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EFFICIENT SYNTHESES OF FLUORINE-CONTAINING PYRIMIDO[5,4-*c*]QUINOLINES AND BENZO[*h*][1,6]NAPHTHYRIDINES BY CONDENSATION REACTIONS OF 3-TRIFLUORO-ACETYLQUINOLIN-4-AMINE WITH ALDEHYDES AND KETONES

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Abstract – 3-Trifluoroacetylquinolin-4-amine 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 under almost the same conditions, mostly gave benzo[*h*][1,6]naphthyridine derivatives in excellent combined yields.

INTRODUCTION

It is common knowledge that pyrimido[5,4-*c*]quinolines are important systems that are encountered in a number of natural products and have wide applications for a variety of purposes such as biological materials, drugs, and agrochemicals because they indicate various biological activities such as analgesic,[1] anticonvulsant,[1,2] antipsychotic,[1] antibacterial,[3] antitumor,[2,4] antioxidant,[5] and PDK-1 inhibitory activities.[6,7]

Similarly, benzo[*h*][1,6]naphthyridines have attracted much attention because of their biological properties. For example, they have demonstrated potential applications as topoisomerase IIα[8] and CK2[9] inhibitors with anticancer properties, analgesic,[10] antimalarial,[11] and bactericide[12] activities, 5-HT4 receptor antagonist,[13,14] and poly ADP-ribose polymerase-1 inhibitor.[15]

Besides, in recent years, 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.[16-18]

However, there has been only one report about compounds directly introduced fluorine atom or perfluoroalkyl to pyrimido[5,4-*c*]quinoline skelton.[7] Moreover the synthesis of only two example of 7-fluoro[13] and 2-trifluoromethyl[17-19] derivatives has been achieved in the benzo[*h*][1,6]naphthyridine system.

Because of the reasons mentioned above, it is really worth to develop 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.

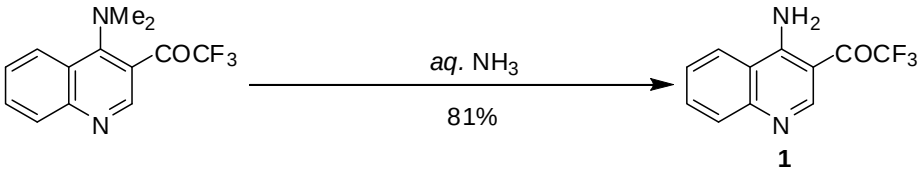
Previously, we have reported the facile synthetic methods of novel heterocycles bearing trifluoromethyl groups by using our originally developed fluorine-containing building blocks. For example, we carried out applying the novel aromatic nucleophilic substitutions (*N*-*N*, *N*-*S*, and *N*-*O* exchanges) of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine[20] and *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine[21] 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-,[22] 8-quinolyl-,[23] and 5-quinolylamines[24] 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.

In continuation of our works, we use 3-trifluoroacetylquinolin-4-amine (**1**) as a new fluorine-containing building block, and herein wish to present simple and efficient syntheses of the title compounds (**2**, **3**, **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]naphthyridine derivatives (**4**) were also obtained by Friedländer-type cyclization. Under the quite similar conditions, the reaction of **1** with ketones gave benzo[*h*][1,6]naphthyridine derivatives (**6**) selectively. As identified above, these novel fluorinated compounds are powerfully expected to show interesting biological properties.

RESULTS AND DISCUSSION

3-Trifluoroacetylquinolin-4-amine (**1**), the new fluorine-containing building block, was easily synthesized in high yield by the dimethylamino-amino exchange reaction of *N*,*N*-dimethyl-3-trifluoroacetylquinolin-4-amine with aqueous ammonia (Scheme 1).[25]

Initially, we attempted to synthesize the novel fluorine-containing pyrimido[5,4-*c*]quinoline derivatives (**2** and **3**) by the reaction of **1** with various aldehydes and aqueous ammonia, and the results are shown in Scheme 2 and summarized in Table 1. The three-component condensation reaction of **1** with

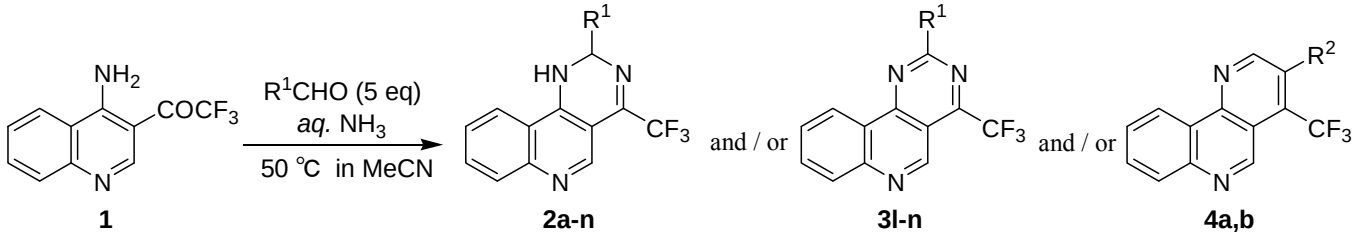


Scheme 1

acetaldehyde (5 eq) in the presence of aqueous ammonia (10 eq) proceeded quickly at 50 °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 46% yield, together with benzo[*h*][1,6]naphthyridine derivative (**4a**) in 31% yield (entry 1). The latter product **4a** would be formed by Friedländer-type cyclization,[26] in which the ammonia works not as a nucleophile but as a base. Similarly in the case of propionaldehyde, **2b** and **4b** were obtained in the presence of 3 eq of aqueous ammonia in 58% and 20% yields, respectively (entry 2). In the cases of other linear aliphatic aldehydes, such as *n*-butyraldehyde, *n*-valeraldehyde, *n*-hexylaldehyde, and *n*-heptylaldehyde, we solely obtained the corresponding dihydropyrimido[5,4-*c*]quinolines (**2c**,**e**,**h**,**i**) in moderate to good yields (entries 3, 5, 8, 9). Isobutyraldehyde, isovaleraldehyde, and 2-methylbutyraldehyde also reacted to afford **2d**, **2f**, and **2g** exclusively and Friedländer-type cyclization was not occurred due to difficulty of deprotonation at sterically hindered α-position (entries 4, 6, 7). The reaction of **1** with aromatic aldehydes, such as *p*-substituted benzaldehydes, and aqueous ammonia gave dihydropyrimido[5,4-*c*]quinolines (**2j**-**n**) in good to high yields (entries 10-14). In the cases with *p*-tolualdehyde, benzaldehyde, and *p*-chlorobenzaldehyde, the dehydrogenated products of **2l**-**n**, pyrimido[5,4-*c*]quinolines (**3l**-**n**) were also obtained in 10-18% yields (entries 12-14).[27]

Treatment of dihydropyrimido[5,4-*c*]quinolines (**2a**-**n**) with DDQ at room temperature for 1 h led to successful dehydrogenation to give fluorine-containing pyrimido[5,4-*c*]quinolines (**3a**-**n**) in 80-100% yields (Scheme 3).

