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A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING DIBENZO[*b*,*h*][1,6]NAPHTHYRIDINES, THIOCHROMENO[3,2-*c*]QUINOLINES, AND CHROMENO[3,2-*c*]-QUINOLINES

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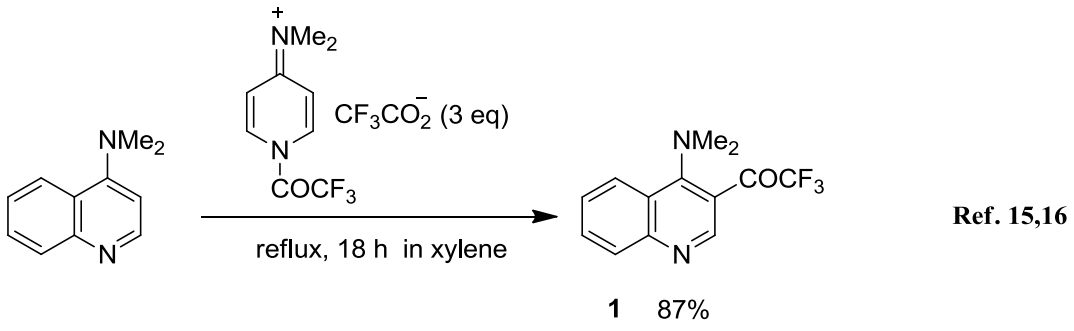
Abstract – Novel fluorine-containing dibenzo[*b*,*h*][1,6]naphthyridines (**3**), thiochromeno[3,2-*c*]quinolines (**5**), and chromeno[3,2-*c*]quinolines (**7**) were synthesized in moderate to high yields by the trifluoromethanesulfonic acid catalyzed cyclization of *N*-aryl-3-trifluoroacetyl-4-quinolylamines (**2**) and aryl 3-trifluoroacetyl-4-quinolyl sulfides (**4**) and ethers (**6**), easily prepared by aromatic nucleophilic substitution reactions of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**) with *p*-substituted anilines, thiophenols, and phenols, respectively.

Dibenzo[*b*,*h*][1,6]naphthyridines have attracted much attention because of their biological properties. For example, they have demonstrated potential applications as antibacterial,[1] fungicidal,[1] neoplasm inhibitory,[2] amebicide,[3] and using for the treatment of Alzheimer's disease.[4] Thiochromenoquinolines and the related derivatives have been known to possess interesting biological activities such as antiproliferative,[5] antitumor,[5] enzyme inhibit,[5] and antifungal activity.[6] Chromenoquinoline derivatives have also constituted an important class of heterocyclic compounds because of its interesting pharmacological properties such as anticancer activity,[7] analgesic effect,[8] and anti-inflammatory activity.[9] 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.[10] Thus, it would be very important to develop facile and convenient synthetic methods for novel fluorine-containing dibenzo[*b*,*h*][1,6]naphthyridines, thiochromeno[3,2-*c*]quinolines, and chromeno[3,2-*c*]quinolines, which would be strongly expected to present new bioactivities or functionalities.

Previously, we have found that in *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine[11] and *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine[12] activated by trifluoroacetyl group, the dimethylamino group, which is not generally lost in aromatic systems, actually behaves as an excellent leaving group and the novel aromatic nucleophilic substitutions (*N*-*N*, *N*-*S*, and *N*-*O* exchanges) takes place with various *N*-, *S*-, and *O*-nucleophiles. Moreover, 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[13] and quinoline[14] fused heterocycles bearing trifluoromethyl groups. Recently, we have reported the synthesis of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**)[15,16] and its aromatic nucleophilic *N*-*N*,[15,16] *N*-*S*,[16] and *N*-*O*[16] exchange reactions with amines, thiols, alcohols, and phenols to give the corresponding 3-trifluoroacetyl-4-quinolylamines, sulfides, and ethers in high yields, respectively. In this paper, we describe the efficient syntheses of novel fluorine-containing dibenzo[*b*,*h*][1,6]naphthyridines (**3**), thiochromeno[3,2-*c*]quinolines (**5**), and chromeno[3,2-*c*]quinolines (**7**) using the intramolecular Friedel-Crafts type reactions of the corresponding cyclization precursors (**2**, **4**, and **6**), prepared by the exchange reactions of **1** with *p*-substituted anilines, thiophenols, and phenols.



