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FACILE AND CONVENIENT SYNTHESES OF FLUORINE-CONTAINING PYRIMIDO[5,4-*c*]QUINOLINES AND BENZO[*h*][1,6]NAPHTHYRIDINES BY CONDENSATION REACTION OF 2-METHOXY-3-TRIFLUOROACETYL-4-QUINOLYLAMINE WITH ALDEHYDES AND KETONES

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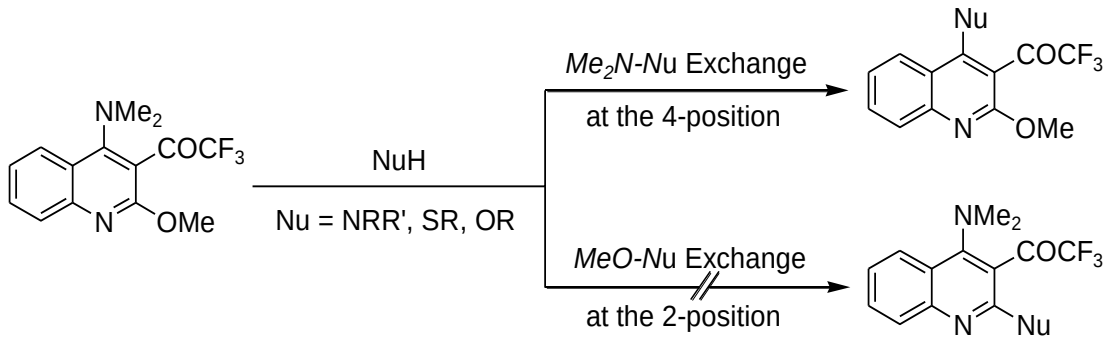
Abstract – 2-Methoxy-3-trifluoroacetyl-4-quinolylamine reacted easily with various aldehydes in the presence of aqueous ammonia to afford mainly trifluoromethylated pyrimido[5,4-*c*]quinoline derivatives in moderate to high yields. In contrast, the use of ketones instead of aldehydes in the presence of pyrrolidine, exclusively gave benzo[*h*][1,6]naphthyridine derivatives in good to excellent yields.

Pyrimido[5,4-*c*]quinolines are of particular importance because of the biological properties exhibited by this class of compounds such as analgesic,[1] anticonvulsant,[1,2] antipsychotic,[1] antibacterial,[3] antitumor,[2,4] antioxidant,[5] PDK-1 inhibitory,[6,7] and influenza A (H1N1) viral growth inhibitory activities.[8] Similarly, benzo[*h*][1,6]naphthyridines are associated with a wide spectrum of biological activities ranging from Pin1,[9] topoisomerase IIα,[10] and CK2[11] inhibitors with anticancer properties, analgesic,[12] antimalarial,[13] bactericide,[14] and toll-like receptor[15] activities, 5-HT4 receptor antagonist,[16,17] and poly ADP-ribose polymerase-1 inhibitor.[18] Moreover, the development of new methodologies for the synthesis of many kinds of fluorine-containing heterocycles has been the subject of much attention because of their importance and potential as the organic materials showing interesting biological activities in medicinal and agricultural scientific fields.[19-21]

As for the syntheses of fluorine-containing pyrimido[5,4-*c*]quinolines[7] and benzo[*h*][1,6]naphthyridines,[16,20-22] there has been only few reports except for our previous work.[23] Because of the reasons mentioned above, it is really worth developing the facile synthetic methods of fluorine-containing pyrimido[5,4-*c*]quinolines and benzo[*h*][1,6]naphthyridines, which would be

expected to present new activities and functionalities.

Previously, we reported the facile synthetic methods of novel heterocycles bearing trifluoromethyl groups by using our originally developed fluorine-containing building blocks. For example, we carried out applying the novel aromatic nucleophilic substitutions (*N*-*N*, *N*-*S*, and *N*-*O* exchanges) of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine,[24] *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine,[25] and *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine[26] with various *N*-, *S*-, and *O*-nucleophiles and the subsequent acid catalyzed cyclizations to the simple syntheses of naphthalene- and quinoline-fused heterocycles bearing trifluoromethyl groups. Moreover, we also succeeded in utilizing trifluoroacetylated 1-naphthyl-,[27] 8-quinolyl-,[28] 5-quinolyl-,[29] and 4-quinolylamines[23] for the simple syntheses of fluorine-containing naphthalene- and quinoline-fused heterocycles by the use of their three-component condensation and pyridine-ring formation reactions. Recently, we have reported the chemoselective aromatic nucleophilic substitution reaction of *N*,*N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine with various nucleophiles (Scheme 1)[30,31] and its application to the simple syntheses of fluorine-containing quinoline-fused heterocycles, such as 4-methoxy-3-(trifluoromethyl)pyrazolo[4,3-*c*]quinolines,[32] 6-methoxy-5-(trifluoromethyl)-1,4-diazepino[6,5-*c*]quinolines,[32] 6-methoxy-7-(trifluoromethyl)dibenzo[*b*,*h*][1,6]naphthyridines,[31] and 6-methoxy-7-(trifluoromethyl)thiochromeno[3,2-*c*]quinolines.[31]

