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## EFFICIENT SYNTHESIS OF FLUORINE-CONTAINING DIBENZO[*b,h*][1,6]NAPHTHYRIDINES AND THIOCHROMENO[3,2-*c*]- QUINOLINES USING HIGHLY CHEMOSELECTIVE NUCLEOPHILIC SUBSTITUTION REACTION OF 4-DIMETHYLAMINO-2-METHOXY- 3-TRIFLUOROACETYLQUINOLINE

Etsuji Okada,\* Mizuki Hatakenaka, Yoshinori Takezawa, and Keisuke Iwakuni

Department of Chemical Science and Engineering, Graduate School of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan.  
E-mail: okaetsu@kobe-u.ac.jp

**Abstract** – Aromatic nucleophilic substitution reaction of *N,N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine with various nucleophiles (NuH) such as amines, thiols, and alcohols proceeded chemoselectively at the 4-position to give the corresponding *Me*<sub>2</sub>*N*-*Nu* exchanged products. Novel fluorine-containing 6-methoxydibenzo[*b,h*][1,6]naphthyridines (**11**) and 6-methoxythiochromeno[3,2-*c*]quinolines (**12**) were synthesized in moderate to high yields by the trifluoromethanesulfonic acid catalyzed cyclization of thus obtained *N*-aryl-2-methoxy-3-trifluoroacetyl-4-quinolylamines (**8**) and aryl 2-methoxy-3-trifluoroacetyl-4-quinolyl sulfides (**9**), respectively.

## INTRODUCTION

Dibenzo[*b,h*][1,6]naphthyridines have represented an important class of heterocycles because of their significant and broad spectrum of biological properties, including antibacterial,<sup>1</sup> fungicidal,<sup>1</sup> neoplasm inhibitory,<sup>2</sup> amebicide,<sup>3</sup> and using for the treatment of Alzheimer's disease.<sup>4</sup> Thiochromenoquinolines have been known to exhibit a diverse range of interesting biological activities such as antiproliferative,<sup>5</sup> antitumor,<sup>5</sup> enzyme inhibit,<sup>5</sup> and antifungal activity.<sup>6</sup> Besides, considerable attention in recent years has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural

scientific fields.<sup>7</sup> However fluorine-containing dibenzo[*b,h*][1,6]naphthyridine has not been known except for only one example seen in our previous report.<sup>8</sup> As for fluorine-containing thiochromenoquinoline, the syntheses of only 2-fluoro derivative<sup>9</sup> and 7-trifluoromethyl derivative<sup>8</sup> have been achieved. Therefore, it is very important to develop efficient synthetic methods for novel fluorine-containing dibenzo[*b,h*][1,6]naphthyridines and thiochromeno[3,2-*c*]quinolines which would be strongly expected to present new bioactivities or functionalities. In particular, those having the functional group enabling transformations to diverse derivatives of dibenzo[*b,h*][1,6]naphthyridines and thiochromeno[3,2-*c*]quinolines are especially required.

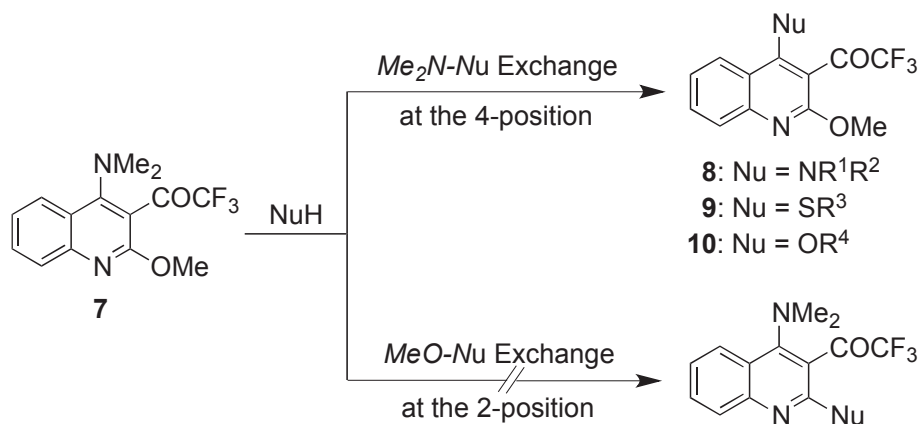
Previously, we reported that dimethylamino group which is hardly substituted by nucleophiles (NuH) in general is easily substituted by various nucleophiles on *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**),<sup>10</sup> *N,N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**2**),<sup>11</sup> and *N,N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**3**)<sup>12,13</sup> to afford the corresponding *Me*<sub>2</sub>*N*-*Nu* exchanged products (**4-6**) in high yields (Scheme 1). We carried out applying this type of aromatic nucleophilic substitution and the subsequent cyclization with the use of acid catalyst to the simple syntheses of naphthalene<sup>14</sup> and quinoline<sup>8,15</sup> fused heterocycles bearing trifluoromethyl groups.



Scheme 1

In the course of our recent investigations about such type of substitution reactions, we have found the highly chemoselective nucleophilic substitution reaction proceeding at the 4-position of *N,N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**7**) to give the corresponding dimethylamino-nucleophile exchanged products (**8-10**) without any formation of methoxy-nucleophile exchanged products resulted by the reaction at the 2-position (Scheme 2).<sup>16</sup> These findings prompted us to try the synthesis of novel fluorine-containing 6-methoxydibenzo[*b,h*][1,6]naphthyridines (**11**) and thiochromeno[3,2-*c*]quinolines (**12**), which have a functional group (methoxy group) at the 6-position enabling further transformations to diverse derivatives of **11** and **12**, via the chemoselective substitution reaction of *N,N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**7**) with anilines and thiophenols. In this paper, we wish to report about the results of the chemoselective substitution reaction of **7** with

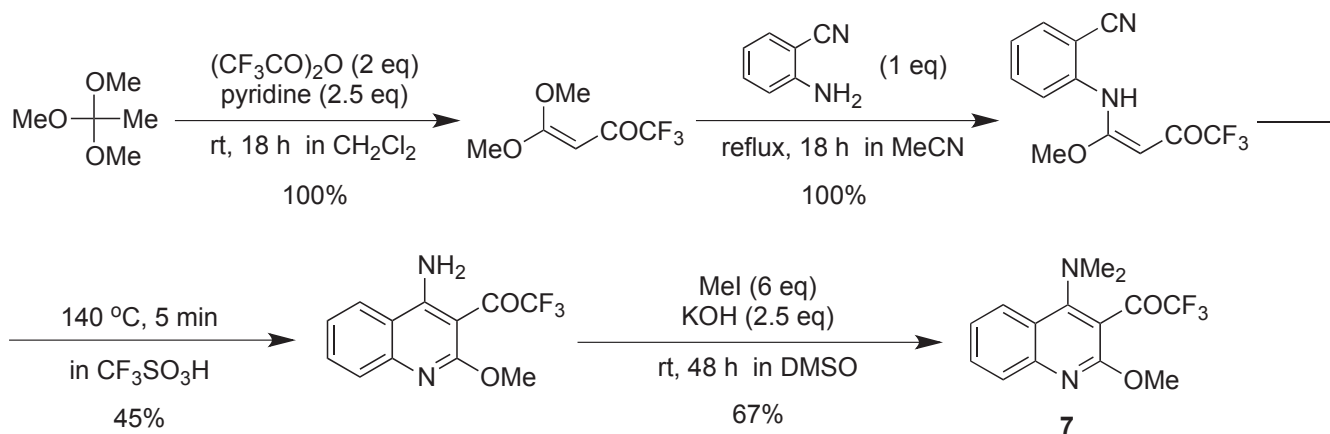
various amines, thiols, and alcohols, and the subsequent acid catalyzed cyclization reaction accessing dibenzonaphthyridines (**11**) and thiochromenoquinolines (**12**).



Scheme 2

## RESULTS AND DISCUSSION

*N,N*-Dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**7**) was prepared by 4-step method from 1,1,1-trimethoxyethane as depicted in Scheme 3. Selective *O-N* exchange reaction of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one prepared by the reported manner<sup>17</sup> with 2-aminobenzonitrile gave (*E*)-1,1,1-trifluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one. The subsequent trifluoromethanesulfonic acid (TFSA) catalyzed cyclization and *N*-methylation of thus obtained 2-methoxy-3-trifluoroacetyl-4-quinolylamine gave **7**.