Scheme 1

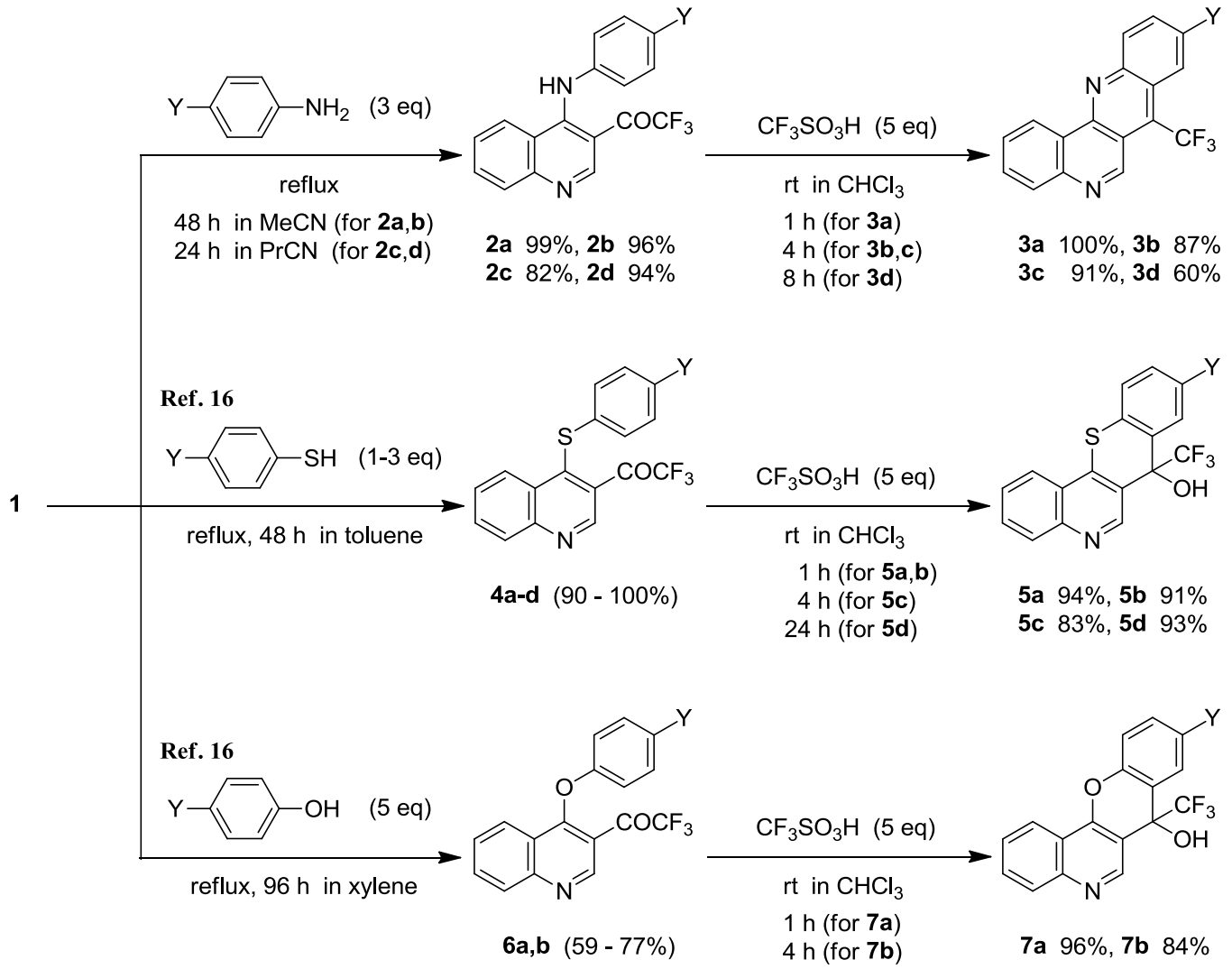
Firstly, we carried out the syntheses of the cyclization precursors, *N*-aryl-3-trifluoroacetyl-4-quinolylamines (**2**) and aryl 3-trifluoroacetyl-4-quinolyl sulfides (**4**) and ethers (**6**). Reaction of *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine (**1**), which was easily synthesized by trifluoroacetylation

