Facile and Convenient Syntheses of Fluorine-Containing Pyrido[2,3-*h*]-quinazolines and 1,7-Phenanthrolines by Condensation Reactions of 6,8-Bis(trifluoroacetyl)quinolin-5-amine with Carbonyl Compounds

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Abstract: 6,8-Bis(trifluoroacetyl)quinolin-5-amine reacted easily with various aldehydes in the presence of aqueous ammonia to afford trifluoromethylated pyrido[2,3-*h*]quinazoline derivatives and 1,7-phenanthroline derivatives in good to excellent yields. Under almost the same conditions, the use of ketones instead of aldehydes gave 1,7-phenanthroline derivatives selectively, except in the case of cyclohexanone.

Key words: pyrido[2,3-*h*]quinazolines, 1,7-phenanthrolines, fluorine, condensation reaction, quinolin-5-amines

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.[1]

Meanwhile, it is common knowledge that heterocyclic compounds that have pyridine and pyrimidine skeletons 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 in particular.[2] From this viewpoint, pyrido[2,3-*h*]quinazolines contain both pyridine and pyrimidine skeletons, and have prospective structure for these purposes. However, a literature survey showed that there are only a few methods for the preparation of pyrido[2,3-*h*]quinazoline derivatives,[3] to say nothing about fluorine-containing derivatives.

Similarly, 1,7-phenanthrolines have attracted much attention because of their biological properties. For example, they have demonstrated potential applications as topoisomerase I inhibitors with cytotoxic properties towards L1210 murine leukemia cells,[4] antimalarials,[5] and telomerase inhibitors.[6] Besides, they have also been shown to be applicable in host-guest chemistry.[7] However, fluorinated 1,7-phenanthroline derivatives are rarely known. Because of these reasons, it is of synthetic value to develop facile synthetic methods to fluorine-containing pyrido[2,3-*h*]quinazolines and 1,7-phenanthrolines, which would be expected to present new activities or functionalities.

Previously, we have reported facile synthetic methods of novel heterocycles bearing CF_3 groups using our originally developed fluorine-containing building blocks.[8] For example, trifluoroacetylated naphthalen-1-amine and quinolin-8-amine were utilized in the syntheses of naphthalene- and quinoline-fused heterocycles by three-component condensation reactions and pyridine-ring formation reactions.[9] More recently, we also described a convenient synthesis of trifluoromethylated 1,7-phenanthroline derivatives by cyclization reactions of *N*-propargylquinolin-5-amine derivative with various nucleophiles.[10] This fluorine-containing building block of a quinolin-5-amine system was easily synthesized by a S_NAr of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (**1**) with propargylamine.

In continuation of our work, 6,8-bis(trifluoroacetyl)quinolin-5-amine (**2**) was synthesized and used as a new fluorine-containing building block, and herein we wish to present an efficient and convenient synthesis of the title compounds **3**–**7**. That is to say, **2** underwent the three-component condensation reaction with aldehydes in the presence of aqueous ammonia to give the pyrido[2,3-*h*]quinazoline derivatives **3** and **4**, and in the case of aliphatic aldehydes, 1,7-phenanthroline derivatives **5** were also obtained by Friedländer-type cyclization. Under the quite similar conditions, the reaction of **2** with ketones gave 1,7-phenanthroline derivatives **6** selectively. As identified above, these novel fluorinated compounds are powerfully expected to show interesting biological properties.

The new fluorine-containing building block **2** was easily synthesized in high yield by the dimethylamino–amino exchange reaction of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (**1**) with aqueous ammonia. Compound **1** was readily prepared in three steps by reduction,[11] N,N-dimethylation,[12] and bis(trifluoroacetylation) from commercially available 5-nitroquinoline (Scheme 1).