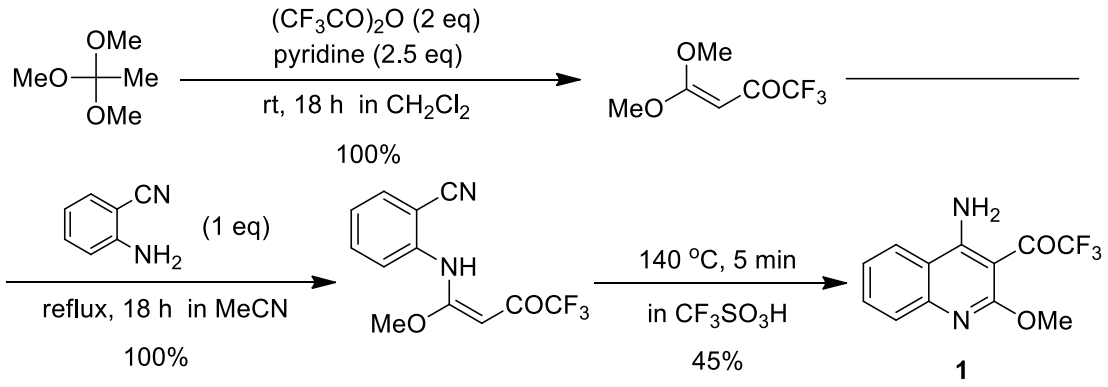


Scheme 1

In continuation of our works, we use 2-methoxy-3-trifluoroacetyl-4-quinolylamine (**1**),[31] the precursor of *N*,*N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine, as a new fluorine-containing building block, and herein wish to present simple and efficient syntheses of the title compounds (**2**-**6**). That is to say, **1** underwent the three-component condensation reaction with aldehydes in the presence of aqueous ammonia to give the pyrimido[5,4-*c*]quinoline derivatives (**2, 3**), and in the case of aliphatic aldehydes, benzo[*h*][1,6]naphthyridines (**4**) were also obtained by Friedländer-type cyclization.[33] The reaction of **1** with ketones in the presence of pyrrolidine gave the corresponding benzo[*h*][1,6]naphthyridines (**5**)

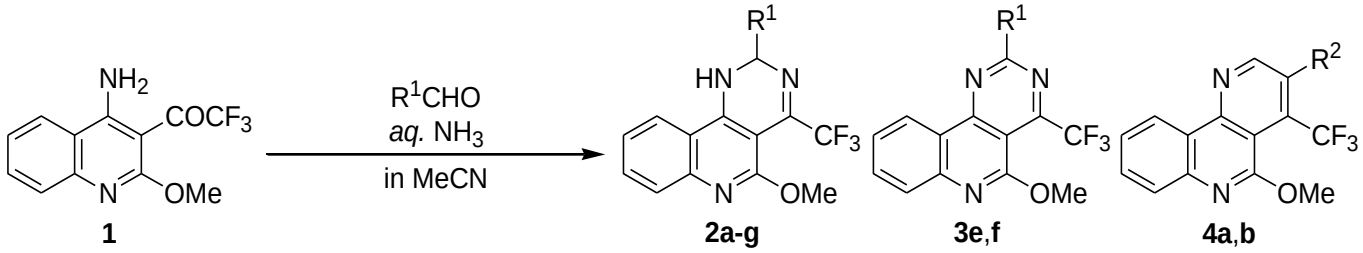
selectively. As mentioned above, these novel fluorine-containing heterocycles are powerfully expected to exhibit interesting biological activities.

2-Methoxy-3-trifluoroacetyl-4-quinolylamine (**1**) was prepared by 3-step method as depicted in Scheme 2. Selective *O*-*N* exchange reaction of 1,1,1-trifluoro-4,4-dimethoxybut-3-en-2-one, prepared from 1,1,1-trimethoxyethane and trifluoroacetic anhydride, with 2-aminobenzonitrile gave (*E*)-1,1,1-trifluoro-4-methoxy-4-(2-cyanophenyl)aminobut-3-en-2-one. The subsequent trifluoromethanesulfonic acid catalyzed cyclization of the precursor thus obtained gave **1**.



Scheme 2

The results from the reaction of **1** with various aldehydes are shown in Scheme 3 and summarized in Table 1. The three-component condensation reaction of **1** with acetaldehyde (5 equiv) in the presence of aqueous ammonia (5 equiv) proceeded cleanly at 60 °C in acetonitrile to give the corresponding fluorine-containing dihydropyrimido[5,4-*c*]quinoline (**2a**), which is the precursor of expected pyrimido[5,4-*c*]quinoline (**3a**), in 52% yield, together with benzo[*h*][1,6]naphthyridine derivative (**4a**) in 35% yield (entry 1). The latter product **4a** would be formed by Friedländer-type cyclization, in which the ammonia works not as a nucleophile but as a base. In the case of propionaldehyde, dihydro-pyrimidoquinoline (**2b**) and benzonaphthyridine (**4b**) were also obtained under the more forced



Scheme 3

Table 1. Three-Component Condensation Reaction of 4-Amino-2-methoxy-3-trifluoroacetylquinoline **1** with Aldehydes and Aqueous Ammonia

Entry	R^1	R^1CHO and *aq.* NH_3 (eq)	Temp. (°C)	Time (h)	Product (s)	Yield (%)[a]
1	Me	5	60	24	**2a** / **4a** (R^2 = H)	52 / 35
2	Et	10	120[b]	24	**2b** / **4b** (R^2 = Me)	69 / 11
3	*i*-Pr	5	70	96	**2c**	80
4	4-$MeOC_6H_4$	5	70	48	**2d**	74
5	4-MeC_6H_4	5	70	48	**2e** / **3e**	79 / 8
6	Ph	5	70	48	**2f** / **3f**	70 / 13
7	4-ClC_6H_4	10	70	24	**2g**	87

[a] Isolated yields.
[b] In a sealed tube using PrCN as a solvent.