of *N*,*N*-dimethyl-4-quinolylamine with 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate (Scheme 1),[15,16] with *p*-anisidine occurred readily in refluxing acetonitrile for 48 h to give the desired dimethylamino-*p*-anisidino exchanged product (**2a**)[15,16] in almost quantitative yield (Scheme 2). Similarly, *p*-toluidine also reacted cleanly to provide **2b** in 96% yield. In the cases of aniline and *p*-chloroaniline, the reactions were performed in refluxing butyronitrile to obtain exclusively the desired products (**2c** and **2d**) in high yields. Aromatic thiols, *p*-substituted benzenethiols, also underwent cleanly the dimethylamino-arylthio exchanges for 48 h in refluxing toluene to afford the corresponding aryl 3-trifluoroacetyl-4-quinolyl sulfides (**4a-d**) in over 90% yields.[16] Moreover, the desired aryl 3-trifluoroacethyl-4-quinolyl ethers (**6a** and **6b**) were prepared in moderate to good yields by the dimethylamino-aryloxy exchange reactions of **1** with *p*-substituted phenols such as *p*-methoxyphenol and *p*-cresol.[16]

Next, we attempted to synthesize the novel fluorine-containing dibenzo[*b*,*h*][1,6]naphthyridines (**3**), thiochromeno[3,2-*c*]quinolines (**5**), and chromeno[3,2-*c*]quinolines (**7**) by the cyclization of the corresponding exchanged products (**2**, **4**, and **6**) with the use of trifluoromethanesulfonic acid (TFSA) as an acid catalyst. The desired cyclization of *N*-(*p*-methoxyphenyl)-3-trifluoroacetyl-4-quinolylamine (**2a**) with TFSA (5 eq) proceeded easily even at room temperature for 1 h in chloroform to afford the target heterocycle, 9-methoxy-7-(trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridine (**3a**) in quantitative yield. Reactions of *p*-methyl and *p*-unsubstituted derivatives (**2b** and **2c**) for 4 h provided 9-methyl and 9-unsubstituted dibenzo[*b*,*h*][1,6]naphthyridines (**3b** and **3c**) in 87% and 91% yields, respectively. In the case of *p*-chloro derivative (**2d**), the prolonged time (8 h) was required for completion of the reaction and the target 9-chloro derivative (**3d**) was obtained in moderate yield (60%). The present synthetic strategy could be extended further to the construction of the fluorine-containing thiochromeno[3,2-*c*]quinoline system from aryl 3-trifluoroacetyl-4-quinolyl sulfides (**4**). All the substrates, 4-arylthioquinolines (**4a-d**) cleanly underwent the TFSA catalyzed cyclization under almost the same conditions as those for 4-arylaminoquinolines (**2a-d**) to give the desired 7*H*-thiochromeno[3,2-*c*]quinolines (**5a-d**) in excellent yields. Lastly, the present method was applied to 4-aryloxyquinolines (**6**) to synthesize the CF_3-containing chromeno[3,2-*c*]quinolines (**7**). Similarly to the cases of arylamino and arylthio derivatives (**2** and **4**) mentioned above, both cyclization reactions of *p*-methoxy and *p*-methyl derivatives (**6a** and **6b**) with TFSA proceeded smoothly at room temperature to afford the corresponding 7*H*-chromeno[3,2-*c*]quinolines (**7a** and **7b**) in high yields over 80%.

The structures of new compounds (**2b-d**, **3**, **5**, and **7**) were determined from their ^{1}H-NMR and IR spectra and elemental analyses, and ^{13}C-NMR spectra were measured for representative products.