Scheme 3

Firstly, we examined the substitution reaction of **7** with various amines (Table 1). The reaction of **7** with *n*-butylamine in refluxing acetonitrile occurred cleanly at the 4-position to give the *Me*<sub>2</sub>*N-NHBu-n* exchanged product (**8a**) in 94% yield (Entry 1). In spite of careful inspection of the crude materials, no

Table 1. Aromatic nucleophilic substitution of **7** with amines (R<sup>1</sup>R<sup>2</sup>NH)

| Entry | R <sup>1</sup> R <sup>2</sup> NH (eq)                          | Temp. (°C) | Solvent | Time (h) | Product   | Yield (%) <sup>a</sup> |
|-------|--|------------|---------|----------|-----------|------------------------|
| 1     | <i>n</i> -BuNH <sub>2</sub> (3)                                | reflux     | MeCN    | 4        | <b>8a</b> | 94                     |
| 2     | PhCH <sub>2</sub> NH <sub>2</sub> (3)                          | reflux     | MeCN    | 48       | <b>8b</b> | 91                     |
| 3     | cyclopropylNH <sub>2</sub> (5)                                 | 50         | MeCN    | 24       | <b>8c</b> | 96                     |
| 4     | cyclohexylNH <sub>2</sub> (5)                                  | reflux     | MeCN    | 24       | <b>8d</b> | 96                     |
| 5     | H <sub>2</sub> C=CHCH <sub>2</sub> NH <sub>2</sub> (3)         | 60         | MeCN    | 24       | <b>8e</b> | 95                     |
| 6     | HC≡CCH <sub>2</sub> NH <sub>2</sub> (5)                        | reflux     | MeCN    | 24       | <b>8f</b> | 86                     |
| 7     | pyrrolidine (20)   | reflux     | MeCN    | 24       | <b>8g</b> | 47                     |
| 8     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (5) | reflux     | BuCN    | 72       | <b>8h</b> | 71                     |
| 9     | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (5)  | reflux     | BuCN    | 96       | <b>8i</b> | 84                     |
| 10    | PhNH <sub>2</sub> (10)   | reflux     | BuCN    | 168      | <b>8j</b> | 88                     |
| 11    | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (20) | reflux     | BuCN    | 168      | <b>8k</b> | 68                     |

<sup>a</sup> Isolated yields.

*MeO-NHBu-n* exchanged product was detected in this reaction. Quite similarly, the reaction of **7** with benzylamine and cycloalkylamines proceeded selectively to afford the corresponding *N-N* exchanged products (**8b-d**) solely in excellent yields (Entries 2-4). The reaction of **7** with allylamine and propargylamine also occurred at the 4-position to give more functionalized *N*-allyl- and *N*-propargyl-4-quinolyamines (**8e** and **8f**) in high yields, respectively (Entries 5 and 6). Although the reaction of **7** with secondary amines such as pyrrolidine required more enhanced conditions, it introduced pyrrolidyl group only at the 4-position of the quinoline ring to afford **8g** (Entry 7). With less nucleophilic aromatic amines such as *p*-substituted anilines, **7** underwent the *N-N* exchange reaction exclusively under more forced conditions (in refluxing valeronitrile for prolonged time) to give the corresponding *N*-aryl-4-quinolyamines (**8h-k**) in good to high yields (Entries 8-11).

Next, we examined the reactions of **7** with thiols (Table 2). Interestingly, **7** reacted with aliphatic thiols, such as *n*-butanethiol, *n*-hexanethiol, and phenylmethanethiol at the 4-position in the absence of any catalyst to afford the corresponding 2-methoxy-3-trifluoroacetyl-4-quinolyl sulfides (**9a-c**) in moderate to high yields (Entries 1-3). Also, the reaction with benzenethiols having various *p*-substituent proceeded cleanly under almost similar conditions to give the corresponding *N-S* exchanged products (**9d-g**) exclusively in good yields (Entries 4-7). Thus, it was found that the reaction of **7** with thiols proceeded chemoselectively at the 4-position quite similar to the case of that with amines.

Table 2. Aromatic nucleophilic substitution of **7** with thiols (R<sup>3</sup>SH)

| Entry | R <sup>3</sup> SH (eq)                            | Temp. (°C)       | Solvent          | Time (h) | Product   | Yield (%) <sup>a</sup> |
|-------|---|------------------|------------------|----------|-----------|------------------------|
| 1     | <i>n</i> -BuSH (40)                               | 160 <sup>b</sup> | mesitylene       | 120      | <b>9a</b> | 84                     |
| 2     | <i>n</i> -hexylSH (40)                            | reflux           | mesitylene       | 120      | <b>9b</b> | 73                     |
| 3     | PhCH <sub>2</sub> SH (5)                          | reflux           | mesitylene       | 96       | <b>9c</b> | 57                     |
| 4     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> SH (5) | reflux           | <i>p</i> -xylene | 72       | <b>9d</b> | 79                     |
| 5     | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SH (5)  | reflux           | mesitylene       | 96       | <b>9e</b> | 79                     |
| 6     | PhSH (5)  | reflux           | mesitylene       | 96       | <b>9f</b> | 66                     |
| 7     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> SH (5)  | reflux           | mesitylene       | 96       | <b>9g</b> | 65                     |

<sup>a</sup> Isolated yields. <sup>b</sup> In a sealed tube.

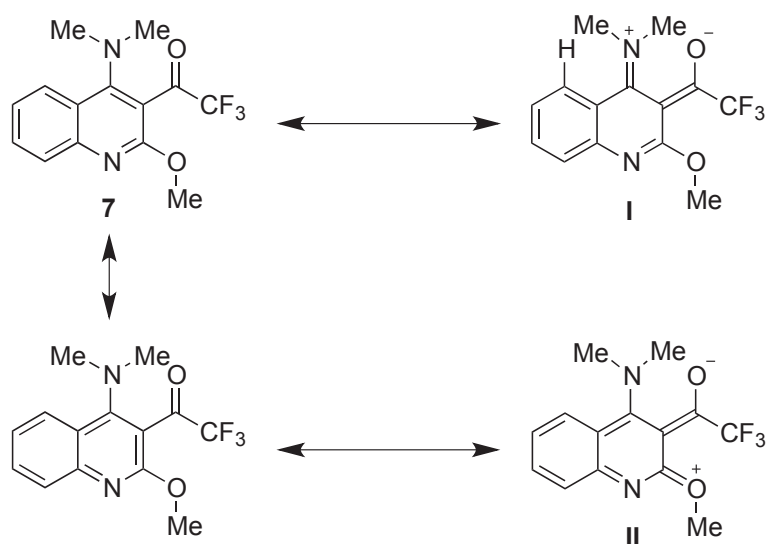
Lastly, we tried the reaction of **7** using alcohols as a nucleophile (Table 3). In spite of the weak nucleophilicity of alcohols relative to the corresponding amines and thiols, the reaction of **7** with *n*-propyl, *n*-butyl, and *n*-pentyl alcohols proceeded successfully at the 4-position under solvolysis conditions to give the corresponding *N*-*O* exchanged products, 2-methoxy-3-trifluoroacetyl-4-quinolyl ethers (**10a-c**) solely in good to high yields (Entries 1-3). Similarly, **7** underwent the dimethylamino-alkoxy exchange reaction with phenethyl and 2-phenoxyethyl alcohols in refluxing mesitylene to afford the corresponding ethers (**10d** and **10e**) in good yields (Entries 4 and 5). Even in the case of more bulky *i*-butyl alcohol, the reaction of **7** was proceeded chemoselectively to convert the corresponding ether (**10f**) in excellent yield (Entry 6). Exchange reaction of **7** with secondary alcohol (cyclohexyl alcohol) was also selective to give *N*-*O* exchanged product (**10g**) in sufficient yield (Entry 7). In all cases in Table 3, no *O*-*O* exchange reaction at 2-position of **7** was observed.

Table 3. Aromatic nucleophilic substitution of **7** with alcohols (R<sup>4</sup>OH)

| Entry | R <sup>4</sup> OH (eq)                     | Temp. (°C)       | Solvent            | Time (h) | Product    | Yield (%) <sup>a</sup> |
|-------|--|------------------|--------------------|----------|------------|------------------------|
| 1     | <i>n</i> -PrOH (excess) <sup>b</sup>       | 180 <sup>c</sup> | <i>n</i> -PrOH     | 72       | <b>10a</b> | 62                     |
| 2     | <i>n</i> -BuOH (excess) <sup>b</sup>       | reflux           | <i>n</i> -BuOH     | 240      | <b>10b</b> | 89                     |
| 3     | <i>n</i> -pentylOH (excess) <sup>b</sup>   | reflux           | <i>n</i> -pentylOH | 120      | <b>10c</b> | 77                     |
| 4     | PhCH <sub>2</sub> CH <sub>2</sub> OH (30)  | reflux           | mesitylene         | 48       | <b>10d</b> | 77                     |
| 5     | PhOCH <sub>2</sub> CH <sub>2</sub> OH (30) | reflux           | mesitylene         | 96       | <b>10e</b> | 77                     |
| 6     | <i>i</i> -BuOH (excess) <sup>b</sup>       | 180 <sup>c</sup> | <i>i</i> -BuOH     | 72       | <b>10f</b> | 92                     |
| 7     | cyclohexylOH (excess) <sup>b</sup>         | reflux           | cyclohexylOH       | 168      | <b>10g</b> | 60                     |

<sup>a</sup> Isolated yields. <sup>b</sup> Under solvolysis conditions. <sup>c</sup> In a sealed tube.