The results from the reaction of **2** with various aldehydes are shown in Scheme 2 and summarized in Table 1. The three-component condensation reaction of **2** with acetaldehyde in the presence of aqueous ammonia proceeded quickly at 50 °C in acetonitrile to give the corresponding

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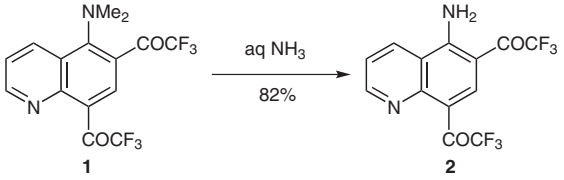
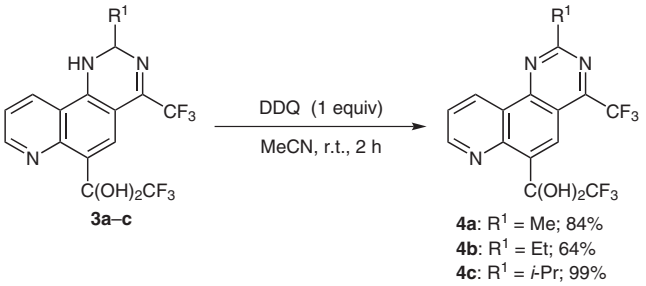


Scheme 1

fluorine-containing dihydropyrido[2,3-*h*]quinazoline **3a**, which is the precursor of expected pyrido[2,3-*h*]quinazoline **4a**, in 48% yield, together with 1,7-phenanthroline derivative **5a** in 24% yield (Table 1, entry 1). The latter product **5a** would be formed by Friedländer-type cyclization,[13] in which the ammonia works not as a nucleophile but as a base. Similarly in the case of propionaldehyde, **3b** and **5b** were obtained in 48% and 16% yields, respectively (entry 2). Isobutyraldehyde also reacted to afford **3c** exclusively and Friedländer-type cyclization had not occurred due to difficulty of deprotonation at sterically hindered α-position (entry 3). Interestingly, the reaction of **2** with aromatic aldehydes, such as *p*-substituted benzaldehydes and aqueous ammonia gave mixtures of **3d–g** and **4d–g**, respectively, in good combined yields (entries 4–7).

Treatment of dihydropyrido[2,3-*h*]quinazolines **3a–c** with DDQ at room temperature for 2 hours led to successful dehydrogenation to give fluorine-containing pyrido[2,3-*h*]quinazolines **4a–c** in 64–99% yield (Scheme 3).

In the case of aromatic aldehydes, the two-step reaction, the condensation reaction and the following dehydrogenation, could be performed easily in a one-pot manner to give the desired **4d–g** in good to high yields (Scheme 4).



Scheme 3

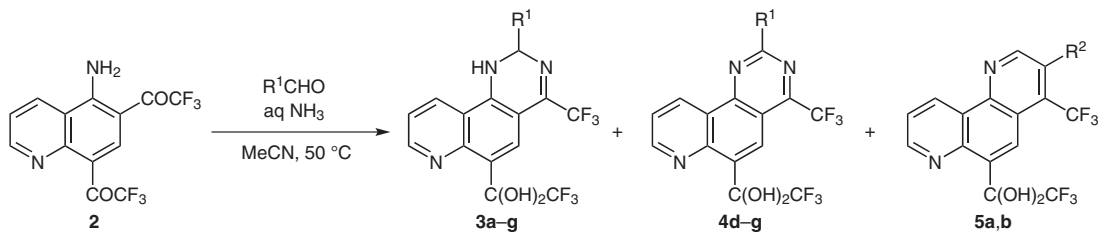
The 6-trifluoroacetyl group of the products was found to exist in the hydrate form and this phenomenon was also observed in our previous experiments of the quinoline-fused heterocycle syntheses.[8d,9c,d,10]

One of the possible mechanistic pathways for the formation of dihydropyrido[2,3-*h*]quinazolines **3**, pyrido[2,3-*h*]quinazolines **4**, and 1,7-phenanthrolines **5** is depicted for the reaction of **2** with acetaldehyde as a representative case in Scheme 5. Initially, the condensation of amino group of **2** with acetaldehyde occur to give an aldimine **I**. When ammonia works as a nucleophile (path A), an aminal **II** or a hemiaminal **III**, or both are formed and the following intramolecular cyclization affords the precursor **3a**, which undergoes dehydrogenation by DDQ to give the final product **4a**. On the other hand, when ammonia acts as a base (path B), the carbanion center of **IV** generated by deprotonation at the α-position attacks the carbonyl carbon of the trifluoroacetyl group to give **5a**.