In conclusion, the present method, composed of only three steps (trifluoroacetylation, *N*-*N*, *N*-*S*, and *N*-*O* exchanges, and cyclization) starting from *N*,*N*-dimethyl-4-quinolylamine, provides a facile and



2-7	a	b	c	d
Y	MeO	Me	H	Cl

Scheme 2

convenient access to dibenzo[*b*,*h*][1,6]naphthyridines, thiochromeno[3,2-*c*]quinolines, and chromeno[3,2-*c*]quinolines bearing trifluoromethyl group, which are difficult to obtain by other methods. Evaluation of biological activities for **3**, **5**, and **7** is now under way.

EXPERIMENTAL

All reagents and solvents were purchased as reagent grade and used without further purification. Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with JEOL PMX 60SI (60 MHz) and Bruker Avance 500 (500 MHz) spectrometers and ^{13}C NMR spectra were obtained with a Bruker Avance 500 (125 MHz) spectrometer; TMS was used as an internal standard. IR spectra were recorded on Hitachi EPI-G3 and PerkinElmer Spectrum ONE spectrophotometers. Microanalyses were taken with a Yanaco CHN-Coder MT-5 analyzer.

N-*N* Exchange Reaction of 1 with Anilines; General Procedure

To a solution of **1**[15,16] (268 mg, 1 mmol) in MeCN (7 mL) and in PrCN (7 mL) was added the appropriate anilines (3 mmol) and the mixture was stirred at reflux temperature for 24-48 h. After removal of the solvent under reduced pressure, CH_2Cl_2 (50 mL) was added to the residue. The mixture was washed with 1N HCl (50 mL), and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated to give the practically pure products (**2b-d**).

Cyclization of 2a-d, 4a-d, and 6a,b with Trifluoromethanesulfonic Acid; General Procedure

To a solution of 1 mmol of the cyclization precursors (**2a**,[15,16] **2b-d, 4a-d,**[16] and **6a,b**[16]) in $CHCl_3$ (7 mL) was added CF_3SO_3H (750 mg, 5 mmol) and the mixture was stirred at room temperature for 1-24 h. Most of the solvent was evaporated and CH_2Cl_2 (50 mL) was then added. The mixture was washed with saturated solution of Na_2CO_3 (50 mL), and the organic layer was separated and dried (Na_2SO_4). Removal of the solvent gave the practically pure cyclized products (**3a-d**, **5a-d,** and **7a**,**b**).

2,2,2-Trifluoro-1-(4-(4-methoxyphenylamino)quinolin-3-yl)ethanone (2a): mp 150-151 °C (*n*-hexane/EtOAc).[16]

2,2,2-Trifluoro-1-(4-(*p*-tolylamino)quinolin-3-yl)ethanone (2b): mp 97-98 °C (*n*-hexane); IR (KBr): 3051, 1638, 1193, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 11.72 (br s, 1H, NH), 9.07 (s, 1H, H-2), 7.94 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.7 Hz, 2H), 7.14-7.03 (m, 3H), 2.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 180.8 (q, J_{CF} = 34.6 Hz), 155.9, 151.0 (q, J_{CF} = 4.6 Hz), 150.5, 138.0, 137.0, 132.9, 130.5, 130.1, 127.2, 124.8, 124.2, 118.1, 117.1 (q, J_{CF} = 290.3 Hz), 106.2, 21.1. Anal. Calcd for $C_{18}H_{13}F_3N_2O$: C, 65.45; H, 3.97; N, 8.48. Found: C, 65.46; H, 4.10; N, 8.34.

2,2,2-Trifluoro-1-(4-(phenylamino)quinolin-3-yl)ethanone (2c): mp 115-116 °C (*n*-hexane/EtOAc); IR (KBr): 3051, 1644, 1197, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 11.69 (br s, 1H, NH), 9.10 (s, 1H, H-2), 7.96 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.20 (d, J =7.2 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): 180.9 (q, J_{CF} = 35.1 Hz), 155.6, 150.9 (q, J_{CF} = 5.5 Hz), 150.5, 140.8, 133.0, 130.2, 129.8, 127.2, 126.8, 124.9, 124.1, 118.1, 117.1 (q, J_{CF} = 290.1 Hz), 106.6. Anal. Calcd for $C_{17}H_{11}F_3N_2O$: C, 64.56; H, 3.51; N, 8.86. Found: C, 64.45; H,

3.65; N, 8.86.