Next, we examined the reaction of **1** with formaldehyde in the presence of aqueous ammonia. In contrast to the results mentioned in Scheme 2 and Table 1, there was no incorporation of the nitrogen atom of ammonia into products in the reaction of **1** with formaldehyde and fluorine-containing 2,4-dihydro-1*H*-[1,3]oxazino[5,4-*c*]quinoline (**5**) was solely obtained in 73% yield without any formation of the corresponding dihydropyrimido[5,4-*c*]quinoline derivative. These phenomena were also observed in our previous experiment of the naphthalene system (Scheme 4).[22]

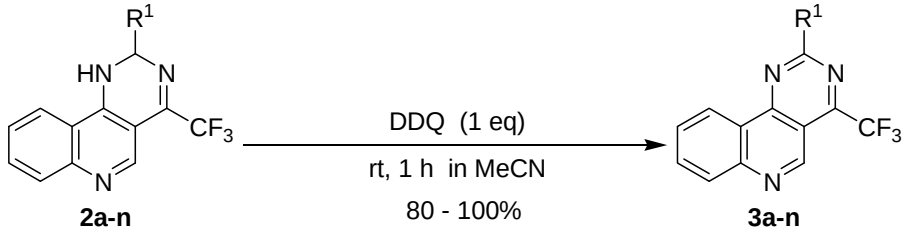


Scheme 2

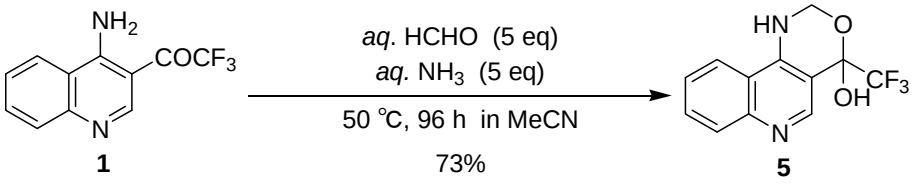
Table 1. Three-Component Condensation Reaction of 3-Trifluoroacetylquinoline-4-amine (**1**) with Aldehydes and Aqueous Ammonia

Entry	R^1	Ammonia (eq)	Time (h)	Product(s)	Yield (%)[a]
1	Me	10	24	**2a** / **4a** (R^2 = H)	46 / 31
2	Et	3	48	**2b** / **4b** (R^2 = Me)	58 / 20
3	*n*-Pr	5	96	**2c**	59
4	*i*-Pr	5	96	**2d**	84
5	*n*-Bu	5	96	**2e**	55
6	*i*-Bu	5	96	**2f**	80
7	*s*-Bu	5	96	**2g**	82
8	*n*-C_5H_{11}	5	96	**2h**	75
9	*n*-C_6H_{13}	5	96	**2i**	60
10	4-HOC_6H_4	3	48	**2j**	91
11	4-$MeOC_6H_4$	3	72	**2k**	90
12	4-MeC_6H_4	3	72	**2l** / **3l**	78 / 11
13	Ph	3	72	**2m** / **3m**	82 / 10
14	4-ClC_6H_4	5	96	**2n** / **3n**	63 / 18

[a] Isolated yields.

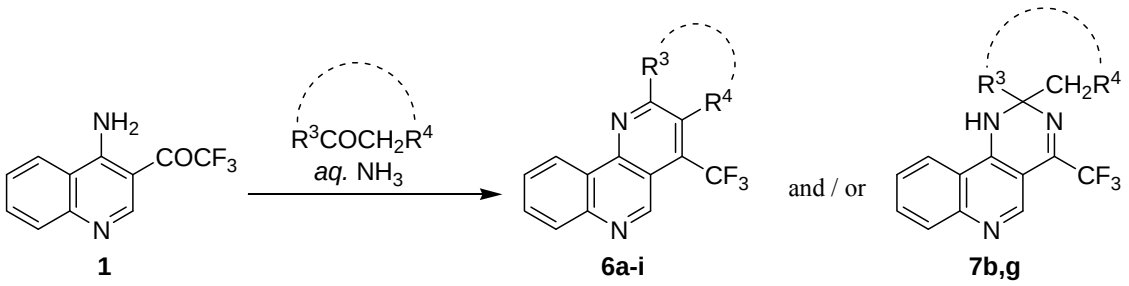


Scheme 3



Scheme 4

Furthermore, the present cyclization reaction was applied to a variety of ketones, and we carried out the syntheses of novel fluorine-containing benzo[*h*][1,6]naphthyridines (**6**) (Scheme 5, Table 2). Reaction of **1** with acetone took place cleanly at 50 °C in acetonitrile in the presence of aqueous ammonia to afford the corresponding benzo[*h*][1,6]naphthyridine (**6a**) in high yield without any formation of pyrimido[5,4-*c*]quinoline derivative (entry 1). In the case of diethyl ketone, the prolonged time (96 h) and more elevated temperature (130 °C) were required for completion of the reaction and **6b** was obtained in 63% yield, together with 37% yield of the product incorporated the nitrogen atom of ammonia, pyrimido[5,4-*c*]quinoline (**7b**) (entry 2). The reaction with asymmetric ketones such as ethyl methyl ketone, isopropyl methyl ketone, and acetophenone, occurred easily to give the corresponding 2-(alkyl or aryl)-benzo[*h*][1,6]naphthyridines (**6c**-**e**) in high yields (entries 3-5). Although two products were possible in the case of ethyl methyl ketone, only 2-ethyl derivative (**6c**) was obtained selectively. Moreover, the reactions with aliphatic cyclic ketones yielded heterotetracyclic compounds (**6f-i**) in moderate to high yields, except for the case of cyclohexanone, which afford spiro-substituted dihydropyrimido[5,4-*c*]quinoline derivative (**7g**) (39%) together with **6g** (59%).