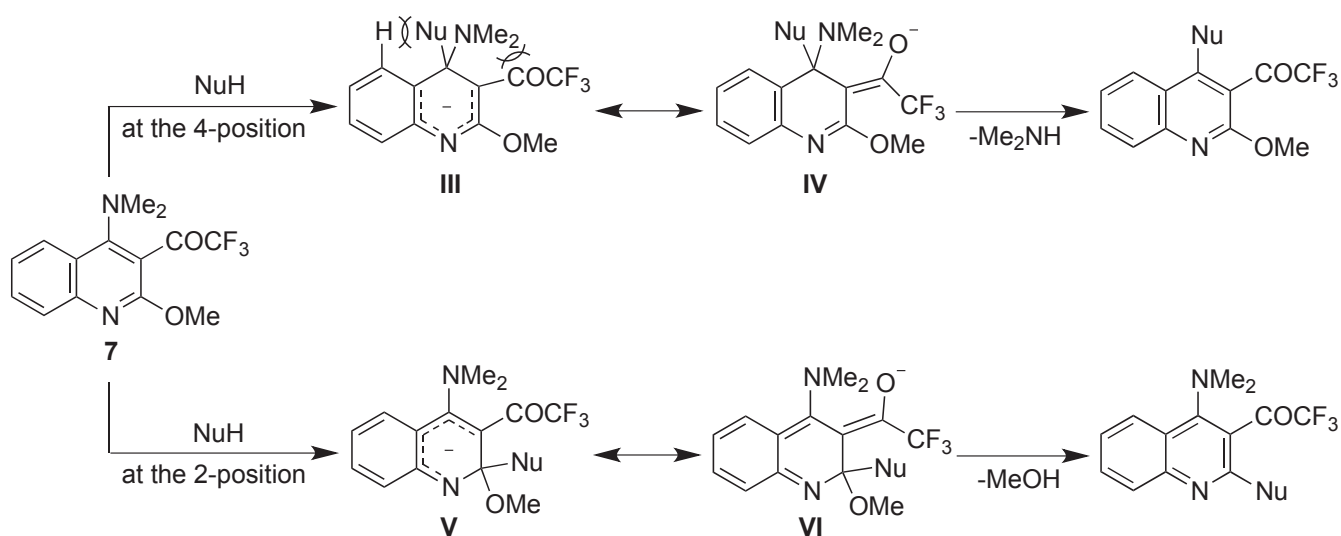
It is common knowledge that alkoxy group such as methoxy group is better leaving group than amino group on nucleophilic substitution reaction.<sup>18</sup> It is also known that nucleophilic substitution occurs at the 2-position more easily than the 4-position on quinoline ring system<sup>19</sup> except for the special case that the leaving group at the 4-position is especially active relative to that at the 2-position.<sup>20</sup> Therefore, the present unexpected chemoselectivity appeared in the reaction of **7** with various nucleophiles is especially interesting. The present unexpected chemoselectivity can be explained as followings. If the dimethylamino group at the 4-position of **7** is conjugated with the trifluoroacetyl group at the 3-position of **7**, it takes a resonance structure **I** (Scheme 4). On the other hand, if the methoxy group at the 2-position of **7** is conjugated with the trifluoroacetyl group at the 3-position of **7**, it takes a resonance structure **II**. Although the aromaticity of benzene ring in the resonance structure **I** is retained, the aromaticity of benzene ring in the resonance structure **II** is not retained. Therefore, the resonance structure **I** is considered to be stable than the resonance structure **II**. In the resonance structure **I**, dimethylamino group has steric repulsion between trifluoroacetyl group and hydrogen atom at the peri-position, but the resonance contribution of **I** is larger than that of **II**. Therefore, it is considered that nucleophiles easily attack the iminium carbon at the 4-position compared to the oxonium carbon at the 2-position.



Scheme 4

Moreover, when nucleophiles (NuH) attack the 4-position of **7**, the Meisenheimer complexes (**III**) are formed (Scheme 5). Meanwhile, the complexes (**V**) are resulted when nucleophiles reacted at the 2-position of **7**. Strong electron-withdrawing trifluoroacetyl group at the 3-position of **7** causes predominant contribution of the canonical form of **IV** in **III** and the canonical form **VI** in **V**. Benzene unit maintains aromatic structure (aromaticity) in the form **IV**, whereas that is destroyed in the form **VI**.

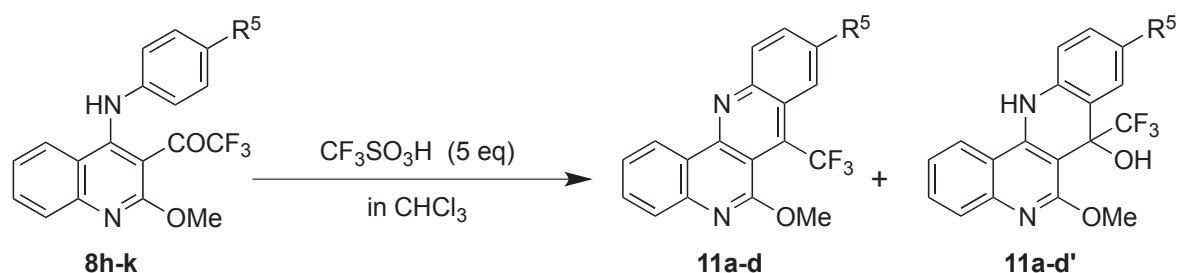
Consequently, the Meisenheimer complexes (**III**) are more stabilized than **V**. This difference of stability between **III** and **V** results the exclusive formation of **III**, and, consequently, the  $Me_2N-Nu$  exchanged products (**8-10**) from **7**. In addition, the significant steric repulsions around the 4-position between peri-hydrogen and 3-trifluoroacetyl group in **III** that are released by elimination of dimethylamino group accelerates the step from **III** to **8-10** (steric acceleration). In the complex **V** in which methoxy group is less bulky than dimethylamino group and no presence of peri-hydrogen around the 2-position, the effect of steric acceleration for the elimination process to  $MeO-Nu$  exchanged products is decreased. Such difference of steric factors between **III** and **V** may also one of the reasons for the present unexpected chemoselectivity.



Scheme 5

As a next step, we attempted to synthesize novel fluorine-containing 6-methoxydibenzo[*b,h*][1,6]-naphthyridines (**11**) by the cyclization of the *N-N* exchanged products (**8h-k**) with the use of TFSA as an acid catalyst (Scheme 6 and Table 4). The desired cyclization of *N*-(*p*-methoxyphenyl)-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**8h**) with TFSA (5 eq) proceeded smoothly even at room temperature for 1 h in chloroform to afford the target heterocycle, 6,9-dimethoxy-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridine (**11a**) in high yield (85%, Entry 1). Unlike the case of the reaction of the 2-unsubstituted *N*-(*p*-methoxyphenyl)-3-trifluoroacetyl-4-quinolylamine (**6**: Nu = *p*-MeOC<sub>6</sub>H<sub>4</sub>NH)<sup>12,13</sup> which gave the corresponding dibenzo[*b,h*][1,6]naphthyridine as a sole product, 6,9-dimethoxy-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridinol (**11a'**), the precursor of **11a**, was given in 14% yield together with **11a** in the present reaction. The reaction of *p*-tolylamino derivative (**8i**) afforded the corresponding dibenzonaphthyridine (**11b**) and dibenzonaphthyridinol (**11b'**) in 76% and 19% yield, respectively (Entry 2). In the cyclization of *p*-unsubstituted phenylamino derivative (**8j**),

dibenzonaphthyridinol (**11c'**) became a major product (63%) along with dibenzonaphthyridine (**11c**) as a minor product (37%, Entry 3). In the case of *p*-chlorophenylamino derivative (**8k**), elevation of the temperature and the prolonged time was required for completion of the reaction to give 9-chlorodibenzonaphthyridinol (**11d'**) as a main product in 78% yield together with 9-chlorodibenzonaphthyridine (**11d**) in 22% yield (Entry 4).



Scheme 6

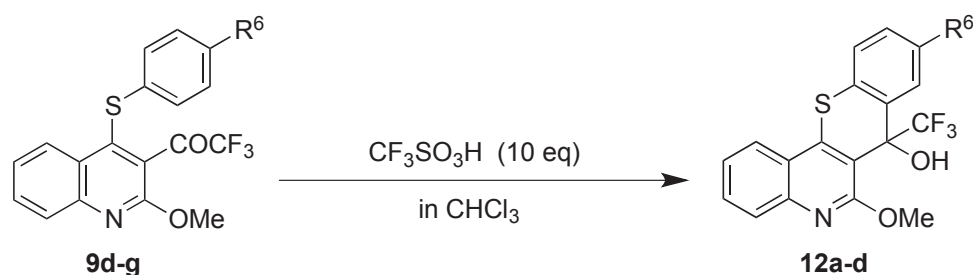
Table 4. Synthesis of dibenzo[*b,h*][1,6]naphthyridines **11** and **11'**

| Entry | $\text{R}^5$ | Temp.  | Time (h) | Product                  | Yield (%) <sup>a</sup> |
|-------|--------------|--------|----------|--------------------------|------------------------|
| 1     | MeO          | rt     | 1        | <b>11a</b> / <b>11a'</b> | 85 / 14                |
| 2     | Me           | rt     | 1        | <b>11b</b> / <b>11b'</b> | 76 / 19                |
| 3     | H            | rt     | 1        | <b>11c</b> / <b>11c'</b> | 37 / 63                |
| 4     | Cl           | reflux | 4        | <b>11d</b> / <b>11d'</b> | 22 / 78                |

<sup>a</sup> Isolated yields.