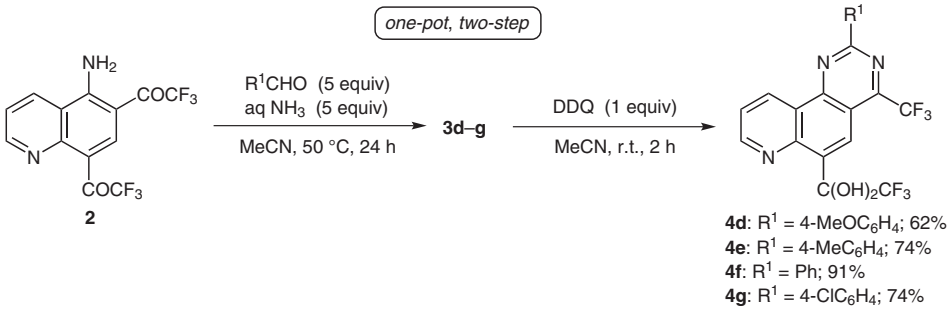
Table 1 Three-Component Condensation Reaction of 6,8-Bis(trifluoroacetyl)quinolin-5-amine (**2**) with Aldehydes and Ammonia

Entry	R^1	R^2	Aldehyde, ammonia (equiv)	Time (h)	Product(s)	Yield (%)[a]
1	Me	H	3	4	**3a**, **5a**	48, 24
2	Et	Me	3	24	**3b**, **5b**	48, 16
3	*i*-Pr	–	3	24	**3c**	84
4	4-$MeOC_6H_4$	–	5	24	**3d**, **4d**	66, 24
5	4-MeC_6H_4	–	5	24	**3e**, **4e**	38, 49
6	Ph	–	5	24	**3f**, **4f**	24, 53
7	4-ClC_6H_4	–	5	24	**3g**, **4g**	54, 26

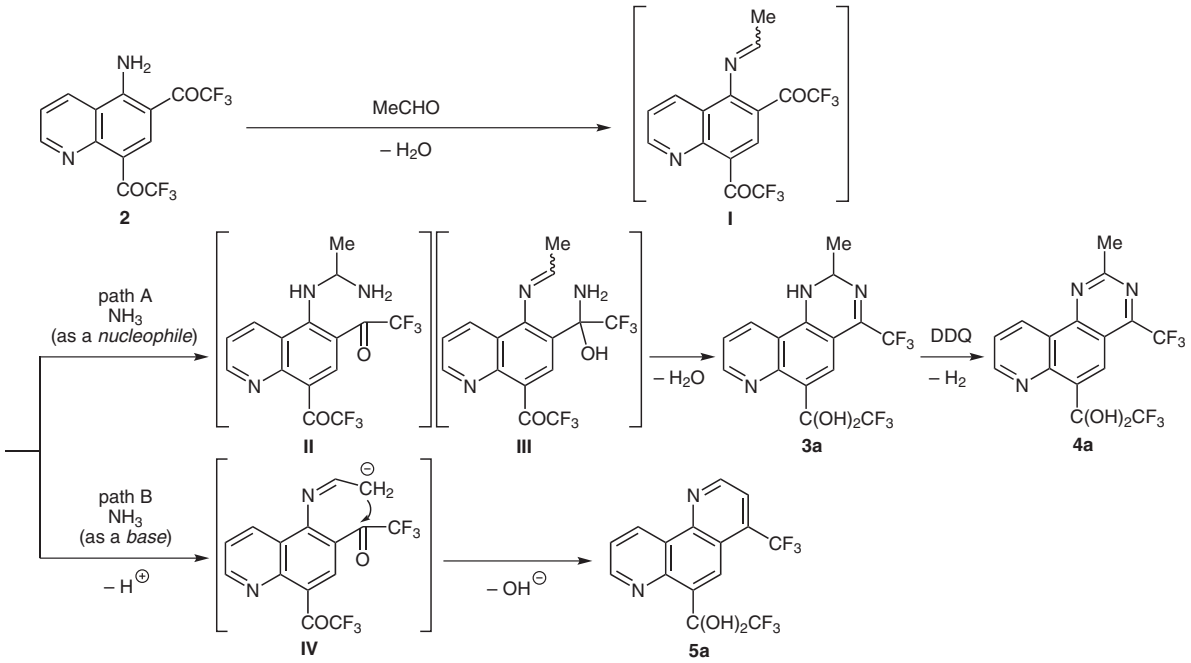
[a] Isolated yields.