Scheme 5

Table 2. Condensation Reaction of **1** with Ketones in the Presence of Aqueous Ammonia

Entry	R^3	R^4	Ketone (eq)	Ammonia (eq)	Solvent	Temp. (°C)	Time (h)	Product(s)	Yield[a] (%)
1	Me	H	3	1.2	MeCN	50	24	**6a**	84
2	Et	Me	5	5	BuCN	130[b]	96	**6b / 7b**	63 / 37
3	Et	H	3	1.2	MeCN	50	24	**6c**	99
4	*i*-Pr	H	3	1.2	MeCN	50	72	**6d**	93
5	Ph	H	3	1.2	PrCN	100[b]	96	**6e**	94
6	$-(CH_2)_3-$		3	1.2	MeCN	50	48	**6f**	90
7	$-(CH_2)_4-$		3	3	MeCN	50	48	**6g / 7g**	59 / 39
8	$-(CH_2)_5-$		3	1.2	MeCN	50	96	**6h**	100
9	$-(CH_2)_6-$		3	1.2	MeCN	50	168	**6i**	88

[a] Isolated yields.
[b] In a sealed tube.

In summary, we succeeded in utilization of **1** as a new fluorine-containing building block and could present a simple and efficient synthetic method for novel fluorine-containing pyrimido[5,4-*c*]quinolines (**2**, **3**, and **7**), and benzonaphthyridines (**4**, **6**), which are not easily accessible by other methods. Moreover, we could obtain the fluorine-containing 2,4-dihydro-1*H*-[1,3]oxazino[5,4-*c*]quinoline (**5**) instead of expected pyrimido[5,4-*c*]quinoline by the reaction of **1** with formaldehyde. Evaluation of biological activities for **2-7** is now underway

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.

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

The appropriate aldehydes (5.00 mmol) and 28% (w/w) aq NH_3 (3.00 to 10.00 mmol) were added to a soln of **1** (240 mg, 1.00 mmol) in MeCN (7 mL), and the mixture was stirred at 50 °C for 24-96 h. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 23:1 to 0:1) to give the corresponding **2a-n**, **3l-n**, and **4a**,**b**.

Dehydrogenation of 2a-n with DDQ; General Procedure

DDQ (1.05 mmol) was added to a soln of the appropriate **2a-n** (1.00 mmol) in MeCN (8 mL), and the mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure, and EtOAc (50 mL) was added to the residue. The solution was washed with sat. aq Na_2CO_3 (50 mL), and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the corresponding pure **3a-n**.

2-Methyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2a): mp 181-182 °C (*n*-hexane-EtOAc); IR (KBr): 3261, 1198, 1128 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN-$CDCl_3$): δ = 8.73 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 5.91-5.36 (br, 1H), 5.58 (q, *J* = 5.9 Hz, 1H), 1.69 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (CD_3CN-$CDCl_3$): δ = 152.3 (q, J_{CF} = 35.3 Hz), 149.8, 149.1, 146.5, 131.7, 129.7, 125.8, 121.2, 117.0, 116.3 (q, J_{CF} = 273.1 Hz), 101.8, 65.9, 22.3. Anal. Calcd for $C_{13}H_{10}F_3N_3$: C, 58.87; H, 3.80; N, 15.48. Found: C, 58.79; H, 4.18; N, 15.54.

2-Ethyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2b): mp 165-166 °C (*n*-hexane-EtOAc); IR (KBr): 3001, 1189, 1111 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.65 (q, *J* = 2.0 Hz, 1H), 8.09-7.34 (m, 4H), 6.90-5.25 (br, 1H), 5.45 (br t, *J* = 6.0 Hz, 1H), 2.19-1.73 (m, 2H), 1.07 (t, *J* = 7.0 Hz, 3H). Anal. Calcd for $C_{14}H_{12}F_3N_3$: C, 60.21; H, 4.33; N, 15.05. Found: C, 60.34; H, 4.34; N, 14.97.

2-Propyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2c): mp 171-172 °C (*n*-hexane-EtOAc); IR (KBr): 3063, 1189, 1120 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.80-8.60 (m, 1H), 8.17-7.44 (m, 4H), 6.90-6.13 (br, 1H), 5.53 (br t, *J* = 5.0 Hz, 1H), 2.17-1.20 (m, 4H), 1.20-0.56 (m, 3H). Anal. Calcd for $C_{15}H_{14}F_3N_3$: C, 61.43; H, 4.81; N, 14.33. Found: C, 61.43; H, 4.91; N, 14.61.

2-Isopropyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2d): mp 170-171 °C (*n*-hexane-EtOAc); IR (KBr): 3061, 1190, 1126 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.63 (q, *J* = 2.0 Hz, 1H), 8.05-7.33 (m, 4H), 7.05-5.57 (br, 1H), 5.35 (br d, *J* = 6.5 Hz, 1H), 2.43-1.86 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 6H). Anal. Calcd for $C_{15}H_{14}F_3N_3$: C, 61.43; H, 4.81; N, 14.33. Found: C, 61.41; H, 4.67; N, 14.22.

2-Butyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2e): mp 194-195 °C (*n*-hexane-EtOAc); IR (KBr): 3061, 1190, 1115 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.93-8.67 (m, 1H), 8.23-7.43 (m, 4H), 6.83-6.37 (br, 1H), 5.57 (br t, *J* = 6.0 Hz, 1H), 2.17-0.63 (m, 9H). Anal. Calcd for $C_{16}H_{16}F_3N_3$: C, 62.53; H, 5.25; N, 13.67. Found: C, 62.37; H, 5.29; N, 13.78.

2-Isobutyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2f): mp 158-159 °C (*n*-hexane-EtOAc); IR (KBr): 3062, 1191, 1125 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.83-8.63 (m, 1H), 8.23-7.33 (m, 4H), 7.00-6.33 (br, 1H), 5.60 (br t, *J* = 6.0 Hz, 1H), 2.27-1.63 (m, 3H), 1.47-0.67 (m, 6H). Anal. Calcd for $C_{16}H_{16}F_3N_3$: C, 62.53; H, 5.25; N, 13.67. Found: C, 62.93; H, 5.21; N, 13.52.

2-*sec*-Butyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2g): mp 148-149 °C (*n*-hexane-EtOAc); IR (KBr): 3203, 1186, 1124 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.83-8.73 (m, 1H), 8.27-7.40 (m, 4H), 7.00-6.32 (br, 1H), 5.56-5.40 (br, 1H), 2.17-0.73 (m, 9H). Anal. Calcd for $C_{16}H_{16}F_3N_3$: C, 62.53; H, 5.25; N, 13.67. Found: C, 62.73; H, 5.42; N, 13.30.