The present synthetic strategy could be extended further to the construction of the fluorine-containing 6-methoxythiochromeno[3,2-*c*]quinoline system (Scheme 7 and Table 5). *p*-Anisyl 2-methoxy-3-trifluoroacetyl-4-quinolyl sulfides (**9d**) cleanly underwent the TFSA (10 eq) catalyzed cyclization to give the desired 6,9-dimethoxy-7*H*-thiochromeno[3,2-*c*]quinoline (**12a**) in excellent yields (Entry 1). Reactions of *p*-tolylthio derivative (**9e**) and *p*-unsubstituted phenylthio derivative (**9f**) for 1 h afforded the corresponding 6-methoxythiochromenoquinolines (**12b** and **12c**) in quantitative yields, respectively (Entries 2 and 3). In the case of *p*-chlorophenylthio derivative (**9g**), the prolonged time (72 h) was required to complete the reaction and 9-chloro-6-methoxythiochromenoquinoline (**12d**) was obtained in 95% yield (Entry 4).





Scheme 7

Table 5. Synthesis of thiochromeno[3,2-*c*]quinolines **12**

| Entry | R <sup>6</sup> | Temp. | Time (h) | Product    | Yield (%) <sup>a</sup> |
|-------|----------------|-------|----------|------------|------------------------|
| 1     | MeO            | rt    | 2        | <b>12a</b> | 97                     |
| 2     | Me             | rt    | 1        | <b>12b</b> | 99                     |
| 3     | H              | rt    | 1        | <b>12c</b> | 100                    |
| 4     | Cl             | rt    | 72       | <b>12d</b> | 95                     |

<sup>a</sup> Isolated yields.

In conclusion, we have presented highly chemoselective nucleophilic substitution reactions of *N,N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**7**) with various amines, thiols, and alcohols giving the corresponding 2-methoxy-3-trifluoroacetyl-4-quinolylamines (**8**), sulfides (**9**), and ethers (**10**). It is also worth of noting that the present nucleophilic substitution occurs at the 4-position which is less active than the 2-position in quinoline ring system in general. Using the products **8** and **9** as substrates, novel fluorine-containing 6-methoxydibenzo[*b,h*][1,6]naphthyridines (**11**) and 6-methoxythiochromeno[3,2-*c*]quinolines (**12**), which are hardly accessible by other methods, were synthesized successfully in moderate to high yields. In the reaction of quinolylamines (**8**), dibenzonaphthyridinols (**11'**), which are the precursor of naphthyridines (**11**), were isolated unlike the case of the cyclization of *N*-aryl-3-trifluoroacetyl-4-quinolylamines (**6**). The synthesized heterocycles (**11**, **11'**, **12**) have the functional group (methoxy group) at the 6-position that enables further transformation to diverse derivatives. Evaluation of biological activities for **11**, **11'**, and **12** is now under way.

## EXPERIMENTAL

<sup>1</sup>H (500 MHz) and <sup>13</sup>C (125 MHz) NMR spectra was obtained with a Bruker Avance 500 spectrometer using TMS as an internal standard. IR spectra were recorded on a PerkinElmer Spectrum ONE

spectrophotometer. Microanalyses were obtained with a Yanaco CHN-Coder MT-5 analyzer. Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. The solvents (CHCl<sub>3</sub>, MeCN, BuCN, *p*-xylene and mesitylene) were used after drying over 4Å molecular sieves. Other reagents were purchased as reagent grade and used without further purification. Column chromatography was carried out with Fuji Silysia Chemical PSQ100B as filler.

#### Synthesis of (*E*)-1,1,1-Trifluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one

To a solution of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one<sup>17</sup> (184 mg, 1 mmol) in MeCN (1 mL) was added 2-aminobenzonitrile (124 mg, 1.05 mmol) and the mixture was stirred under reflux for 18 h. The solvent was evaporated in vacuo to give the practically pure (*E*)-1,1,1-trifluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one; colorless solid; mp 171-172 °C (*n*-hexane/AcOEt); IR (KBr): 3444, 2224, 1624, 1179 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>CN): δ 12.90-11.97 (br, 1H), 7.90-7.03 (m, 4H), 5.37 (s, 1H), 3.92 (s, 3H); <sup>13</sup>C NMR (CD<sub>3</sub>CN): 176.0 (q, *J*<sub>CF</sub> = 33.2 Hz), 169.6, 138.6, 133.9, 133.3, 126.2, 124.8, 117.9 (q, *J*<sub>CF</sub> = 287.8 Hz), 116.2, 106.6, 74.0, 57.7. Anal. Calcd for C<sub>12</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 53.34; H, 3.36; N, 10.37. Found: C, 53.09; H, 3.72; N, 10.31.

#### Synthesis of 2-Methoxy-3-trifluoroacetyl-4-quinolylamine

The mixture of TFSA (1 mL, 11 mmol) and (*E*)-1,1,1-trifluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one (270 mg, 1 mmol) was stirred at 140 °C for 5 min. To the reaction mixture was added saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (50 mL), then the whole mixture was extracted with AcOEt (50 mL), and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated in vacuo and the crude mixture was purified by silica gel column chromatography using *n*-hexane/AcOEt (10/1) as an eluent to give 2-methoxy-3-trifluoroacetyl-4-quinolylamine; pale yellow solid; mp 65-66 °C (*n*-hexane/AcOEt); IR (KBr): 3471, 3324, 1612, 1201, 1178, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.75-7.45 (m, 5H), 7.35 (t, *J* = 7.6 Hz, 1H), 4.08 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 182.1 (q, *J*<sub>CF</sub> = 35.7 Hz), 160.6, 157.6, 147.8, 133.0, 128.0, 123.8, 121.1, 117.1 (q, *J*<sub>CF</sub> = 288.7 Hz), 115.7, 96.3, 53.3. Anal. Calcd for C<sub>12</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 53.34; H, 3.36; N, 10.37. Found: C, 53.43; H, 3.36; N, 10.06.

#### Synthesis of *N,N*-Dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (7)

To a solution of KOH (140 mg, 2.5 mmol) in DMSO (9.5 mL) was added 2-methoxy-3-trifluoroacetyl-4-quinolylamine (270 mg, 1 mmol) and MeI (0.4 mL, 6 mmol), and the mixture was stirred at room temperature for 48 h. H<sub>2</sub>O (50 mL) was added to the reaction mixture, then the whole mixture was extracted with AcOEt (50 mL), and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated in vacuo to give the crude mixture which was purified by silica gel column chromatography using *n*-hexane/AcOEt (20/1) as an eluent to give 7; yellow solid; mp 77-78 °C (*n*-hexane/AcOEt); IR (KBr): 1719, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 4.06 (s, 3H), 2.98 (s, 6H); <sup>13</sup>C

NMR (125 MHz, CDCl<sub>3</sub>): 187.5 (q,  $J_{CF}$  = 38.5 Hz), 160.0, 159.9, 148.6, 131.0, 128.1, 125.5, 123.7, 122.0, 115.5 (q,  $J_{CF}$  = 292.0 Hz), 109.7, 53.7, 45.0. Anal. Calcd for C<sub>14</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.54; H, 4.62; N, 9.26.

***N-N* Exchange Reaction of 7 with Amines to Give 2-Methoxy-3-trifluoroacetyl-4-quinolyamines (8a-k); General Procedure**

To a solution of 7 (298 mg, 1 mmol) in MeCN (4 mL) was added amines (3-20 mmol) and the mixture was stirred at appropriate temperature for 4-168 h. Evaporation of the solvent in vacuo gave the crude mixture which was subjected to column chromatography (silica gel, *n*-hexane/AcOEt, 200:1 to 10:1) to give the corresponding 8a-k. In the case of 8h-k, BuCN was used instead of MeCN as a solvent.

***N*-(*n*-Butyl)-2-methoxy-3-trifluoroacetyl-4-quinolyamine (8a):** pale yellow solid; mp 88-89 °C (*n*-hexane/AcOEt); IR (KBr): 3269, 1628, 1197, 1182, 1168 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.40 (br s, 1H), 8.02 (d,  $J$  = 7.6 Hz, 1H), 7.65 (d,  $J$  = 7.6 Hz, 1H), 7.57 (t,  $J$  = 7.6 Hz, 1H), 7.21 (t,  $J$  = 7.6 Hz, 1H), 4.03 (s, 3H), 3.67 (q,  $J$  = 4.8 Hz, 2H), 1.72 (quint,  $J$  = 7.4 Hz, 2H), 1.47 (sext,  $J$  = 7.4 Hz, 2H), 0.96 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 182.3 (q,  $J_{CF}$  = 35.9 Hz), 161.1, 158.8, 149.1, 132.3, 128.0, 125.7, 122.7, 117.2, 117.2 (q,  $J_{CF}$  = 289.3 Hz), 97.2, 53.1, 48.7, 32.7, 19.9, 13.6. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 58.90; H, 5.25; N, 8.59. Found: C, 58.78; H, 5.44; N, 8.50.