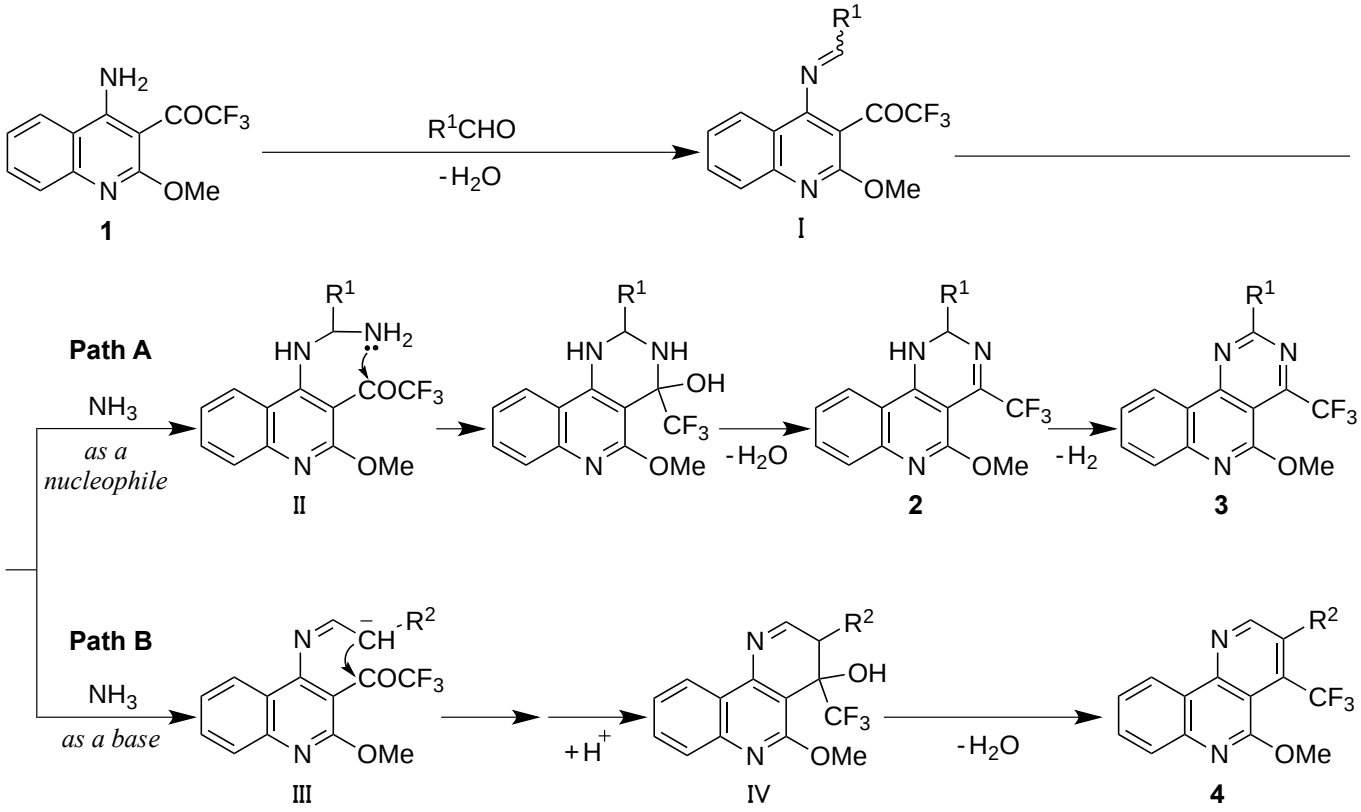
conditions (the use of 10 equiv of reagents at 120 °C in butyronitrile) in 69% and 11% yields, respectively (entry 2). Isobutyraldehyde reacted to afford **2c** exclusively in high yield and Friedländer-type cyclization did not occurred due to difficulty of deprotonation at sterically hindered α-position (entry 3). The reaction of **1** with aromatic aldehydes, such as *p*-substituted benzaldehydes, and aqueous ammonia gave dihydropyrimido[5,4-*c*]quinolines (**2d-g**) in good to high yields (entries 4-7). In the cases with *p*-tolualdehyde and benzaldehyde, the dehydrogenated products of **2e** and **2f**, pyrimido[5,4-*c*]quinolines (**3e** and **3f**) were also obtained in 8-13% yields (entries 5 and 6).[34]

Treatment of dihydropyrimido[5,4-*c*]quinolines (**2a-g**) with DDQ at room temperature for 1 hour led to successful dehydrogenation to give fluorine-containing pyrimido[5,4-*c*]quinolines (**3a-g**) in 84-99% yield (Scheme 4).

R^1(Yield): Me (93%), Et (84%), *i*-Pr (92%), 4-$MeOC_6H_4$ (90%), 4-MeC_6H_4 (99%), Ph (99%), 4-ClC_6H_4 (84%)

Scheme 4

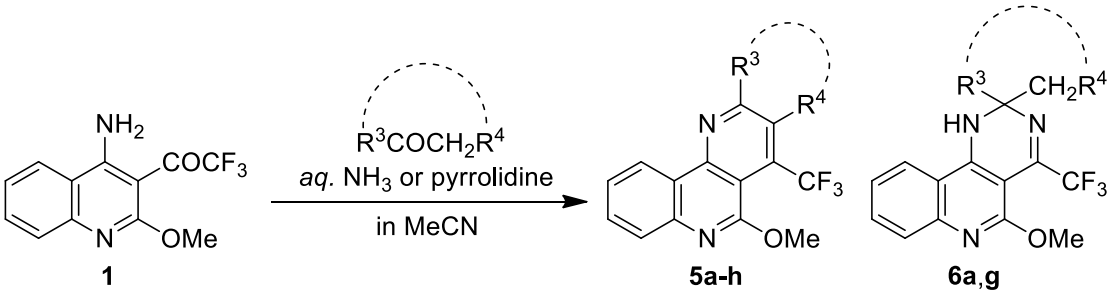
The plausible mechanism for the reactions of **1** with aldehydes in the presence of aqueous ammonia giving pyrimidoquinolines (**2**, **3**) and benzonaphthyridines (**4**) is illustrated in Scheme 5. At first, the condensation of **1** with aldehydes gives imines (**I**). If ammonia acts as a nucleophile to attack