2-Pentyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2h): mp 171-172 °C (*n*-hexane-EtOAc); IR (KBr): 3060, 1186, 1129 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.83-8.70 (m, 1H), 8.17-7.33 (m, 4H), 7.00-6.27 (br, 1H), 5.50 (br t, *J* = 6.0 Hz, 1H), 2.07-0.63 (m, 11H). Anal. Calcd for $C_{17}H_{18}F_3N_3$: C, 63.54; H, 5.65; N, 13.08. Found: C, 63.61; H, 5.48; N, 12.85.

2-Hexyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2i): mp 141-142 °C (*n*-hexane-EtOAc); IR (KBr): 3062, 1190, 1130 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.83-8.57

(m, 1H), 8.20-7.47 (m, 4H), 6.97-6.20 (br, 1H), 5.50 (br t, *J* = 6.0 Hz, 1H), 2.13-0.57 (m, 13H). Anal. Calcd for $C_{18}H_{20}F_3N_3$: C, 64.46; H, 6.01; N, 12.53. Found: C, 64.63; H, 6.03; N, 12.33.

4-(4-(Trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinolin-2-yl)phenol (2j): mp 210-211 °C (*n*-hexane-EtOAc); IR (KBr): 3363, 3261, 1199, 1124 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.92-8.62 (m, 1H), 8.55-6.85 (m, 9H), 6.55 (s, 1H), 6.25-5.28 (br, 1H). Anal. Calcd for $C_{18}H_{13}F_3N_3O$: C, 62.97; H, 3.52; N, 12.24. Found: C, 62.97; H, 3.91; N, 11.85.

2-(4-Methoxyphenyl)-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2k): mp 166-167 °C (*n*-hexane-EtOAc); IR (KBr): 3423, 1193, 1131 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.64 (q, *J* = 2.0 Hz, 1H), 8.03-7.33 (m, 6H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.48 (br s, 1H), 4.37-3.00 (br, 1H), 3.77 (s, 3H). Anal. Calcd for $C_{19}H_{14}F_3N_3O$: C, 63.86; H, 3.95; N, 11.76. Found: C, 64.09; H, 4.06; N, 11.41.

2-*p*-Tolyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2l): mp 185-186 °C (*n*-hexane-EtOAc); IR (KBr): 3434, 1192, 1125 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.63 (q, *J* = 2.0 Hz, 1H), 8.04-7.09 (m, 8H), 6.49 (br s, 1H), 3.36-1.68 (br, 1H), 2.33 (s, 3H). Anal. Calcd for $C_{19}H_{14}F_3N_3$: C, 66.86; H, 4.13; N, 12.31. Found: C, 67.00; H, 4.18; N, 12.33.

2-Phenyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2m): mp 168-169 °C (*n*-hexane-EtOAc); IR (KBr): 3412, 1191, 1138 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 8.69 (q, *J* = 2.0 Hz, 1H), 8.08-7.33 (m, 9H), 6.55 (br s, 1H), 6.22-3.85 (br, 1H). Anal. Calcd for $C_{18}H_{12}F_3N_3$: C, 66.05; H, 3.70; N, 12.84. Found: C, 65.88; H, 3.99; N, 12.71.

2-(4-Chlorophenyl)-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (2n): mp 198-199 °C (*n*-hexane-EtOAc); IR (KBr): 3399, 1197, 1134 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 9.08-8.00 (br, 1H), 8.63 (br s, 1H), 8.43-8.23 (m, 1H), 7.99-7.29 (m, 7H), 6.58 (br s, 1H). Anal. Calcd for $C_{18}H_{11}ClF_3N_3$: C, 59.76; H, 3.07; N, 11.62. Found: C, 59.57; H, 3.23; N, 11.52.

2-Methyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3a): yield 98%; mp 173-174 °C (*n*-hexane-EtOAc); IR (KBr): 1192, 1137 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 9.22 (q, *J* = 2.0 Hz, 1H), 9.13-8.98 (m, 1H), 8.32-7.59 (m, 3H), 3.05 (s, 3H). Anal. Calcd for $C_{13}H_8F_3N_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.33; H, 3.33; N, 16.03.

2-Ethyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3b): yield 99%; mp 172-173 °C (*n*-hexane-EtOAc); IR (KBr): 1196, 1142 cm^{-1}; ^1H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 9.57 (q, *J* = 2.0 Hz, 1H), 9.23-9.06 (m, 1H), 8.31-7.68 (m, 3H), 3.33 (q, *J* = 7.0 Hz, 2H), 1.55 (t, *J* = 7.0 Hz, 3H). Anal. Calcd for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.64; N, 15.16. Found: C, 60.26; H, 3.56; N, 15.01.

2-Propyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3c): yield 87%; mp 114-115 °C (*n*-hexane-EtOAc); IR (KBr): 1189, 1137 cm^{-1}; ^1H NMR (500 MHz, CD_3CN-$CDCl_3$): δ = 9.62 (s, 1H),

9.19 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.01 (t, J = 7.6 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 3.29 (t, J = 7.3 Hz, 2H), 2.16-2.03 (m, 2H), 1.11 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CD_3CN-$CDCl_3$): δ = 171.0, 154.6, 154.2 (q, J_{CF} = 33.7 Hz), 147.5, 147.1, 132.9, 129.6, 128.4, 124.2, 123.0, 121.0 (q, J_{CF} = 275.2 Hz), 111.2, 41.6, 21.4, 13.6. Anal. Calcd for $C_{15}H_{12}F_3N_3$: C, 61.85; H, 4.15; N, 14.43. Found: C, 62.11; H, 4.22; N, 14.10.

2-Isopropyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3d): yield 96%; mp 116-117 °C (*n*-hexane-EtOAc); IR (KBr): 1194, 1134 cm^{-1}; ^{1}H NMR (60 MHz, CD_3CN-$CDCl_3$): δ = 9.54 (q, J = 2.0 Hz, 1H), 9.18-9.02 (m, 1H), 8.25-7.58 (m, 3H), 3.56 (hept, J = 7.0 Hz, 1H), 1.54 (d, J = 7.0 Hz, 6H). Anal. Calcd for $C_{15}H_{12}F_3N_3$: C, 61.85; H, 4.15; N, 14.43. Found: C, 61.81; H, 4.11; N, 14.51.