***N*-Benzyl-2-methoxy-3-trifluoroacetyl-4-quinolyamine (8b):** pale yellow solid; mp 72-73 °C (*n*-hexane/AcOEt); IR (KBr): 3428, 1626, 1195, 1167, 1145 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.08 (br s, 1H), 7.99 (d,  $J$  = 7.5 Hz, 1H), 7.71 (d,  $J$  = 7.5 Hz, 1H), 7.62 (t,  $J$  = 7.5 Hz, 1H), 7.45-7.30 (m, 5H), 7.22 (t,  $J$  = 7.5 Hz, 1H), 4.78 (d,  $J$  = 5.4 Hz, 2H), 4.06 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 183.2 (q,  $J_{CF}$  = 35.3 Hz), 160.9, 158.2, 149.0, 137.1, 132.4, 129.2, 128.4, 128.2, 127.5, 125.2, 123.1, 117.1, 117.0 (q,  $J_{CF}$  = 289.1 Hz), 98.4, 53.3, 52.8. Anal. Calcd for C<sub>19</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 63.33; H, 4.20; N, 7.77. Found: C, 63.22; H, 4.27; N, 7.80.

***N*-Cyclopropyl-2-methoxy-3-trifluoroacetyl-4-quinolyamine (8c):** pale yellow solid; mp 69-70 °C (*n*-hexane/AcOEt); IR (KBr): 3355, 1704, 1193, 1176, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.44 (br s, 1H), 8.64 (d,  $J$  = 7.6 Hz, 1H), 7.69 (d,  $J$  = 7.6 Hz, 1H), 7.64 (t,  $J$  = 7.6 Hz, 1H), 7.28 (t,  $J$  = 7.6 Hz, 1H), 4.05 (s, 3H), 3.12-3.04 (m, 1H), 1.14-1.00 (m, 2H), 0.88-0.76 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 182.8 (q,  $J_{CF}$  = 35.5 Hz), 160.9, 158.3, 148.8, 132.3, 127.9, 125.6, 122.8, 117.0 (q,  $J_{CF}$  = 289.3 Hz), 117.0, 97.1, 53.2, 29.9, 10.8. Anal. Calcd for C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 59.30; H, 4.70; N, 8.60. Found: C, 59.23; H, 4.98; N, 8.35.

***N*-Cyclohexyl-2-methoxy-3-trifluoroacetyl-4-quinolyamine (8d):** pale yellow solid; mp 79-80 °C (*n*-hexane/AcOEt); IR (KBr): 3277, 1620, 1200, 1189, 1167 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.31-9.20 (br m, 1H), 7.96 (d,  $J$  = 7.9 Hz, 1H), 7.68 (d,  $J$  = 7.9 Hz, 1H), 7.61 (t,  $J$  = 7.9 Hz, 1H), 7.25 (t,  $J$  = 7.9 Hz, 1H), 4.11-3.98 (m, 1H), 4.04 (s, 3H), 2.16-2.02 (m, 2H), 1.88-1.74 (m, 2H), 1.68-1.58 (m, 1H), 1.52-1.22 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 182.6 (q,  $J_{CF}$  = 35.7 Hz), 161.1, 158.3, 149.1, 132.3, 128.2, 125.7, 122.9, 117.5,

117.1 (q,  $J_{CF} = 289.0$  Hz), 98.9, 56.4, 53.2, 34.2, 25.3, 24.5. Anal. Calcd for  $C_{18}H_{19}F_3N_2O_2$ : C, 61.40; H, 5.40; N, 8.00. Found: C, 61.12; H, 5.46; N, 8.17.

***N*-Allyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8e)**: pale yellow solid; mp 67-68 °C (*n*-hexane/AcOEt); IR (KBr): 3232, 1619, 1203, 1172, 1155  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  9.20 (br s, 1H), 7.99 (d,  $J = 7.8$  Hz, 1H), 7.67 (d,  $J = 7.8$  Hz, 1H), 7.60 (t,  $J = 7.8$  Hz, 1H), 7.23 (t,  $J = 7.8$  Hz, 1H), 6.06-5.95 (m, 1H), 5.45 (d,  $J = 17.2$  Hz, 1H), 5.35 (d,  $J = 10.3$  Hz, 1H), 4.33-4.24 (m, 2H), 4.04 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 182.8 (q,  $J_{CF} = 36.7$  Hz), 160.9, 158.7, 149.0, 133.1, 132.4, 128.1, 125.5, 122.9, 118.3, 117.0, 117.0 (q,  $J_{CF} = 289.3$  Hz), 98.3, 53.3, 50.7. Anal. Calcd for  $C_{15}H_{13}F_3N_2O_2$ : C, 58.10; H, 4.20; N, 9.00. Found: C, 57.64; H, 4.50; N, 9.18.

***N*-Propargyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8f)**: pale yellow solid; mp 117-118 °C (*n*-hexane/AcOEt); IR (KBr): 3433, 1664, 1195, 1173, 1159  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.58 (br s, 1H), 8.08 (d,  $J = 8.0$  Hz, 1H), 7.74 (d,  $J = 8.0$  Hz, 1H), 7.67 (t,  $J = 8.0$  Hz, 1H), 7.33 (t,  $J = 8.0$  Hz, 1H), 4.33 (dd,  $J = 6.0, 2.4$  Hz, 2H), 4.07 (s, 3H), 2.45 (t,  $J = 2.4$  Hz, 1H);  $^{13}C$  NMR ( $CDCl_3$ ): 183.7 (q,  $J_{CF} = 36.4$  Hz), 160.4, 157.4, 148.8, 132.5, 128.2, 124.9, 123.4, 117.1, 116.7 (q,  $J_{CF} = 289.5$  Hz), 100.5, 78.5, 74.3 (q,  $J_{CF} = 2.7$  Hz), 53.4, 38.0. Anal. Calcd for  $C_{15}H_{11}F_3N_2O_2$ : C, 58.40; H, 3.60; N, 9.09. Found: C, 58.35; H, 3.62; N, 8.85.

**2-Methoxy-4-(pyrrolidin-1-yl)-3-trifluoroacetylquinoline (8g)**: pale yellow solid; mp 80-81 °C (*n*-hexane/AcOEt); IR (KBr): 1678, 1200, 1179, 1153  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.02 (d,  $J = 7.8$  Hz, 1H), 7.72 (d,  $J = 7.8$  Hz, 1H), 7.57 (t,  $J = 7.8$  Hz, 1H), 7.24 (t,  $J = 7.8$  Hz, 1H), 4.04 (s, 3H), 3.47 (t,  $J = 6.5$  Hz, 4H), 2.00 (t,  $J = 6.5$  Hz, 4H);  $^{13}C$  NMR ( $CDCl_3$ ): 185.3 (q,  $J_{CF} = 36.0$  Hz), 160.2, 156.2, 148.2, 130.5, 127.4, 126.0, 122.0, 119.9, 116.1 (q,  $J_{CF} = 291.2$  Hz), 102.5, 55.7, 53.4, 25.7. Anal. Calcd for  $C_{16}H_{15}F_3N_2O_2$ : C, 59.30; H, 4.70; N, 8.60. Found: C, 59.23; H, 4.98; N, 8.35.

***N*-(4-Methoxyphenyl)-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8h)**: pale yellow solid; mp 106-107 °C (*n*-hexane/AcOEt); IR (KBr): 3256, 1619, 1195, 1184, 1145  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  10.53 (br s, 1H), 7.67 (d,  $J = 8.0$  Hz, 1H), 7.51 (t,  $J = 8.0$  Hz, 1H), 7.47 (d,  $J = 8.0$  Hz, 1H), 7.04 (d,  $J = 8.7$  Hz, 2H), 6.93 (t,  $J = 8.0$  Hz, 1H), 6.85 (d,  $J = 8.7$  Hz, 2H), 4.09 (s, 3H), 3.81 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 183.2 (q,  $J_{CF} = 36.2$  Hz), 160.4, 157.9, 155.8, 149.3, 134.4, 132.4, 128.0, 127.1, 125.3, 122.6, 116.9 (q,  $J_{CF} = 289.0$  Hz), 116.8, 114.9, 101.1, 55.5, 53.4. Anal. Calcd for  $C_{19}H_{15}F_3N_2O_3$ : C, 60.64; H, 4.02; N, 7.44. Found: C, 60.46; H, 4.24; N, 7.40.

***N*-(*p*-Tolyl)-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8i)**: pale yellow solid; mp 119-120 °C (*n*-hexane/AcOEt); IR (KBr): 3269, 1620, 1199, 1177, 1156  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  10.36 (br s, 1H), 7.68 (d,  $J = 8.1$  Hz, 1H), 7.58-7.48 (m, 2H), 7.10 (d,  $J = 8.0$  Hz, 2H), 7.01-6.90 (m, 3H), 4.09 (s, 3H), 2.34 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 183.4 (q,  $J_{CF} = 36.9$  Hz), 160.3, 155.3, 149.2, 139.1, 135.6, 132.4, 130.2,

128.0, 127.2, 123.3, 122.7, 117.0, 116.8 (q,  $J_{CF} = 289.2$  Hz), 102.1, 53.4, 20.9. Anal. Calcd for  $C_{19}H_{15}F_3N_2O_2$ : C, 63.33; H, 4.20; N, 7.77. Found: C, 63.57; H, 4.21; N, 8.07.