Scheme 2

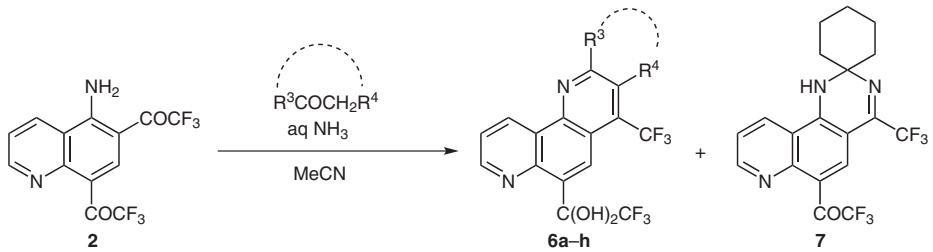


Scheme 4



Scheme 5

Furthermore, the present cyclization reaction was applied to a variety of ketones (Scheme 6, Table 2). Reaction of **2** with acetone took place cleanly at 50 °C in acetonitrile in the presence of aqueous ammonia to afford the corresponding 1,7-phenanthroline **6a** in high yield without any formation of pyrido[2,3-*h*]quinazoline derivative (Table 2, entry 1). In the case of diethyl ketone, **6b** was also obtained selectively though a prolonged reaction time and more elevated temperature were necessary (entry 2). Similarly, 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)-1,7-phenanthrolines **6c**–**e** in high yield (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**–**h** in high yield, except in the case of cyclohexanone, which afforded spiro-substituted dihydropyrido[2,3-*h*]quinazoline derivative **7** together with **6g**. In our previous report[9d] on the similar condensation reaction of 5,7-bis(trifluoroacetyl)quinolin-8-amine, we found that use ethyl methyl ketone, an unsymmetrical acyclic ketone, led to the formation of a mixture of the two regioiso-



Scheme 6

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

Entry	R^3	R^4	Ketone, ammonia (equiv)	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	Me	H	3	50	24	**6a**	90
2	Et	Me	5	80[b]	72	**6b**	67
3	Et	H	5	50	24	**6c**	85
4	*i*-Pr	H	5	50	24	**6d**	87
5	Ph	H	5	50	120	**6e**	85
6	$-(CH_2)_3-$		3	50	24	**6f**	87
7	$-(CH_2)_4-$		3	50	24	**6g/7**	52/46
8	$-(CH_2)_5-$		3	50	24	**6h**	87

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

mers, 2-ethyl (**6c**-type) and 2,3-dimethyl substituted 1,10-phenanthrolines. However, in the case of cyclohexanone, a symmetrical cyclic ketone, a single product (**6g**-type) was obtained without any formation of the spiral compound (**7**-type). The interesting product selectivity appear to be specific for the substrates used, when comparing the results obtained from both systems of 5- and 8-quinolylamines. At the present time it is not clear why these differences, dependent upon the substrates, have resulted.

In summary, we have succeeded in the utilization of **2** as a new fluorine-containing building block and could present an efficient and convenient synthetic method for novel fluorine-containing pyrido[2,3-*h*]quinazolines **3**, **4**, and **7**, and 1,7-phenanthrolines **5** and **6**, which are not easily accessible by other methods. Evaluation of biological activities for **3**–**7** is now underway.

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker Avance 500 spectrometer (at 500 MHz); 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.