Scheme 5

the imino carbon of **I**, the adducts **II** are formed (**Path A**). The intramolecular nucleophilic attack of primary amino nitrogen to carbonyl carbon on **II** and the subsequent dehydration afford dihydropyrimidoquinolines (**2**). The dehydrogenation of **2** gives pyrimidoquinolines (**3**). On the other hand, if ammonia acts as a base, the anions (**III**) are generated from **I** (**Path B**). The cyclization by the intramolecular nucleophilic attack of carbanion to carbonyl carbon on **III** affords **IV**, which undergoes dehydration to give benzonaphthyridines (**4**).

Furthermore, the present cyclization reaction was applied to a variety of ketones (Scheme 6, Table 2). Reaction of **1** with acetone (10 equiv) took place cleanly at 50 °C for 72 hours in acetonitrile in the presence of aqueous ammonia (10 equiv) to afford the corresponding benzo[*h*][1,6]naphthyridine (**5a**) in 88% yield, together with 10% yield of dihydropyrimido[5,4-*c*]quinoline derivative (**6a**) (entry 1). Interestingly, it was found that the use of pyrrolidine instead of aqueous ammonia as an amine base accelerates the present condensation reaction effectively to give **5a** as a sole product. Even in the presence of a catalytic amount (0.1 equiv) of pyrrolidine, **1** readily reacted with acetone (1 equiv) at room temperature to give **5a** in 96% yield (entry 2). In the case of the reaction with diethyl ketone, the corresponding benzonaphthyridine (**5b**) was obtained selectively in 44% yield though large excess amounts (10 equiv) of diethyl ketone and pyrrolidine together with elevated temperature (80 °C) were necessary (entry 3). In contrast to this, the reaction with asymmetric ketones such as ethyl methyl



Scheme 6

Table 2. Condensation Reaction of 4-Amino-2-methoxy-3-trifluoroacetylquinoline **1** with Ketones in the Presence of Amine Bases

Entry	R^3	R^4	Amine Bases	Ketones and Amine Bases (eq)	Temp. (°C)	Time (h)	Product (s)	Yield (%)[a]
1	Me	H	*aq*. NH_3	10	50	72	**5a** / **6a**	88 / 10
2	Me	H	pyrrolidine	1[b]	rt	36	**5a**	96
3	Et	Me	pyrrolidine	10	80	48	**5b**	44
4	Et	H	pyrrolidine	1	rt	24	**5c**	90
5	*i*-Pr	H	*aq*. NH_3	10	70	48	**5d**	16 (77)
6	*i*-Pr	H	pyrrolidine	3	80	48	**5d**	66
7	Ph	H	*aq*. NH_3	10	70	48	**5e**	32 (59)
8	Ph	H	pyrrolidine	5	80	48	**5e**	66
9	$-(CH_2)_3-$		*aq*. NH_3	10	70	48	**5f**	46 (45)
10	$-(CH_2)_3-$		pyrrolidine	1	rt	24	**5f**	82
11	$-(CH_2)_4-$		*aq*. NH_3	10	50	48	**5g** / **6g**	7 / 77
12	$-(CH_2)_4-$		pyrrolidine	2	80	48	**5g**	60
13	$-(CH_2)_5-$		*aq*. NH_3	10	70	48	**5h**	37 (54)
14	$-(CH_2)_5-$		pyrrolidine	2	50	24	**5h**	75

[a] Isolated yields. Values in parentheses are the recovery of substrate **1**.
[b] 0.1 Equiv of pyrrolidine was used.

ketone readily occurred at room temperature to give the corresponding 2-ethylbenzo[*h*][1,6]naphthyridine (**5c**) in high yield (entry 4). Although two products were possible from asymmetric ethyl methyl ketone, 2-ethyl derivative (**5c**) was obtained exclusively. In the case of the reaction with the other ketones in Table 2, aqueous ammonia no more acted as an efficient base catalyst (entries 5, 7, 9, 11, and 13). With the use of pyrrolidine, the reaction with isopropyl methyl ketone and acetophenone proceeded successfully to afford the corresponding 2-(*i*-propyl and phenyl)benzo[*h*][1,6]naphthyridines (**5d**,**e**) in good yields (entries 6 and 8). Moreover, the reaction with aliphatic cyclic ketones yielded tetracyclic heterocycles (**5f**-**h**) in 60-82% yields (entries 10, 12, and 14). In contrast, the reaction of **1** with

cyclohexanone in the presence of aqueous ammonia gave spiro-type dihydropyrimido[5,4-*c*]quinoline derivative (**6g**) predominantly (77% yield) together with small amounts (7% yield) of **5g** (entry 11).

In summary, we have succeeded in the utilization of **1** as a new fluorine-containing building block and could present a facile and convenient synthetic method for novel fluorine-containing pyrimido[5,4-*c*]quinolines (**2**, **3** and **6**), and benzo[*h*][1,6]naphthyridines (**4** and **5**), which are not easily accessible by other methods. The synthesized heterocycles (**2**-**6**) have the functional group (methoxy group) at the 5-position that enables further transformation to diverse derivatives. Evaluation of biological activities for **2**-**6** is now underway.

EXPERIMENTAL

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra was obtained with a Bruker Avance 500 spectrometer; TMS was used 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. Solvents such as MeCN and PrCN were used after drying with 4 Å 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.