***N*-Phenyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8j)**: pale yellow solid; mp 103-104 °C (*n*-hexane/AcOEt); IR (KBr): 3297, 1616, 1194, 1183, 1163  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  10.26 (br s, 1H), 7.72 (d,  $J = 7.7$  Hz, 1H), 7.57 (t,  $J = 7.7$  Hz, 1H), 7.53 (d,  $J = 7.7$  Hz, 1H), 7.33 (d,  $J = 7.7$  Hz, 2H), 7.20 (t,  $J = 7.7$  Hz, 1H), 7.08 (d,  $J = 7.7$  Hz, 2H), 6.99 (t,  $J = 7.7$  Hz, 1H), 4.12 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 183.6 (q,  $J_{CF} = 36.7$  Hz), 160.1, 154.7, 149.1, 141.7, 132.5, 129.5, 128.0, 127.1, 125.4, 122.9, 122.8, 117.0, 116.7 (q,  $J_{CF} = 289.3$  Hz), 102.8, 53.5. Anal. Calcd for  $C_{18}H_{13}F_3N_2O_2$ : C, 62.43; H, 3.78; N, 8.09. Found: C, 62.30; H, 3.51; N, 7.72.

***N*-(4-Chlorophenyl)-2-methoxy-3-trifluoroacetyl-4-quinolylamine (8k)**: pale yellow solid; mp 121-122 °C (*n*-hexane/AcOEt); IR (KBr): 3301, 1618, 1199, 1185, 1159  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  10.06 (br s, 1H), 7.74 (d,  $J = 7.4$  Hz, 1H), 7.59 (t,  $J = 7.4$  Hz, 1H), 7.52 (d,  $J = 7.4$  Hz, 1H), 7.28 (d,  $J = 8.6$  Hz, 2H), 7.05 (t,  $J = 7.4$  Hz, 1H), 6.99 (d,  $J = 8.6$  Hz, 2H), 4.12 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 183.9 (q,  $J_{CF} = 36.4$  Hz), 159.9, 154.1, 149.2, 140.5, 132.6, 130.5, 129.6, 128.2, 126.9, 123.7, 123.1, 116.9, 116.6 (q,  $J_{CF} = 289.3$  Hz), 103.5, 53.6. Anal. Calcd for  $C_{18}H_{12}ClF_3N_2O_2$ : C, 56.78; H, 3.18; N, 7.36. Found: C, 57.08; H, 2.94; N, 7.31.

#### ***N*-S Exchange Reaction of 7 with Thiols to Give 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfides (9a-g); General Procedure**

To a solution of 7 (298 mg, 1 mmol) in mesitylene (4 mL) was added thiols (5-40 mmol) and the mixture was stirred under reflux for 72-120 h. Evaporation of the solvent in vacuo gave the crude products which were subjected to column chromatography (silica gel, *n*-hexane/AcOEt, 500:1 to 10:1) to give the corresponding 9a-g. In the case of 9a and 9d, the mixture was heated at 160 °C in a sealed tube and in refluxing *p*-xylene instead of mesitylene, respectively.

***n*-Butyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9a)**: pale yellow oil; bp 164 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1589, 1206, 1170  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.39 (d,  $J = 7.6$  Hz, 1H), 7.91 (d,  $J = 7.6$  Hz, 1H), 7.75 (t,  $J = 7.6$  Hz, 1H), 7.54 (t,  $J = 7.6$  Hz, 1H), 4.10 (s, 3H), 2.88 (t,  $J = 7.4$  Hz, 2H), 1.54 (quint,  $J = 7.4$  Hz, 2H), 1.37 (sext,  $J = 7.4$  Hz, 2H), 0.87 (t,  $J = 7.4$  Hz, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 185.0 (q,  $J_{CF} = 38.7$  Hz), 157.5, 147.2, 145.5, 131.6, 128.1, 126.0, 125.5, 125.4, 125.4, 115.3 (q,  $J_{CF} = 291.3$  Hz), 54.1, 37.5, 31.6, 21.7, 13.4. Anal. Calcd for  $C_{16}H_{16}F_3NO_2S$ : C, 55.97; H, 4.70; N, 4.08. Found: C, 56.32; H, 4.76; N, 4.17.

***n*-Hexyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9b)**: pale yellow oil; bp 188 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1589, 1207, 1170  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.38 (d,  $J = 7.7$  Hz, 1H), 7.91 (d,  $J = 7.7$  Hz, 1H), 7.75 (t,  $J = 7.7$  Hz, 1H), 7.54 (t,  $J = 7.7$  Hz, 1H), 4.09 (s, 3H), 2.87 (t,  $J = 7.4$  Hz, 2H), 1.55 (quint,  $J = 7.4$  Hz, 2H), 1.37-1.19 (m, 7H), 0.86 (t,  $J = 7.4$  Hz, 3H);  $^{13}C$  NMR ( $CDCl_3$ ):

184.9 (q,  $J_{CF} = 38.9$  Hz), 157.5, 147.2, 145.5, 131.5, 128.1, 126.0, 125.5, 125.4, 125.3, 115.3 (q,  $J_{CF} = 291.4$  Hz), 54.0, 37.8, 31.1, 29.6, 28.2, 22.4, 13.8. Anal. Calcd for  $C_{18}H_{20}F_3NO_2S$ : C, 58.21; H, 5.43; N, 3.77. Found: C, 58.25; H, 5.77; N, 3.40.

**Benzyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9c):** pale yellow solid; mp 87-88 °C (*n*-hexane/AcOEt); IR (KBr): 1740, 1206, 1167  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.28 (d,  $J = 7.7$  Hz, 1H), 7.89 (d,  $J = 7.7$  Hz, 1H), 7.73 (t,  $J = 7.7$  Hz, 1H), 7.46 (t,  $J = 7.7$  Hz, 1H), 7.24-7.18 (m, 3H), 7.15-7.09 (m, 2H), 4.10 (s, 3H), 4.04 (s, 2H);  $^{13}C$  NMR ( $CDCl_3$ ): 184.9 (q,  $J_{CF} = 38.9$  Hz), 157.6, 147.2, 144.3, 135.9, 131.6, 128.9, 128.6, 128.0, 127.7, 126.1, 125.7, 125.5, 125.5, 115.2 (q,  $J_{CF} = 291.2$  Hz), 54.1, 42.2. Anal. Calcd for  $C_{19}H_{14}F_3NO_2S$ : C, 60.47; H, 3.74; N, 3.71. Found: C, 60.86; H, 3.45; N, 3.60.

**4-Methoxyphenyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9d):** pale yellow solid; mp 93-94 °C (*n*-hexane/AcOEt); IR (KBr): 1745, 1199, 1157  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.21 (d,  $J = 7.6$  Hz, 1H), 7.88 (d,  $J = 7.6$  Hz, 1H), 7.68 (t,  $J = 7.6$  Hz, 1H), 7.39 (t,  $J = 7.6$  Hz, 1H), 7.21 (d,  $J = 8.9$  Hz, 2H), 6.78 (d,  $J = 8.9$  Hz, 2H), 4.11 (s, 3H), 3.75 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 184.9 (q,  $J_{CF} = 39.2$  Hz), 159.4, 157.7, 147.5, 144.4, 131.9, 131.6, 128.0, 126.4, 125.5, 124.5, 124.5, 124.3, 115.3 (q,  $J_{CF} = 291.6$  Hz), 115.1, 55.3, 54.2. Anal. Calcd for  $C_{19}H_{14}F_3NO_3S$ : C, 58.01; H, 3.59; N, 3.56. Found: C, 58.10; H, 3.57; N, 3.49.

***p*-Tolyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9e):** pale yellow solid; mp 121-122 °C (*n*-hexane/AcOEt); IR (KBr): 1748, 1202, 1157  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.16 (d,  $J = 7.3$  Hz, 1H), 7.89 (d,  $J = 7.3$  Hz, 1H), 7.69 (t,  $J = 7.3$  Hz, 1H), 7.38 (t,  $J = 7.3$  Hz, 1H), 7.08 (d,  $J = 8.2$  Hz, 2H), 7.03 (d,  $J = 8.2$  Hz, 2H), 4.12 (s, 3H), 2.27 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 184.7 (q,  $J_{CF} = 39.2$  Hz), 157.7, 147.5, 143.4, 137.5, 131.6, 130.6, 130.2, 129.2, 128.0, 126.5, 125.6, 125.0, 124.6, 115.3 (q,  $J_{CF} = 291.4$  Hz), 54.2, 20.9. Anal. Calcd for  $C_{19}H_{14}F_3NO_2S$ : C, 60.50; H, 3.74; N, 3.71. Found: C, 60.81; H, 3.74; N, 3.37.

**Phenyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9f):** pale yellow solid; mp 84-85 °C (*n*-hexane/AcOEt); IR (KBr): 1751, 1210, 1172  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.14 (d,  $J = 7.5$  Hz, 1H), 7.91 (d,  $J = 7.5$  Hz, 1H), 7.70 (t,  $J = 7.5$  Hz, 1H), 7.38 (t,  $J = 7.5$  Hz, 1H), 7.25-7.13 (m, 5H), 4.13 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 184.6 (q,  $J_{CF} = 39.1$  Hz), 157.7, 147.5, 142.7, 134.2, 131.7, 129.4, 128.8, 128.1, 127.2, 126.4, 125.7, 125.3, 124.6, 115.2 (q,  $J_{CF} = 291.1$  Hz), 54.2. Anal. Calcd for  $C_{18}H_{12}F_3NO_2S$ : C, 59.50; H, 3.33; N, 3.86. Found: C, 59.38; H, 3.32; N, 3.55.