2-Butyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3e): yield 96%; mp 92-93 °C (*n*-hexane-EtOAc); IR (KBr): 1193, 1139 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN-$CDCl_3$): δ = 9.58 (s, 1H), 9.14 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 7.4 Hz, 1H), 7.98 (t, J = 7.4 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 3.30 (t, J = 6.7 Hz, 2H), 2.09-1.93 (m, 2H), 1.60-1.47 (m, 2H), 1.03 (t, J = 6.7 Hz, 3H); ^{13}C NMR (CD_3CN-$CDCl_3$): δ = 171.1, 154.4, 154.1 (q, J_{CF} = 34.8 Hz), 147.3, 146.9, 132.7, 129.4, 128.2, 124.1, 122.9, 120.8 (q, J_{CF} = 277.7 Hz), 111.0, 39.3, 30.0, 22.1, 13.5. Anal. Calcd for $C_{16}H_{14}F_3N_3$: C, 62.95; H, 4.62; N, 13.76. Found: C, 63.00; H, 4.69; N, 13.64.

2-Isobutyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3f): yield 98%; mp 96-97 °C (*n*-hexane-EtOAc); IR (KBr): 1192, 1141 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN-$CDCl_3$): δ = 9.61 (s, 1H), 9.18 (d, J = 7.3 Hz, 1H), 8.24 (d, J = 7.3 Hz, 1H), 8.01 (t, J = 7.3 Hz, 1H), 7.84 (t, J = 7.3 Hz, 1H), 3.19 (t, J = 6.0 Hz, 2H), 2.60-2.48 (m, 1H), 1.07 (d, J = 6.0 Hz, 6H); ^{13}C NMR (CD_3CN-$CDCl_3$): δ = 170.6, 154.7, 154.3 (q, J_{CF} = 35.7 Hz), 147.6, 147.2, 133.0, 129.7, 128.5, 124.4, 123.2, 121.1 (q, J_{CF} = 277.7 Hz), 111.3, 48.7, 28.2, 22.4. Anal. Calcd for $C_{16}H_{14}F_3N_3$: C, 62.95; H, 4.62; N, 13.76. Found: C, 63.06; H, 4.64; N, 13.63.

2-*sec*-Butyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3g): yield 80%; mp 77-78 °C (*n*-hexane-EtOAc); IR (KBr): 1188, 1145 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6-$CDCl_3$): δ = 9.62 (s, 1H), 9.21 (d, J = 7.4 Hz, 1H), 8.25 (d, J = 7.4 Hz, 1H), 8.00 (t, J = 7.4 Hz, 1H), 7.85 (t, J = 7.4 Hz, 1H), 3.37 (sext, J = 7.2 Hz, 1H), 2.19-2.02 (m, 1H), 1.93-1.79 (m, 1H), 1.51 (d, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): δ = 174.1, 154.0, 153.7 (q, J_{CF} = 37.6 Hz), 146.9, 146.5, 132.3, 129.0, 127.8, 123.7, 122.6, 120.4 (q, J_{CF} = 281.8 Hz), 110.7, 44.5, 28.3, 18.6, 11.2. Anal. Calcd for $C_{16}H_{14}F_3N_3$: C, 62.95; H, 4.62; N, 13.76. Found: C, 63.17; H, 4.75; N, 13.41.

2-Pentyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3h): yield 98%; mp 73-74 °C (*n*-hexane-EtOAc); IR (KBr): 1191, 1136 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6-$CDCl_3$): δ = 9.61 (s, 1H), 9.19 (d, J = 7.9 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.03 (t, J = 7.9 Hz, 1H), 7.86 (t, J = 7.9 Hz, 1H), 3.30 (t,

J = 7.0 Hz, 2H), 1.68-1.22 (m, 6H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): δ = 171.2, 157.1, 154.2 (q, J_{CF} = 38.3 Hz), 148.3, 147.4, 132.8, 129.5, 128.3, 124.2, 122.4, 120.8 (q, J_{CF} = 277.5 Hz), 111.1, 39.6, 31.2, 27.6, 22.2, 13.7. Anal. Calcd for $C_{17}H_{16}F_3N_3$: C, 63.94; H, 5.05; N, 13.16. Found: C, 63.94; H, 5.12; N, 13.10.

2-Hexyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3i): yield 89%; mp 76-77 °C (*n*-hexane-EtOAc); IR (KBr): 1193, 1137 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6-$CDCl_3$): δ = 9.60 (s, 1H), 9.16 (d, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.02 (quint, *J* = 7.2 Hz, 2H), 1.53-1.18 (m, 6H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): δ = 171.0, 154.4, 154.0 (q, J_{CF} = 35.7 Hz), 147.3, 146.9, 132.6, 129.3, 128.2, 124.0, 122.8, 120.7 (q, J_{CF} = 277.5 Hz), 110.9, 39.5, 31.2, 28.5, 27.7, 22.1, 13.5. Anal. Calcd for $C_{18}H_{18}F_3N_3$: C, 64.85; H, 5.44; N, 12.61. Found: C, 64.95; H, 5.44; N, 12.51.

4-(4-(Trifluoromethyl)pyrimido[5,4-*c*]quinolin-2-yl)phenol (3j): yield 98%; mp 309-310 °C (*n*-hexane-EtOAc); IR (KBr): 3076, 1183, 1127 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6-$CDCl_3$): δ = 9.76 (br s, 1H), 9.57 (s, 1H), 9.27 (d, *J* = 7.4 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 2H), 8.24 (d, *J* = 7.4 Hz, 1H), 8.00 (t, *J* = 7.4 Hz, 1H), 7.86 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): δ = 160.9, 160.3, 152.8, 152.1 (q, J_{CF} = 35.7 Hz), 145.7, 145.0, 131.1, 129.4, 127.7, 126.5, 124.9, 122.3, 121.5 (q, J_{CF} = 277.5 Hz), 121.2, 118.1, 108.9. Anal. Calcd for $C_{18}H_{10}F_3N_3O$: C, 63.35; H, 2.95; N, 12.31. Found: C, 63.29; H, 2.99; N, 12.33.

2-(4-Methoxyphenyl)-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3k): yield 93%; mp 182-183 °C (*n*-hexane-EtOAc); IR (KBr): 1182, 1130 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$): δ = 9.43 (q, *J* = 2.0 Hz, 1H), 9.11-8.95 (m, 1H), 8.55 (d, *J* = 9.0 Hz, 2H), 8.21-7.54 (m, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H). Anal. Calcd for $C_{19}H_{12}F_3N_3O$: C, 64.23; H, 3.40; N, 11.83. Found: C, 64.15; H, 3.58; N, 11.58.