Three-Component Condensation Reaction of 1[31] with Aldehydes in the Presence of Ammonia; General Procedure

Aldehydes (5 or 10 mmol) and 28% (w/w) *aq*. NH_3 (5 or 10 mmol) were added to a solution of **1** (270 mg, 1 mmol) in MeCN (7 mL), and the mixture was stirred at 60 or 70 °C for 24-96 h. In the case of propionaldehyde, the mixture was heated at 120 °C in PrCN in a sealed tube. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 20:1 to 1:1) to give **2a**-**g**, **3e**,**f**, and **4a**,**b**.

Dehydrogenation of 2a-g with DDQ; General Procedure

DDQ (1 mmol) was added to a solution of the appropriate **2a**-**g** (1 mmol) in MeCN (8 mL), and the mixture was stirred at rt for 1 h. Extractant, CH_2Cl_2 (80 mL) was added to the reaction mixture and then was washed with sat. *aq* Na_2CO_3 (20 mL). After separation the organic layer was dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the corresponding practically pure **3a**-**g**.

5-Methoxy-2-methyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2a): pale yellow oil; bp 148 °C/2 torr (oven temperature of Kugelrohr); IR (KBr): 3266, 1195, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.73 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 5.75 (s, 1H), 4.96 (q, *J* = 5.7 Hz, 1H), 4.10 (s, 3H), 1.66 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.5, 154.0 (q, J_{CF} = 35.0 Hz), 152.3, 147.7, 132.0, 128.0, 123.6, 120.5, 120.2 (q, J_{CF} = 265.0 Hz), 115.1, 96.6, 64.9,

53.4, 20.2. Anal. Calcd for $C_{14}H_{12}F_3N_3O$: C, 56.95; H, 4.10; N, 14.23. Found: C, 56.93; H, 4.29; N, 14.06.

2-Ethyl-5-methoxy-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2b): colorless solid; mp 111-112 °C (*n*-hexane); IR (KBr): 3277, 1200, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 5.20 (br s, 1H), 4.90-4.83 (m, 1H), 4.08 (s, 3H), 2.09-1.98 (m, 2H), 1.13 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.4, 153.7 (q, J_{CF} = 35.1 Hz), 151.9, 147.7, 131.9, 128.1, 123.6, 120.1 (q, J_{CF} = 268.1 Hz), 120.0 (q, J_{CF} = 3.7 Hz), 115.0, 96.7 (q, J_{CF} = 2.7 Hz), 69.8, 53.3, 26.7, 9.0. Anal. Calcd for $C_{15}H_{14}F_3N_3O$: C, 58.25; H, 4.56; N, 13.59. Found: C, 57.91; H, 4.56; N, 13.35.

2-Isopropyl-5-methoxy-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2c): colorless solid; colorless solid; mp 111-112 °C (*n*-hexane); IR (KBr): 3229, 1209, 1194, 1168 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.71-7.57 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.37 (s, 1H), 4.63 (br d, *J* = 5.4 Hz, 1H), 4.01 (s, 3H), 2.30-2.22 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 158.2, 153.2, 152.9 (q, J_{CF} = 34.7 Hz), 147.4, 131.9, 127.5, 123.5, 121.8, 120.4 (q, J_{CF} = 276.4 Hz), 115.4, 95.6, 73.3, 52.7, 31.0, 17.5, 16.5. Anal. Calcd for $C_{16}H_{16}F_3N_3O$: C, 59.44; H, 4.99; N, 13.00. Found: C, 59.06; H, 4.63; N, 12.64.

5-Methoxy-2-(4-methoxyphenyl)-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2d): colorless solid; mp 143-144 °C (*n*-hexane-EtOAc); IR (KBr): 3245, 1202, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.67-7.55 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 2H), 5.68 (s, 1H), 5.44 (s, 1H), 4.10 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 160.3, 158.5, 154.3 (q, J_{CF} = 34.7 Hz), 151.8, 147.8, 132.1, 131.3, 128.7, 128.1, 123.7, 120.4, 120.1 (q, J_{CF} = 277.6 Hz), 114.9, 114.3, 97.0, 70.5, 55.4, 53.4. Anal. Calcd for $C_{20}H_{16}F_3N_3O_2$: C, 62.01; H, 4.16; N, 10.85. Found: C, 61.74; H, 4.24; N, 11.04.

5-Methoxy-2-(*p*-tolyl)-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2e): colorless solid; mp 163-164 °C (*n*-hexane); IR (KBr): 3233, 1205, 1185, 1169, 1148 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.71 (s, 1H), 5.40 (s, 1H), 4.09 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.4, 154.3 (q, J_{CF} = 35.3 Hz), 151.8, 147.8, 139.2, 136.2, 132.1, 129.6, 128.1, 127.3, 123.7, 120.4, 120.1 (q, J_{CF} = 277.3 Hz), 114.9, 97.1, 70.7, 53.4, 21.2. Anal. Calcd for $C_{20}H_{16}F_3N_3O$: C, 64.69; H, 4.34; N, 11.32. Found: C, 64.77; H, 4.38; N, 11.20.

5-Methoxy-2-phenyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2f): colorless solid; mp 171-172 °C (*n*-hexane); IR (KBr): 3237, 1201, 1163, 1124 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.62-7.56 (m, 3H), 7.48-7.38 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 1H), 5.77 (s,

1H), 5.36 (s, 1H), 4.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.4, 154.4 (q, J_{CF} = 35.0 Hz), 151.8, 147.9, 139.1, 132.1, 129.3, 129.0, 128.2, 127.5, 123.7, 120.3, 120.1 (q, J_{CF} = 277.4 Hz), 114.9, 97.2, 70.9, 53.4. Anal. Calcd for $C_{19}H_{14}F_3N_3O$: C, 63.86; H, 3.95; N, 11.76. Found: C, 63.99; H, 4.08; N, 11.50.

