refluxed for 72 h. A removal of the solvent under reduced pressure gave precipitation of *N-O* exchanged product which was isolated by filtration (**9a**, 127 mg, 96%).

The similar procedure gave **9b** by the reaction of **7a** with 5 molar equivalents of *p*-methoxyphenol for 96 h.

1-(4-*n*-Butoxy-7-chloroquinolin-3-yl)-2,2,2-trifluoroethanone (9a): mp 89-90 °C (*n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.08 (1H, q, *J* = 2.0 Hz, 2-H), 8.25 (1H, d, *J* = 9.0 Hz, 5-H), 8.13 (1H, d, *J* = 2.0 Hz, 8-H), 7.58 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 4.17 (2H, t, *J* = 6.0 Hz, CH_2O), 2.04-0.83 (7H, m, $(CH_2)_2CH_3$); IR (KBr): 1610, 1182, 1130 cm^{-1}. Anal. Calcd for $C_{15}H_{13}ClF_3NO_2$: C, 54.31; H, 3.95; N, 4.22. Found: C, 54.71; H, 3.97; N, 4.30.

1-[7-Chloro-4-(*p*-methoxy)phenoxyquinolin-3-yl]-2,2,2-trifluoroethanone (9b): bp 150 °C/3 mmHg (oven temperature); ^{1}H NMR ($CDCl_3$): δ 9.13 (1H, s, 2-H), 8.18 (1H, d, *J* = 2.0 Hz, 8-H), 8.06 (1H, d, *J* = 9.0 Hz, 5-H), 7.50 (1H, dd, *J* = 2.0, 9.0 Hz, 6-H), 6.83 (4H, s, C_6H_4), 3.77 (3H, s, CH_3O); IR (neat): 1679, 1188, 1150 cm^{-1}. Anal. Calcd for $C_{18}H_{11}ClF_3NO_3$: C, 56.63; H, 2.90; N, 3.67. Found: C, 56.61; H, 3.21; N, 3.71.

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