2-*p*-Tolyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3l): yield 94% (from **2l**); mp 187-188 °C (*n*-hexane-EtOAc); IR (KBr): 1195, 1139 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$): δ = 9.44 (q, *J* = 2.0 Hz, 1H), 9.08-8.93 (m, 1H), 8.41 (d, *J* = 8.0 Hz, 2H), 8.31-7.51 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H). Anal. Calcd for $C_{19}H_{12}F_3N_3$: C, 67.25; H, 3.56; N, 12.38. Found: C, 67.14; H, 3.68; N, 12.39.

2-Phenyl-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3m): yield 100% (from **2m**); mp 167-168 °C (*n*-hexane-EtOAc); IR (KBr): 1189, 1139 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$): δ = 9.57 (q, *J* = 2.0 Hz, 1H), 9.21-9.04 (m, 1H), 8.76-8.56 (m, 2H), 8.26-7.41 (m, 6H). Anal. Calcd for $C_{18}H_{10}F_3N_3$: C, 66.46; H, 3.10; N, 12.92. Found: C, 66.46; H, 3.37; N, 12.83.

2-(4-Chlorophenyl)-4-(trifluoromethyl)pyrimido[5,4-*c*]quinoline (3n): yield 94% (from **2n**); mp 186-187 °C (*n*-hexane-EtOAc); IR (KBr): 1188, 1146 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$): δ = 9.49 (q, *J* =

2.0 Hz, 1H), 9.09-8.93 (m, 1H), 8.59 (d, *J* = 9.0 Hz, 2H), 8.26-7.68 (m, 3H), 7.40 (d, *J* = 9.0 Hz, 2H). Anal. Calcd for $C_{18}H_9ClF_3N_3$: C, 60.10; H, 2.52; N, 11.68. Found: C, 60.09; H, 2.52; N, 11.74.

4-(Trifluoromethyl)benzo[*h*][1,6]naphthyridine (4a): mp 125-126 °C (*n*-hexane-EtOAc); IR (KBr): 1192, 1122 cm^{-1}; ^1H NMR (500 MHz, CD_3CN-$CDCl_3$): δ = 9.62 (s, 1H), 9.33 (d, *J* = 7.0 Hz, 1H), 9.18 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.99-7.87 (m, 2H), 7.83 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (CD_3CN-$CDCl_3$): δ = 153.1, 149.3, 147.8, 146.2, 134.8 (q, J_{CF} = 33.2 Hz), 131.1, 129.4, 128.2, 124.5, 124.0, 123.0 (q, J_{CF} = 274.9 Hz), 119.0 (q, J_{CF} = 5.3 Hz), 115.4. Anal. Calcd for $C_{13}H_7F_3N_2$: C, 62.91; H, 2.84; N, 11.29. Found: C, 63.09; H, 3.06; N, 11.37.

3-Methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (4b): mp 132-133 °C (EtOAc); IR (KBr): 1159, 1124 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.61 (q, *J* = 2.0 Hz, 1H), 9.18-8.95 (m, 2H), 8.28-7.55 (m, 3H), 2.71 (q, *J* = 4.0 Hz, 3H). Anal. Calcd for $C_{14}H_9F_3N_2$: C, 64.12; H, 3.46; N, 10.68. Found: C, 63.96; H, 3.46; N, 10.77.

4-(Trifluoromethyl)-2,4-dihydro-1*H*-[1,3]oxazino[5,4-*c*]quinolin-4-ol (5)

Aq. HCHO (5.00 mmol) and 28% (w/w) aq NH_3 (5.00 mmol) were added to a soln of **1** (240 mg, 1.00 mmol) in MeCN (7 mL), and the mixture was stirred at 50 °C for 96 h. The solvent was evaporated under reduced pressure, and EtOAc (80 mL) was added to the residue. The solution was washed with H_2O (20 mL), and dried (Na_2SO_4). After removal of the solvent, the crude mixture was subjected to column chromatography (silica gel, EtOAc) to give **5**. mp 237-238 °C (*n*-hexane-EtOAc); IR (KBr): 3416, 3071, 1192, 1125 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6-$CDCl_3$): δ = 8.83 (s, 1H), 8.16-7.60 (br, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.28 (br s, 1H), 4.99 (q_{AB}, *J* = 7.6 Hz, Δδ = 0.09 ppm, 2H); ^{13}C NMR (DMSO-d_6-$CDCl_3$): δ = 147.9, 146.8, 146.6, 129.6, 128.1, 124.9, 122.8 (q, J_{CF} = 287.8 Hz), 121.1, 118.0, 107.6, 92.1 (q, J_{CF} = 32.5 Hz), 67.3. Anal. Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.34; H, 3.36; N, 10.37. Found: C, 53.18; H, 3.42; N, 10.52.

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

The appropriate ketones (3.00 or 5.00 mmol) and 28% (w/w) aq NH_3 (1.20 or 5.00 mmol) were added to a soln of **1** (240 mg, 1.00 mmol) in MeCN (7 mL), and the mixture was stirred at 50 °C for 24-168 h. In the case of diethylketone and acetophenone, the mixture was heated 100 °C and 130 °C in PrCN and BuCN in a sealed tube, respectively. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 30:1 to 1:1) to give the corresponding **6a-i** and **7b**,**g**.

2-Methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (6a): mp 129-130 °C (*n*-hexane); IR (KBr): 1193, 1120 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.45 (q, *J* = 2.0 Hz, 1H), 9.27-8.93 (m, 1H), 8.18-7.57 (m, 4H), 2.76 (s, 3H). Anal. Calcd for $C_{14}H_9F_3N_2$: C, 64.12; H, 3.46; N, 10.68. Found: C, 64.08; H, 3.73;

N, 10.64.

2-Ethyl-3-methyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (6b): mp 158-159 °C (*n*-hexane); IR (KBr): 1159, 1129 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.67 (q, *J* = 2.0 Hz, 1H), 9.33-9.08 (m, 1H), 8.29-7.73 (m, 3H), 3.14 (q, *J* = 7.0 Hz, 2H), 2.63 (q, *J* = 2.0 Hz, 3H), 1.50 (t, *J* = 7.0 Hz, 3H). Anal. Calcd for $C_{16}H_{13}F_3N_2$: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.01; H, 4.58; N, 9.58.