**4-Chlorophenyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Sulfide (9g):** pale yellow solid; mp 97-98 °C (*n*-hexane/AcOEt); IR (KBr): 1751, 1203, 1157  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  8.10 (d,  $J = 7.7$  Hz, 1H), 7.91 (d,  $J = 7.7$  Hz, 1H), 7.70 (t,  $J = 7.7$  Hz, 1H), 7.39 (t,  $J = 7.7$  Hz, 1H), 7.18 (d,  $J = 8.6$  Hz, 2H), 7.08 (d,  $J = 8.6$  Hz, 2H), 4.13 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ ): 184.5 (q,  $J_{CF} = 39.4$  Hz), 157.7, 147.6, 142.0, 133.4, 132.7, 131.9, 130.0, 129.6, 128.2, 126.2, 125.9, 125.5, 124.4, 115.2 (q,  $J_{CF} = 291.2$  Hz), 54.3. Anal. Calcd for  $C_{18}H_{11}ClF_3NO_2S$ : C, 54.35; H, 2.79; N, 3.52. Found: C, 54.54; H, 2.87; N, 3.22.

### ***N-O* Exchange Reaction of 7 with Alcohols to Give 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ethers (10a-g); General Procedure**

The solution of 7 (298 mg, 1 mmol) in alcohols (30-108 mmol) was stirred under reflux for 48-240 h. Evaporation of the solvent in vacuo gave the crude mixture which was subjected to column chromatography (silica gel, *n*-hexane/AcOEt, 1:0 to 20:1) to give the corresponding **10a-g**. In the case of **10a** and **10f**, the solution of 7 in the corresponding alcohols was heated at 180 °C in a sealed tube. In the case of **10d** and **10e**, mesitylene (4 mL) was used as a solvent.

***n*-Propyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10a)**: pale yellow oil; bp 110 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1733, 1189, 1163 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.09 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 4.09 (s, 3H), 4.01 (t, *J* = 6.9 Hz, 2H), 1.93-1.86 (m, 2H), 1.08 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.0 (q, *J*<sub>CF</sub> = 37.8 Hz), 163.7, 159.6, 148.0, 131.9, 127.4, 124.5, 123.2, 120.0, 115.4 (q, *J*<sub>CF</sub> = 291.2 Hz), 106.5, 77.6, 54.0, 23.4, 10.3. Anal. Calcd for C<sub>15</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub>: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.20; H, 4.44; N, 4.67.

***n*-Butyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10b)**: pale yellow oil; bp 128 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1744, 1204, 1161 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 4.08 (s, 3H), 4.04 (t, *J* = 6.9 Hz, 2H), 1.87-1.82 (m, 2H), 1.56-1.50 (m, 2H), 0.98 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.0 (q, *J*<sub>CF</sub> = 38.3 Hz), 163.6, 159.6, 147.9, 131.9, 127.4, 124.5, 123.2, 120.0, 115.4 (q, *J*<sub>CF</sub> = 292.2 Hz), 106.4, 75.9, 54.0, 32.0, 19.0, 13.7. Anal. Calcd for C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub>: C, 58.71; H, 4.93; N, 4.28. Found: C, 58.79; H, 4.95; N, 4.46.

***n*-Pentyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10c)**: pale yellow oil; bp 170 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1733, 1239, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 4.08 (s, 3H), 4.03 (t, *J* = 7.1 Hz, 2H), 1.87 (quint, *J* = 7.1 Hz, 2H), 1.47 (quint, *J* = 7.1 Hz, 2H), 1.39 (sext, *J* = 7.1 Hz, 2H), 0.94 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.0 (q, *J*<sub>CF</sub> = 38.1 Hz), 163.6, 159.6, 147.9, 131.8, 127.3, 124.5, 123.2, 120.0, 115.4 (q, *J*<sub>CF</sub> = 291.4 Hz), 106.2, 76.1, 54.0, 29.6, 27.8, 22.3, 13.9. Anal. Calcd for C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>3</sub>: C, 59.82; H, 5.32; N, 4.10. Found: C, 59.93; H, 4.97; N, 4.17.

**2-Phenylethyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10d)**: pale yellow oil; bp 146 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1729, 1207, 1189, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.34-7.23 (m, 6H), 4.27 (t, *J* = 6.7 Hz, 2H), 4.07 (s, 3H), 3.16 (t, *J* = 6.7 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 185.8 (q, *J*<sub>CF</sub> = 38.2 Hz), 163.5, 159.5, 148.1, 137.1, 132.0, 129.0, 128.7, 128.3, 127.4, 126.9, 124.6, 123.2, 120.0, 115.4 (q, *J*<sub>CF</sub> = 291.1 Hz), 107.3, 54.1, 36.4. Anal. Calcd for C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub>: C, 64.00; H, 4.30; N, 3.73. Found: C, 64.08; H, 4.63; N, 3.32.

**2-Phenoxyethyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10e):** pale yellow solid; mp 65-66 °C (*n*-hexane/AcOEt); IR (KBr): 1719, 1202, 1188, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.2, 7.3 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 2H), 4.44 (t, *J* = 3.9 Hz, 2H), 4.35 (t, *J* = 3.9 Hz, 2H), 4.10 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 185.5 (q, *J*<sub>CF</sub> = 37.6 Hz), 163.7, 159.4, 158.4, 148.3, 132.2, 129.6, 127.4, 124.8, 123.5, 121.4, 120.0, 115.4 (q, *J*<sub>CF</sub> = 292.0 Hz), 114.7, 108.3, 74.6, 66.5, 54.1. Anal. Calcd for C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>4</sub>: C, 61.38; H, 4.12; N, 3.58. Found: C, 61.56; H, 3.97; N, 3.42.

**Isobutyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10f):** pale yellow oil; bp 125 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1733, 1190, 1164 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 4.07 (s, 3H), 3.80 (d, *J* = 6.5 Hz, 2H), 2.20-2.14 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 186.1 (q, *J*<sub>CF</sub> = 38.0 Hz), 163.6, 159.6, 147.9, 131.9, 127.4, 124.5, 123.2, 120.0, 115.4 (q, *J*<sub>CF</sub> = 291.2 Hz), 106.2, 82.0, 54.0, 29.3, 18.9. Anal. Calcd for C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub>: C, 58.71; H, 4.93; N, 4.28. Found: C, 59.07; H, 4.87; N, 4.77.

**Cyclohexyl 2-Methoxy-3-trifluoroacetyl-4-quinolyl Ether (10g):** pale yellow oil; bp 173 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 1736, 1189, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 4.22 (m, 2H), 4.08 (s, 3H), 2.00-1.21 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 185.6 (q, *J*<sub>CF</sub> = 37.7 Hz), 163.1, 159.4, 148.3, 131.9, 127.5, 124.4, 123.6, 121.1, 115.4 (q, *J*<sub>CF</sub> = 291.0 Hz), 109.2, 85.0, 54.0, 32.3, 25.1, 23.9. Anal. Calcd for C<sub>18</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>3</sub>: C, 61.19; H, 5.13; N, 3.96. Found: C, 61.19; H, 5.02; N, 4.06.

#### Cyclization of 8h-k and 9d-g with TFSA; General Procedure

To a solution of 1 mmol of the cyclization precursors (**8h-k** and **9d-g**) in CHCl<sub>3</sub> (7 mL) was added TFSA (5 or 10 mmol) and the mixture was stirred at room temperature-reflux temperature for 1-72 h. Most of the solvent was evaporated and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was then added. The mixture was washed with saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (50 mL), and the organic layer was separated and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent gave the crude products. In the case of **11a-d** and **11a-d'**, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane/AcOEt, 40:1 to 0:1) to give the corresponding **11a-d** and **11a-d'**. The crude products **12a-d** were practically pure without further purification.

**6,9-Dimethoxy-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridine (11a):** pale yellow solid; mp 200-201 °C (*n*-hexane/AcOEt); IR (KBr): 1257, 1143 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.07 (d, *J* = 7.9 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.60-7.56 (m, 3H), 4.24 (s, 3H), 4.03 (s, 3H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): 158.4, 156.9, 148.2, 147.3, 143.9, 132.4 (q, *J*<sub>CF</sub> = 32.3 Hz), 131.7, 130.6, 126.9, 126.8, 125.8, 125.1, 124.7, 124.7 (q, *J*<sub>CF</sub> = 280.2 Hz), 123.0, 111.5, 101.7, 54.7, 53.7. Anal. Calcd for C<sub>19</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 63.69; H, 3.66; N, 7.82. Found: C, 63.57; H, 3.80; N, 7.80.