2-(4-Chlorophenyl)-5-methoxy-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2g): colorless solid; mp 176-177 °C (*n*-hexane); IR (KBr): 3221, 1190, 1159, 1125 cm^{-1}; ^{1}H NMR (CD_3CN): δ 7.88 (d, *J* = 8.2 Hz, 1H), 7.65-7.59 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 1H), 6.82 (s, 1H), 5.93 (s, 1H), 4.02 (s, 3H); ^{13}C NMR (CD_3CN): δ 158.1, 153.6 (q, J_{CF} = 34.9 Hz), 152.6, 147.6, 138.3, 134.2, 132.2, 129.1, 128.5, 127.5, 123.8, 122.0, 120.4 (q, J_{CF} = 276.5 Hz), 115.3, 96.0, 69.5, 52.9. Anal. Calcd for $C_{19}H_{13}ClF_3N_3O$: C, 58.25; H, 3.34; N, 10.73. Found: C, 58.18; H, 3.42; N, 10.72.

5-Methoxy-2-methyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3a): pale yellow solid; mp 134-135 °C (*n*-hexane); IR (KBr): 1206, 1179, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.91 (d, *J* = 7.5 Hz, 1H), 7.86-7.76 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 4.22 (s, 3H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.6, 158.5, 155.9, 153.5 (q, J_{CF} = 36.7 Hz), 146.3, 133.2, 127.0, 125.3, 124.8, 121.2, 120.8 (q, J_{CF} = 276.2 Hz), 106.7, 54.2, 26.5. Anal. Calcd for $C_{14}H_{10}F_3N_3O$: C, 57.34; H, 3.44; N, 14.33. Found: C, 57.73; H, 3.43; N, 13.95.

2-Ethyl-5-methoxy-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3b): pale yellow solid; mp 139-140 °C (*n*-hexane); IR (KBr): 1198, 1169, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.99 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 4.23 (s, 3H), 3.29 (q, *J* = 7.5 Hz, 2H), 1.54 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.5, 158.5, 156.1, 153.6 (q, J_{CF} = 36.5 Hz), 146.4, 133.1, 127.0, 125.3, 124.9, 121.4, 120.9 (q, J_{CF} = 276.2 Hz), 106.8, 54.2, 33.0, 12.2. Anal. Calcd for $C_{15}H_{12}F_3N_3O$: C, 58.63; H, 3.94; N, 13.68. Found: C, 58.63; H, 3.88; N, 13.74.

2-Isopropyl-5-methoxy-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3c): pale yellow solid; mp 123-124 °C (*n*-hexane); IR (KBr): 1197, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.96 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 4.22 (s, 3H), 3.51 (hept, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 174.7, 158.4, 156.0, 153.6 (q, J_{CF} = 36.6 Hz), 146.3, 133.0, 126.9, 125.2, 124.8, 121.5, 120.9 (q, J_{CF} = 276.1 Hz), 106.8, 54.1, 38.0, 21.5. Anal. Calcd for $C_{16}H_{14}F_3N_3O$: C, 59.81; H, 4.39; N, 13.08. Found: C, 59.78; H, 4.47; N, 13.04.

5-Methoxy-2-(4-methoxyphenyl)-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3d): pale yellow solid; mp 195-196 °C (*n*-hexane); IR (KBr): 1182, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.00 (d, *J* = 7.5 Hz, 1H), 8.65 (d, *J* = 8.5 Hz, 2H), 7.83-7.74 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.22 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.1, 162.6, 158.8, 156.2, 153.7 (q, J_{CF} = 37.7 Hz), 146.5, 133.0,

131.1, 128.8, 127.0, 125.1, 124.9, 121.7, 120.9 (q, J_{CF} = 275.8 Hz), 114.2, 106.5, 55.4, 54.1. Anal. Calcd for $C_{20}H_{14}F_3N_3O_2$: C, 62.34; H, 3.66; N, 10.91. Found: C, 62.30; H, 3.80; N, 10.80.

5-Methoxy-2-(*p*-tolyl)-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3e): pale yellow solid; mp 184-185 °C (*n*-hexane); IR (KBr): 1178, 1164 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.99 (d, *J* = 7.2 Hz, 1H), 8.56 (d, *J* = 7.6 Hz, 2H), 7.82-7.72 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 4.21 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.8, 158.7, 156.1, 153.8 (q, J_{CF} = 35.9 Hz), 146.4, 142.8, 133.5, 133.0, 129.5, 129.2, 127.0, 125.2, 124.9, 121.7, 120.9 (q, J_{CF} = 277.1 Hz), 106.8, 54.1, 21.6. Anal. Calcd for $C_{20}H_{14}F_3N_3O$: C, 65.04; H, 3.82; N, 11.38. Found: C, 64.94; H, 3.91; N, 11.42.

5-Methoxy-2-phenyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3f): pale yellow solid; mp 194-195 °C (*n*-hexane); IR (KBr): 1209, 1183, 1158 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.07 (d, *J* = 7.7 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 2H), 7.89-7.77 (m, 2H), 7.64-7.53 (m, 4H), 4.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.9, 158.9, 156.1, 153.9 (q, J_{CF} = 34.0 Hz), 146.5, 136.2, 133.2, 132.2, 129.3, 128.8, 127.1, 125.3, 124.9, 121.7, 120.9 (q, J_{CF} = 276.8 Hz), 107.0, 54.2. Anal. Calcd for $C_{19}H_{12}F_3N_3O$: C, 64.23; H, 3.40; N, 11.83. Found: C, 64.07; H, 3.59; N, 11.79.