2-Ethyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (6c): mp 112-113 °C (*n*-hexane); IR (KBr): 1183, 1130 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.57 (q, *J* = 2.0 Hz, 1H), 9.27-9.10 (m, 1H), 8.30-7.70 (m, 4H), 3.13 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H). Anal. Calcd for $C_{15}H_{11}F_3N_2$: C, 65.21; H, 4.01; N, 10.14. Found: C, 64.92; H, 3.92; N, 9.99.

2-Isopropyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (6d): mp 110-111 °C (*n*-hexane); IR (KBr): 1156, 1130 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.68 (q, *J* = 2.0 Hz, 1H), 9.45-9.27 (m, 1H), 8.45-7.78 (m, 4H), 3.53 (hept, *J* = 7.0 Hz, 1H), 1.65 (d, *J* = 7.0 Hz, 6H). Anal. Calcd for $C_{16}H_{13}F_3N_2$: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.25; H, 4.70; N, 9.41.

2-Phenyl-4-(trifluoromethyl)benzo[*h*][1,6]naphthyridine (6e): mp 128-129 °C (*n*-hexane); IR (KBr): 1187, 1137 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.83 (q, *J* = 2.0 Hz, 1H), 9.60-9.45 (m, 1H), 8.65-7.77 (m, 9H). Anal. Calcd for $C_{19}H_{11}F_3N_2$: C, 70.37; H, 3.42; N, 8.64. Found: C, 70.23; H, 3.47; N, 8.73.

7-(Trifluoromethyl)-9,10-dihydro-8*H*-benzo[*h*]cyclopenta[*b*][1,6]naphthyridine (6f): mp 199-200 °C (*n*-hexane); IR (KBr): 1162, 1127 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.56 (q, *J* = 2.0 Hz, 1H), 9.22-9.08 (m, 1H), 8.27-7.57 (m, 3H), 3.55-3.12 (m, 4H), 2.48-1.93 (m, 2H). Anal. Calcd for $C_{16}H_{11}F_3N_2$: C, 66.66; H, 3.85; N, 9.72. Found: C, 66.64; H, 4.02; N, 9.80.

7-(Trifluoromethyl)-8,9,10,11-tetrahydrodibenzo[*b*,*h*][1,6]naphthyridine (6g): mp 156-157 °C (*n*-hexane); IR (KBr): 1158, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 9.10 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 3.34-3.15 (m, 4H), 2.18-1.86 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 163.8, 148.5 (q, J_{CF} = 6.9 Hz), 146.5, 145.5, 132.3 (q, J_{CF} = 30.5 Hz), 131.2, 130.4, 129.1, 127.6, 124.8 (q, J_{CF} = 278.8 Hz), 124.4, 123.9, 115.4, 35.0, 27.0, 22.5, 21.7. Anal. Calcd for $C_{17}H_{13}F_3N_2$: C, 67.54; H, 4.33; N, 9.27. Found: C, 67.15; H, 4.65; N, 9.34.

7-(Trifluoromethyl)-9,10,11,12-tetrahydro-8*H*-benzo[*h*]cyclohepta[*b*][1,6]naphthyridine (6h): mp 107-108 °C (*n*-hexane); IR (KBr): 1191, 1133 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.70 (q, *J* = 2.0 Hz, 1H), 9.17-9.03 (m, 1H), 8.27-7.65 (m, 3H), 3.47-2.97 (m, 4H), 2.03-1.60 (m, 6H). Anal. Calcd for $C_{18}H_{15}F_3N_2$: C, 68.35; H, 4.78; N, 8.86. Found: C, 68.10; H, 5.12; N, 8.77.

7-(Trifluoromethyl)-8,9,10,11,12,13-hexahydro-8*H*-benzo[*h*]cycloocta[*b*][1,6]naphthyridine (6i): mp 137-138 °C (*n*-hexane); IR (KBr): 1160, 1125 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$): δ = 9.60 (q, *J* = 2.0 Hz, 1H), 9.23-9.05 (m, 1H), 8.24-7.63 (m, 3H), 3.39-3.02 (m, 4H), 2.00-1.13 (m, 8H). Anal. Calcd for

$C_{19}H_{17}F_3N_2$: C, 69.08; H, 5.19; N, 8.48. Found: C, 69.23; H, 5.38; N, 8.14.

2,2-Diethyl-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (7b): mp 198-199 °C (*n*-hexane-EtOAc); IR (KBr): 3176, 1147, 1131 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6-CD_3CN): δ = 8.56 (q, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.05-6.70 (br, 1H), 1.98-1.86 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (DMSO-d_6-CD_3CN): δ = 151.0 (q, J_{CF} = 33.9 Hz), 150.4, 149.5, 146.0 (q, J_{CF} = 4.1 Hz), 131.6, 129.5, 125.4, 122.1, 120.3 (q, J_{CF} = 278.1 Hz), 116.7, 99.4, 77.2, 34.5, 7.1. Anal. Calcd for $C_{16}H_{16}F_3N_3$: C, 62.53; H, 5.25; N, 13.67. Found: C, 62.78; H, 5.25; N, 13.42.

2-Spirocyclohexane-4-(trifluoromethyl)-1,2-dihydropyrimido[5,4-*c*]quinoline (7g): mp 170-171 °C (*n*-hexane-EtOAc); IR (KBr): 3247, 1152, 1129 cm^{-1}; ^1H NMR (500 MHz, CD_3CN): δ = 8.69 (s, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 6.15 (br s, 1H), 2.19-2.03 (m, 2H), 1.92-1.78 (m, 4H), 1.68-1.22 (m, 4H); ^{13}C NMR (CD_3CN): δ = 157.0, 150.7 (q, J_{CF} = 4.4 Hz), 148.5 (q, J_{CF} = 32.1 Hz), 147.9, 132.5, 129.0, 125.5, 122.7, 121.8 (q, J_{CF} = 288.7 Hz), 117.7, 102.3, 71.5, 37.6, 24.8, 20.6. Anal. Calcd for $C_{17}H_{16}F_3N_3$: C, 63.94; H, 5.05; N, 13.16. Found: C, 63.94; H, 5.42; N, 13.16.