1-(4-(4-Chlorophenylamino)quinolin-3-yl)-2,2,2-trifluoroethanone (2d): mp 143-144 °C (*n*-hexane/EtOAc); IR (KBr): 3031, 1645, 1191, 1139 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.56 (br s, 1H, NH), 9.11 (q, J_{HF} = 2.1 Hz, 1H, H-2), 7.99 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 8.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.19 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): 181.1 (q, J_{CF} = 35.5 Hz), 155.3, 150.8 (q, J_{CF} = 5.3 Hz), 150.6, 139.4, 133.2, 132.2, 130.3, 130.0, 126.9, 125.2, 125.1, 118.0, 117.0 (q, J_{CF} = 289.8 Hz), 107.0. Anal. Calcd for $C_{17}H_{10}ClF_3N_2O$: C, 58.22; H, 2.87; N, 7.99. Found: C, 57.82; H, 3.13; N, 8.13.

9-Methoxy-7-(trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridine (3a): mp 178-179 °C (*n*-hexane/EtOAc); IR (KBr): 1215, 1164, 1132, 1115 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.75 (q, J_{HF} = 2.0 Hz, 1H, H-6), 9.18-9.02 (m, 1H), 8.18-7.38 (m, 6H), 3.90 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{11}F_3N_2O$: C, 65.85; H, 3.38; N, 8.53. Found: C, 65.80; H, 3.39; N, 8.58.

9-Methyl-7-(trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridine (3b): mp 191-192 °C (*n*-hexane/EtOAc); IR (KBr): 1225, 1171, 1141, 1120 cm^{-1}; ^1H NMR (DMSO-d_6-$CDCl_3$): δ 9.71 (s, 1H, H-6), 9.08 (d, J = 7.4 Hz, 1H), 8.09-7.99 (m, 3H), 7.75 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 2.50 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6-$CDCl_3$): 144.6 (q, J_{CF} = 7.8 Hz), 144.3, 141.7, 139.6, 134.2, 129.5, 126.1, 125.9 (q, J_{CF} = 32.8 Hz), 125.6, 124.5, 123.4, 120.3 (q, J_{CF} = 279.1 Hz), 119.7, 119.6, 118.4 (q, J_{CF} = 5.3 Hz), 117.9, 110.7, 17.8. Anal. Calcd for $C_{18}H_{11}F_3N_2$: C, 69.23; H, 3.55; N, 8.97. Found: C, 69.33; H, 3.59; N, 8.84.

7-(Trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridine (3c): mp 159-160 °C (*n*-hexane/EtOAc); IR (KBr): 1217, 1164, 1142, 1126 cm^{-1}; ^1H NMR (DMSO-d_6-$CDCl_3$): δ 9.76 (s, 1H, H-6), 9.15 (d, J = 7.5 Hz, 1H), 8.41 (d, J = 7.5 Hz, 1H), 8.27 (d, J = 7.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.76-7.63 (m, 2H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): 145.2, 144.4 (q, J_{CF} = 7.3 Hz), 142.3, 139.5, 126.8, 126.3, 125.9, 124.7 (q, J_{CF} = 37.3 Hz), 124.3, 123.8, 123.4, 119.9 (q, J_{CF} = 5.5 Hz), 119.6, 119.3, 117.9 (q, J_{CF} = 280.4 Hz), 117.6, 110.5. Anal. Calcd for $C_{17}H_9F_3N_2$: C, 68.46; H, 3.04; N, 9.39. Found: C, 68.35; H, 3.17; N, 9.37.

9-Chloro-7-(trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridine (3d): mp 195-196 °C (*n*-hexane/EtOAc); IR (KBr): 1217, 1159, 1142, 1126 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.91 (s, 1H, H-6), 9.35 (d, J = 7.5 Hz, 1H), 8.56 (s, 1H, H-8), 8.42 (d, J = 9.2 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 7.97-7.89 (m, 2H), 7.84 (t, J = 7.5 Hz, 1H). Anal. Calcd for $C_{17}H_8ClF_3N_2$: C, 61.37; H, 2.42; N, 8.42. Found: C, 61.23; H, 2.61; N, 8.37.