2-(4-Chlorophenyl)-5-methoxy-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3g): pale yellow solid; mp 202-203 °C (*n*-hexane); IR (KBr): 1209, 1181, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.01 (d, *J* = 7.2 Hz, 1H), 8.65 (d, *J* = 7.3 Hz, 2H), 7.93-7.77 (m, 2H), 7.65-7.45 (m, 3H), 4.23 (s, 3H); ^{13}C NMR (C_6D_6): δ 161.6, 158.7, 155.9, 153.3 (q, J_{CF} = 36.9 Hz), 146.7, 138.6, 134.8, 133.1, 130.7, 129.1, 127.1, 125.1, 124.9, 121.7, 120.6 (q, J_{CF} = 276.3 Hz), 107.1, 53.8. Anal. Calcd for $C_{19}H_{11}ClF_3N_3O$: C, 58.55; H, 2.84; N, 10.78. Found: C, 58.26; H, 2.87; N, 11.04.

5-Methoxy-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (4a): colorless solid; mp 96-97 °C (*n*-hexane); IR (KBr): 1167 cm^{-1}; ^1H NMR (CD_3CN): δ 9.18 (d, *J* = 4.7 Hz, 1H), 8.86 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 4.7 Hz, 1H), 7.80-7.70 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (CD_3CN): δ 156.3, 153.4, 152.5, 144.3, 134.2 (q, J_{CF} = 33.6 Hz), 131.2, 126.5, 125.1, 124.3, 123.1 (q, J_{CF} = 273.1 Hz), 122.7, 110.4, 95.7, 53.6. Anal. Calcd for $C_{14}H_9F_3N_2O$: C, 60.44; H, 3.26; N, 10.07. Found: C, 60.35; H, 3.38; N, 10.04.

5-Methoxy-3-methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (4b): colorless solid; mp 98-99 °C (*n*-hexane); IR (KBr): 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.99 (s, 1H), 8.92 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 4.20 (s, 3H), 2.73 (q, J_{HF} = 3.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.7, 156.6, 150.8, 144.0, 133.1 (q, J_{CF} = 32.5 Hz), 131.3 (q, J_{CF} = 1.8 Hz), 130.7, 126.4, 124.9, 124.0, 123.9 (q, J_{CF} = 275.8 Hz), 122.6, 111.1, 53.9, 19.5. Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.56. Found: C, 61.53; H, 3.88; N, 9.52.

Condensation Reaction of 1 with Ketones in the Presence of Ammonia; General Procedure

Using aq NH_3 as a base: Ketones (10 mmol) and 28% (w/w) aq NH_3 (10 mmol) were added to a solution of **1** (270 mg, 1 mmol) in MeCN (7 mL), and the mixture was stirred at 50 or 70 ℃ for 48-72 h. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 5:1 to 1:1) to give **5a**,**d**-**h** and **6a**,**g**.

Using pyrrolidine as a base: Ketones (1-10 mmol) and pyrrolidine (0.1-10 mmol) were added to a solution of **1** (270 mg, 1 mmol) in MeCN (7 mL), and the mixture was stirred at room temperature-80 ℃ for 24-48 h. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 5:1 to 1:1) to give **5a**-**h**.

5-Methoxy-2-methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (5a): colorless solid; mp 150-151 °C (*n*-hexane); IR (KBr): 1190, 1152, 1130 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.91 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.71-7.59 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.18 (s, 3H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.4, 156.6, 152.6, 144.6, 135.0 (q, J_{CF} = 33.6 Hz), 130.9, 126.6, 124.8, 124.6, 123.0 (q, J_{CF} = 274.1 Hz), 122.8, 120.6 (q, J_{CF} = 7.0 Hz), 108.7, 53.8, 25.5. Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.59. Found: C, 61.59; H, 3.82; N, 9.58.

2-Ethyl-5-methoxy-3-methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (5b): colorless solid; mp 94-95 °C (*n*-hexane); IR (KBr): 1190, 1159, 1121 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.05 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 4.22 (s, 3H), 3.16-3.05 (m, 2H), 2.03-1.92 (m, 3H), 1.12-1.05 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 166.1, 156.7, 152.6, 144.7, 135.0 (q, J_{CF} = 33.5 Hz), 130.9, 126.6, 124.8, 124.7, 123.0, 123.0 (q, J_{CF} = 275.6 Hz), 120.3 (q, J_{CF} = 6.6 Hz), 108.9, 53.9, 41.0, 22.4, 13.9. Anal. Calcd for $C_{17}H_{15}F_3N_2O$: C, 63.75; H, 4.72; N, 8.75. Found: C, 63.70; H, 4.72; N, 8.68.

2-Ethyl-5-methoxy-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (5c): colorless solid; mp 102-103 °C (*n*-hexane); IR (KBr): 1178, 1152, 1130 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.98 (d, *J* = 7.3 Hz, 1H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.75-7.62 (m, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 4.19 (s, 3H), 3.10 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.0, 156.7, 152.6, 144.7, 135.1 (q, J_{CF} = 33.3 Hz), 130.9, 126.6, 124.8, 124.7, 123.0 (q, J_{CF} = 274.1 Hz), 123.0, 119.8 (q, J_{CF} = 6.3 Hz), 108.9, 53.8, 32.1, 12.9. Anal. Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.74; H, 4.28; N, 9.00.