REFERENCES AND NOTES

1. A. Stanczak, W. Pakulska, B. Pietrzak, and W. Lewgowd, *Pharmazie*, 2001, **56**, 501.
2. W. Lewgowd, A. Stanczak, B. Pietrzak, and K. Rzeszowska-Modzelewska, *Acta Pol. Pharm.*, 2005, **62**, 271.
3. O. A. Fathalla, N. A. Mohamed, W. S. El-Serwy, H. F. AbdelHamid, S. I. Abd El-Moez, and A. M. Soliman, *Res. Chem. Intermediates*, 2013, **39**, 821; A. C. Ranade, H. R. Deshpande, and S. A. Phadke, *Indian J. Microbiol.*, 1981, **21**, 159.
4. F. Zhang, X. Zhai, L. Chen, J. Qi, B. Cui, Y. Gu, and P. Gong, *Chin. Chem. Lett.*, 2011, **22**, 1277; W. Lewgowd, A. Stanczak, Z. Ochocki, U. Krajewska, and M. Rozalski, *Acta Pol. Pharm.*, 2005, **62**, 105.
5. M. Sankaran, C. Kumarasamy, U. Chokkalingam, and P. S. Mohan, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7147.
6. Q. Li, Z. Ge, T. Cheng, and R. Li, *Mol. Divers.*, 2012, **16**, 431.
7. A. Wissner and A. M. Venkatesan, *PCT Int. Appl.* WO2008109599.
8. H. Huang, Q. Chen, K. Xin, L. Meng, L. Lin, X. Wang, C. Zhu, Y. Wang, Z. Chen, M. Li, H. Jiang, K. Chen, J. Ding, and H. Liu, *J. Med. Chem.*, 2010, **53**, 3048.
9. F. Pierre, P. C. Chua, S. E. O'Brien, A. Siddiqui-Jain, P. Bourbon, M. Haddach, J. Michaux, J. Nagasawa, M. K. Schwaebe, E. Stefan, A. Vialettes, J. P. Whitten, T. K. Chen, L. Darjania, R.

Stansfield, K. Anderes, J. Bliesath, D. Drygin, C. Ho, M. Omori, C. Proffitt, N. Streiner, K. Trent, W. G. Rice, and D. M. Ryckman, *J. Med. Chem.*, 2011, **54**, 635.

10. S. Saito, H. Ohta, T. Ishizaka, M. Yoshinaga, M. Tatsuzuki, Y. Yokobori, Y. Tomishima, A. Morita, Y. Toda, K. Tokugawa, A. Kaku, T. Murakami, H. Yoshimura, S. Sekine, and T. Yoshimizu, *PCT Int. Appl.* WO2006051704.
11. R. Franke and W. J. Streich, *Quant. Struct. Act. Relat.*, 1985, **4**, 51; K. H. Kim, C. Hansch, J. Y. Fukunaga, E. E. Steller, P. Y. C. Jow, P. N. Craig, and J. Page, *J. Med. Chem.*, 1979, **22**, 366; K. Goerlitzer, M. Bode, P. G. Jones, H. Jomaa, and J. Wiesner, *Pharmazie*, 2007, **62**, 15.
12. G. Matusiak and W. Sliwa, *Pol.* PL144840.
13. E. Dubost, N. Dumas, C. Fossey, R. Magnelli, S. Butt-Gueulle, C. Ballandonne, D. H. Caignard, F. Dulin, J. Sopkova de-Oliveira-Santos, P. Millet, Y. Charnay, S. Rault, T. Cailly, and F. Fabis, *J. Med. Chem.*, 2012, **55**, 9693.
14. A. Hinschberger, S. Butt, V. Lelong, M. Boulouard, A. Dumuis, F. Dauphin, R. Bureau, B. Pfeiffer, P. Renard, and S. Rault, *J. Med. Chem.*, 2003, **46**, 138.
15. D. Ferraris, Y. Ko, T. Pahutski, R. P. Ficco, L. Serdyuk, C. Alemu, C. Bradford, T. Chiou, R. Hoover, S. Huang, S. Lautar, S. Liang, Q. Lin, M. X.-C. Lu, M. Mooney, L. Morgan, Y. Qian, S. Tran, L. R. Williams, Q. Y. Wu, J. Zhang, Y. Zou, and V. Kalish, *J. Med. Chem.*, 2003, **46**, 3138.
16. E. B. Nyquist and M. M. Joullié, *J. Heterocycl. Chem.,* 1967, **4**, 539; R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry,' Kodansha & Elsevier Biomedical, Tokyo, 1982, pp. 1-240; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993, pp. 1-380; K. Burger, U. Wucherpfennig, and E. Brunner, *Adv. Heterocycl. Chem*., 1994, **60**, 1.
17. A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.,* 1965, **2**, 120.
18. M. Loy and M. M. Joullié, *J. Med. Chem.,* 1973, **16**, 549.
19. A. V. London, *Brit. Chem. Eng.*, 1965, **10**, 400; D. L. Stevenson, *Trans. Nation. Vac. Symp.*, 1963, **10**, 134; A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.*, 1965, **2**, 113; F. Yoneda, T. Miyamae, and Y. Nitta, *Chem. Pharm. Bull.*, 1965, **13**, 500.
20. M. Hojo, R. Masuda, E. Okada, T. Tomifuji, and N. Imazaki, *Synthesis*, 1990, 1135; E. Okada, R. Masuda, M. Hojo, N. Imazaki, and K. Takahashi, *Synthesis*, 1991, 536.
21. E. Okada, N. Tsukushi, and T. Sakaemura, *Heterocycles*, 1999, **51**, 2697; E. Okada and N. Tsukushi, *Heterocycles*, 2000, **53**, 709.
22. E. Okada, R. Masuda, M. Hojo, H. Tone, N. Gotoh, and T.-K. Huang, *Heterocycles*, 1995, **40**, 905; E. Okada, N. Tsukushi, T.-K. Huang, H. Tone, N. Gotoh, H. Takeuchi, and M. Hojo, *Heterocycles*,

1998, **48**, 95.

23. E. Okada and N. Tsukushi, *Heterocycles*, 1999, **51**, 2471; E. Okada and N. Tsukushi, *Synthesis*, 2000, 499.
24. M. Hinoshita, D. Shibata, M. Hatakenaka, and E. Okada, *Synthesis*, 2011, 2754.
25. E. Okada, T. Sakaemura, and N. Shimomura, *Chem. Lett.*, 2000, **29**, 50; E. Okada, M. Hatakenaka, T. Sakaemura, N. Shimomura, and T. Ashida, *Heterocycles*, 2012, **86**, 1177.
26. Reviewed in: J. Marco-Contelles, E. Pérez-Mayoral, A. Samadi, M. do C. Carreiras, and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652.
27. The condensation reactions were carried out without replacement by an inert gas, and so it is thought that the oxidative dehydrogenation and aromatization of **2l-n** to **3l-n** were performed by atmospheric oxygen.