**6-Methoxy-9-methyl-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridine (11b):** pale yellow solid; mp 198-199 °C (*n*-hexane/AcOEt); IR (KBr): 1176, 1138 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.11 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.20 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78-7.74 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 4.25 (s, 3H), 2.66 (s, 3H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): 157.0, 149.6, 149.1, 144.2, 137.6, 133.7, 131.5 (q, *J*<sub>CF</sub> = 34.1 Hz), 131.0, 129.8, 128.1, 126.9, 125.1, 125.0, 124.5 (q, *J*<sub>CF</sub> = 276.8 Hz), 123.7 (q, *J*<sub>CF</sub> = 5.3 Hz), 123.0, 111.4, 53.7, 21.7. Anal. Calcd for C<sub>19</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O: C, 66.66; H, 3.83; N, 8.18. Found: C, 66.37; H, 3.85; N, 8.15.

**6-Methoxy-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridine (11c):** pale yellow solid; mp 162-163 °C (*n*-hexane/AcOEt); IR (KBr): 1161, 1124 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.23 (d, *J* = 7.7 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 3.99 (s, 3H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): 156.9, 150.1, 150.1, 144.2, 132.6 (q, *J*<sub>CF</sub> = 32.8 Hz), 131.2, 131.0, 130.1, 127.3, 126.9, 125.2 (q, *J*<sub>CF</sub> = 5.5 Hz), 125.1, 125.1, 124.3 (q, *J*<sub>CF</sub> = 276.8 Hz), 123.4, 122.8, 111.3, 53.7. Anal. Calcd for C<sub>18</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O: C, 65.85; H, 3.38; N, 8.53. Found: C, 65.75; H, 3.53; N, 8.38.

**9-Chloro-6-methoxy-7-(trifluoromethyl)dibenzo[*b,h*][1,6]naphthyridine (11d):** pale yellow solid; mp 214-215 °C (*n*-hexane/AcOEt); IR (KBr): 1170, 1137 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.07 (d, *J* = 8.0 Hz, 1H), 8.43 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.24 (s, 3H). Anal. Calcd for C<sub>18</sub>H<sub>10</sub>ClF<sub>3</sub>N<sub>2</sub>O: C, 59.60; H, 2.78; N, 7.72. Found: C, 59.93; H, 2.95; N, 7.72.

**6,9-Dimethoxy-7-(trifluoromethyl)-7*H*-12*H*-dibenzo[*b,h*][1,6]naphthyridin-7-ol (11a’):** colorless solid; mp 154-155 °C (*n*-hexane/AcOEt); IR (KBr): 3502, 3305, 1252, 1155 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.50-7.37 (m, 3H), 7.00 (br s, 2H), 6.44 (br s, 1H), 4.22 (s, 3H), 3.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 160.5, 155.7, 145.7, 142.8, 130.4, 129.3, 128.1, 125.6 (q, *J*<sub>CF</sub> = 285.9 Hz), 124.1, 119.4, 118.6, 117.4, 115.5, 115.2, 111.9, 92.5, 71.7 (q, *J*<sub>CF</sub> = 31.2 Hz), 55.8, 53.8. Anal. Calcd for C<sub>19</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 60.64; H, 4.02; N, 7.44. Found: C, 60.83; H, 3.92; N, 7.28.

**6-Methoxy-9-methyl-7-(trifluoromethyl)-7*H*-12*H*-dibenzo[*b,h*][1,6]naphthyridin-7-ol (11b’):** colorless solid; mp 217-218 °C (*n*-hexane/AcOEt); IR (KBr): 3471, 3456, 1189, 1146 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.75 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.10 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.40 (s, 1H), 4.15 (s, 3H), 2.37 (s, 3H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): 160.7, 146.2, 142.9, 133.3, 132.5, 130.4, 130.1, 129.1, 128.3, 126.5 (q, *J*<sub>CF</sub> = 289.6 Hz), 123.7, 119.7, 118.3, 115.3, 114.5, 93.7, 72.1 (q, *J*<sub>CF</sub> = 31.2 Hz), 53.4, 20.6. Anal. Calcd for C<sub>19</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 63.33; H, 4.20; N, 7.77. Found: C, 63.37; H, 4.13; N, 7.79.

**6-Methoxy-7-(trifluoromethyl)-7H-12H-dibenzo[*b,h*][1,6]naphthyridin-7-ol (11c')**: colorless solid; mp 221-222 °C (*n*-hexane/AcOEt); IR (KBr): 3337, 3194, 1154, 1117 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.49-7.45 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.38 (s, 1H), 4.22 (s, 3H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>): 160.5, 146.2, 142.7, 135.5, 130.2, 129.5, 128.9, 128.3, 128.1, 124.2 (q, *J*<sub>CF</sub> = 289.8 Hz), 123.8, 122.9, 119.7, 118.4, 115.3, 114.5, 94.0, 71.9 (q, *J*<sub>CF</sub> = 30.5 Hz), 53.4. Anal. Calcd for C<sub>18</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.21; H, 3.66; N, 8.43.

**9-Chloro-6-methoxy-7-(trifluoromethyl)-7H-12H-dibenzo[*b,h*][1,6]naphthyridin-7-ol (11d')**: pale yellow solid; mp 371-372 °C (*n*-hexane/AcOEt); IR (KBr): 3491, 3309, 1182, 1118 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.91 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.53-7.45 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.37 (s, 1H), 4.23 (s, 3H). Anal. Calcd for C<sub>18</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 56.78; H, 3.18; N, 7.36. Found: C, 56.58; H, 3.16; N, 7.58.

**6,9-Dimethoxy-7-(trifluoromethyl)-7H-thiochromeno[3,2-*c*]quinolin-7-ol (12a)**: colorless solid; mp 109-110 °C (*n*-hexane/AcOEt); IR (KBr): 3426, 1241, 1174 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.10 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.21 (s, 1H), 7.01-6.93 (m, 2H), 4.24 (s, 3H), 3.85 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 160.0, 158.8, 144.6, 144.3, 131.0, 130.4, 128.8, 127.8, 125.9 (q, *J*<sub>CF</sub> = 290.7 Hz), 125.2, 123.8, 122.0, 121.7, 114.0, 111.3, 109.6, 73.9 (q, *J*<sub>CF</sub> = 30.9 Hz), 55.5, 54.3. Anal. Calcd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub>S: C, 58.01; H, 3.59; N, 3.56. Found: C, 58.26; H, 3.56; N, 3.16.

**6-Methoxy-9-methyl-7-(trifluoromethyl)-7H-thiochromeno[3,2-*c*]quinolin-7-ol (12b)**: colorless solid; mp 136-137 °C (*n*-hexane/AcOEt); IR (KBr): 3439, 1232, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.09 (d, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.28-7.20 (m, 3H), 4.23 (s, 3H), 2.38 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 158.7, 144.8, 144.2, 139.4, 130.9, 128.9, 128.3, 127.7, 127.4, 126.7, 125.9 (q, *J*<sub>CF</sub> = 291.5 Hz), 125.5, 125.1, 123.8, 122.0, 111.1, 73.9 (q, *J*<sub>CF</sub> = 31.1 Hz), 54.3, 21.0. Anal. Calcd for C<sub>19</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>2</sub>S: C, 60.47; H, 3.74; N, 3.71. Found: C, 60.78; H, 3.73; N, 3.41.

**6-Methoxy-7-(trifluoromethyl)-7H-thiochromeno[3,2-*c*]quinolin-7-ol (12c)**: colorless solid; mp 149-150 °C (*n*-hexane/AcOEt); IR (KBr): 3429, 1232, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.15 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.47-7.36 (m, 4H), 7.28 (s, 1H), 4.23 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 158.7, 144.6, 144.2, 131.0, 129.5, 129.2, 129.1, 127.7, 127.2, 125.8 (q, *J*<sub>CF</sub> = 291.4 Hz), 125.2, 125.2, 123.8, 122.0, 110.9, 73.9 (q, *J*<sub>CF</sub> = 31.0 Hz), 54.3. Anal. Calcd for C<sub>18</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>2</sub>S: C, 59.50; H, 3.33; N, 3.85. Found: C, 59.10; H, 3.28; N, 3.45.

**9-Chloro-6-methoxy-7-(trifluoromethyl)-7H-thiochromeno[3,2-*c*]quinolin-7-ol (12d)**: colorless solid; mp 103-104 °C (*n*-hexane/AcOEt); IR (KBr): 3438, 1245, 1174 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.05 (d, *J* =

7.8 Hz, 1H), 8.02 (d,  $J = 7.8$  Hz, 1H), 7.82 (d,  $J = 7.8$  Hz, 1H), 7.67 (t,  $J = 7.8$  Hz, 1H), 7.48-7.42 (m, 2H), 7.37 (d,  $J = 7.8$  Hz, 1H), 7.23 (br s, 1H), 4.23 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 158.6, 144.3, 143.9, 135.4, 131.2, 130.6, 129.6, 128.2, 127.8, 127.5, 125.7 (q,  $J_{\text{CF}} = 291.7$  Hz), 125.4, 124.8, 123.7, 121.9, 110.9, 73.9 (q,  $J_{\text{CF}} = 31.2$  Hz), 54.4. Anal. Calcd for  $\text{C}_{18}\text{H}_{11}\text{ClF}_3\text{NO}_2\text{S}$ : C, 54.35; H, 2.79; N, 3.52. Found: C, 54.65; H, 2.85; N, 3.20.

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