2-Isopropyl-5-methoxy-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (5d): colorless solid; mp 95-96 °C (*n*-hexane); IR (KBr): 1162, 1121 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.07 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.80-7.68 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 4.22 (s, 3H), 3.37 (hept, *J* = 6.7 Hz, 1H), 1.48 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 170.7, 156.7, 152.5, 144.7, 135.2 (q, J_{CF} = 33.9 Hz), 130.9, 126.6, 124.8, 124.8, 123.1, 123.1 (q, J_{CF} = 274.0 Hz), 118.8 (q, J_{CF} = 6.2 Hz), 109.0, 53.9, 37.3, 22.2. Anal. Calcd for $C_{17}H_{15}F_3N_2O$: C, 63.75; H, 4.72; N, 8.75. Found: C, 63.41; H, 4.93; N, 8.87.

5-Methoxy-2-phenyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (5e): colorless solid; mp 169-170 °C (*n*-hexane); IR (KBr): 1187, 1172, 1154 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.07 (d, *J* = 7.4 Hz, 1H), 8.31-8.22 (m, 3H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.58-7.47 (m, 4H), 4.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.3, 156.6, 152.8, 144.8, 137.6, 135.9 (q, J_{CF} = 33.2 Hz), 131.1, 130.8, 129.1, 127.7, 126.7, 124.9, 124.8, 123.1, 123.1 (q, J_{CF} = 273.0 Hz), 117.3 (q, J_{CF} = 6.9 Hz), 109.3, 53.9. Anal. Calcd for $C_{20}H_{13}F_3N_2O$: C, 67.79; H, 3.70; N, 7.91. Found: C, 67.84; H, 3.72; N, 7.85.

6-Methoxy-7-(trifluoromethyl)-9,10-dihydro-8*H*-benzo[*h*]cyclopenta[*b*][1,6]naphthyridine (5f): colorless solid; mp 157-158 °C (*n*-hexane); IR (KBr): 1163, 1136 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.91 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 4.18 (s, 3H), 3.38-3.29 (m, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 2.18 (quint, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 171.9, 157.0, 152.0, 144.2, 135.9, 130.6 (q, J_{CF} = 33.8 Hz), 130.5, 126.4, 124.6, 124.3, 124.1 (q, J_{CF} = 275.5 Hz), 123.0, 109.3, 53.7, 34.8, 32.6, 22.6. Anal. Calcd for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12; N, 8.80. Found: C, 64.22; H, 4.18; N, 8.66.

6-Methoxy-7-(trifluoromethyl)-8,9,10,11-tetrahydrodibenzo[*b*,*h*][1,6]naphthyridine (5g): colorless solid; mp 139-140 °C (*n*-hexane); IR (KBr): 1209, 1128 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.90 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 4.17 (s, 3H), 3.28-3.22 (m, 2H), 3.20-3.13 (m, 2H), 2.06-1.98 (m, 2H), 1.92-1.85 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 163.0, 157.0, 149.2, 144.0, 133.1 (q, J_{CF} = 32.2 Hz), 132.2, 130.3, 126.3, 124.6, 124.0 (q, J_{CF} = 276.8 Hz), 124.0, 122.4, 109.9, 53.7, 34.2, 28.1 (q, J_{CF} = 4.4 Hz), 22.6, 21.9. Anal. Calcd for $C_{18}H_{15}F_3N_2O$: C, 65.06; H, 4.55; N, 8.43. Found: C, 65.17; H, 4.61; N, 8.27.

6-Methoxy-7-(trifluoromethyl)-9,10,11,12-tetrahydro-8*H*-benzo[*h*]cyclohepta[*b*][1,6]naphthyridine (5h): colorless solid; mp 163-164 °C (*n*-hexane); IR (KBr): 1204, 1172, 1140 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.93 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 4.18 (s, 3H), 3.41-3.33 (m, 2H), 3.14-3.06 (m, 2H), 1.96-1.77 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 168.8, 157.1, 149.0, 144.2, 137.6, 132.6 (q, J_{CF} = 32.0 Hz), 130.3, 126.4, 124.6, 124.1, 123.9 (q, J_{CF} = 276.7 Hz), 122.6, 109.9, 53.7, 39.6, 31.4, 31.0, 27.1, 26.6. Anal. Calcd for $C_{19}H_{17}F_3N_2O$: C, 65.89; H, 4.95; N, 8.09. Found: C, 66.04; H, 4.92; N, 7.98.

5-Methoxy-2,2-dimethyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (6a): colorless solid; mp 166-167 °C (*n*-hexane); IR (KBr): 3305, 1191, 1145 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 5.14 (br s, 1H), 4.08 (s, 3H), 1.62 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 158.2, 151.6 (q, J_{CF} = 35.1 Hz), 150.4, 147.7, 131.8, 128.0, 123.5, 120.2 (q, J_{CF} = 277.5 Hz), 120.0, 115.1, 94.9, 69.4, 53.3, 27.1. Anal. Calcd for $C_{15}H_{14}F_3N_3O$: C, 58.25; H, 4.56; N, 13.59. Found: C, 57.91; H, 4.61; N, 13.37.

5-Methoxy-2-spirocyclohexane-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (6g): colorless solid; mp 162-163 °C (*n*-hexane); IR (KBr): 3325, 1192, 1166, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73 (d, *J* = 7.9 Hz, 1H), 7.67-7.60 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 5.17 (br s, 1H), 4.07 (s, 3H), 2.07-1.96 (m, 2H), 1.94-1.75 (m, 4H), 1.58-1.47 (m, 4H); ^{13}C NMR (CD_3CN): δ 159.1, 152.1, 151.6 (q, J_{CF} = 34.5 Hz), 148.6, 132.8, 128.4, 124.4, 122.8, 121.5 (q, J_{CF} = 276.3 Hz), 116.8, 95.8, 71.8, 53.6, 36.3, 26.2, 22.4. Anal. Calcd for $C_{18}H_{18}F_3N_3O$: C, 61.88; H, 5.19; N, 12.03. Found: C, 61.91; H, 5.22; N, 11.97.

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