9-Methoxy-7-(trifluoromethyl)-7*H*-thiochromeno[3,2-*c*]quinoline-7-ol (5a): mp 231-232 °C (*n*-hexane/EtOAc); IR (KBr): 3038, 1164, 1118 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.39 (br s, 1H, H-6), 8.20-6.87 (m, 8H), 3.87 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{12}F_3NO_2S$: C, 59.50; H, 3.33; N, 3.85. Found: C, 59.33; H, 3.33; N, 4.02.

9-Methyl-7-(trifluoromethyl)-7*H*-thiochromeno[3,2-*c*]quinoline-7-ol (5b): mp 246-247 °C (*n*-hexane/EtOAc); IR (KBr): 3041, 1156, 1120 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.33 (br s, 1H, H-6), 8.26-7.13 (m, 8H), 2.43 (s, 3H, CH_3). Anal. Calcd for $C_{18}H_{12}F_3NOS$: C, 62.24; H, 3.48; N, 4.03. Found: C, 61.95; H, 3.76; N, 4.03.

7-(Trifluoromethyl)-7*H*-thiochromeno[3,2-*c*]quinoline-7-ol (5c): mp 245-246 °C (*n*-hexane/EtOAc); IR (KBr): 3058, 1164, 1112 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.33 (br s, 1H, H-6), 8.30-7.40 (m, 9H). Anal. Calcd for $C_{17}H_{10}F_3NOS$: C, 61.26; H, 3.02; N, 4.20. Found: C, 61.08; H, 3.11; N, 4.29.

9-Chloro-7-(trifluoromethyl)-7*H*-thiochromeno[3,2-*c*]quinoline-7-ol (5d): mp 214-215 °C (*n*-hexane/EtOAc); IR (KBr): 3068, 1172, 1118 cm^{-1}; ^1H NMR (DMSO-d_6-$CDCl_3$): δ 9.38 (s, 1H, H-6), 8.86-8.14 (m, 3H), 7.85 (br s, 1H, OH), 7.78 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.54 (s, 1H, H-8), 7.42 (d, J = 7.9 Hz, 1H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): 149.6, 146.6, 139.9, 135.4, 130.9, 130.9, 130.7, 129.9, 129.5, 127.4, 127.4, 125.5, 125.2 (q, J_{CF} = 288.2 Hz), 123.7, 123.4, 122.3, 73.0 (q, J_{CF} = 30.5 Hz). Anal. Calcd for $C_{17}H_9ClF_3NOS$: C, 55.52; H, 2.47; N, 3.81. Found: C, 55.37; H, 2.55; N, 3.88.

9-Methoxy-7-(trifluoromethyl)-7*H*-chromeno[3,2-*c*]quinoline-7-ol (7a): mp 239-240 °C (*n*-hexane/EtOAc); IR (KBr): 3068, 1214, 1171 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.12 (br s, 1H, H-6), 8.80-7.28 (m, 8H), 4.10 (s, 3H, OCH_3). Anal. Calcd for $C_{18}H_{12}F_3NO_3$: C, 62.25; H, 3.48; N, 4.03. Found: C, 61.93; H, 3.67; N, 4.16.

9-Methyl-7-(trifluoromethyl)-7*H*-chromeno[3,2-*c*]quinoline-7-ol (7b): mp 231-232 °C (*n*-hexane/$CHCl_3$); IR (KBr): 3065, 1221, 1168 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.04 (s, 1H, H-6), 8.19 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H, H-8), 7.66 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 5.69-5.49 (br, 1H, OH), 2.48 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6-$CDCl_3$): 148.3, 145.6, 143.9, 143.1, 129.3, 126.5, 125.7, 124.0, 123.6, 121.9, 119.8 (q, J_{CF} = 286.8 Hz), 116.9, 115.1, 113.5, 111.4, 105.0, 63.4 (q, J_{CF} = 31.2 Hz), 16.0. Anal. Calcd for $C_{18}H_{12}F_3NO_2$: C, 65.26; H, 3.65; N, 4.23. Found: C, 65.30; H, 3.84; N, 4.00.

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