6,8-Bis(trifluoroacetyl)quinolin-5-amine (2)
A solution of 28% (w/w) aq NH_3 (2.7 mL, 40 mmol) and *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (**1**;[10–12] 1.46 g, 4 mmol) in MeCN (32 mL) was heated in a sealed tube at 80 °C for 4 h. After removal of the solvent, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 4:1) to give **2**; yield: 1.16 g (82%); mp 220 °C (*n*-hexane–EtOAc).

IR (KBr): 3520, 3323, 1662, 1623 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (monohydrate form) = 8.89 (d, *J* = 4.5 Hz, 1 H, H-2), 8.60–8.03 (br, 2 H, NH or OH), 8.56 (d, *J* = 9.0 Hz, 1 H, H-4), 8.40 (s, 1 H, H-7), 7.63 (br s, 2 H, NH or OH), 7.54 (dd, *J* = 4.5, 9.0 Hz, 1 H, H-3).

Anal. Calcd for $C_{13}H_8F_6N_2O_3$ (354.0) (monohydrate form): C, 44.08; H, 2.28; N, 7.91. Found: C, 43.90; H, 2.48; N, 7.68.

Three-Component Condensation Reaction of 2 with Aldehydes in the Presence of Ammonia; General Procedure
The appropriate aldehyde (3 or 5 mmol) and 28% (w/w) aq NH_3 (3 or 5 mmol) were added to a solution of **2** (354 mg, 1 mmol) in MeCN (5 mL), and the mixture was stirred at 50 °C for 4–24 h. Evaporation of the solvent in vacuo gave a crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 6:1 to 2:1) to give the corresponding **3a**–**g**, **4d**–**g**, and **5a**,**b**.

Dehydrogenation of 3a–c with DDQ; General Procedure
DDQ (1.05 mmol) was added to a solution of the appropriate **3a**–**c** (1 mmol) in MeCN (16 mL), and the mixture was stirred at r.t. for 2 h. The mixture was washed with sat. aq Na_2CO_3 (20 mL), extracted with EtOAc (80 mL), and the extract was dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the corresponding pure **4a**–**c**.

One-Pot Syntheses of 4d–g; General Procedure
The appropriate aromatic aldehyde (5.00 mmol) and 28% (w/w) aq NH_3 (5.00 mmol) were added to a solution of **2** (354 mg, 1.00 mmol) in MeCN (5 mL), and the mixture was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure, and MeCN (16 mL) was added to the residue. DDQ (1.05 mmol) was added to the solution, and the mixture was stirred at r.t. for 2 h. The mixture was washed with sat. aq Na_2CO_3 (20 mL), extracted with EtOAc (80 mL), and the extract was dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 2:1) to give the corresponding **4d**–**g**.

2,2,2-Trifluoro-1-(2-methyl-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (3a)
Mp 175–176 °C (*n*-hexane–EtOAc).

IR (KBr): 3380 cm^{-1}.

^{1}H NMR (CD_3CN–$CDCl_3$): δ = 8.97 (d, *J* = 4.0 Hz, 1 H, H-8), 8.46 (d, *J* = 8.5 Hz, 1 H, H-10), 8.05 (s, 1 H, H-5), 7.54–7.51 (m, 1 H, H-9), 7.45 (br s, 2 H, OH), 6.85–6.67, 6.07 (br s, 1 H, NH), 5.59, 5.37 (q, *J* = 6.0 Hz, 1 H, H-2), 1.65–1.63 (m, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{11}F_6N_3O_2$ (379.1): C, 47.50; H, 2.92; N, 11.08. Found: C, 47.74; H, 3.00; N, 10.76.

1-(2-Ethyl-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (3b)
Mp 158–159 °C (*n*-hexane–EtOAc).

IR (KBr): 3385, 3323 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 9.26–7.45 (br, 2 H, OH), 9.00 (d, *J* = 4.0 Hz, 1 H, H-8), 8.73 (d, *J* = 9.0 Hz, 1 H, H-10), 8.18 (br s, 1 H, H-5), 7.67 (dd, *J* = 4.0, 9.0 Hz, 1 H, H-9), 7.05–6.63, 6.40–6.05 (br, 1 H, NH), 5.62–5.15 (m, 1 H, CH), 2.33–1.72 (m, 2 H, CH_2), 1.10 (t, *J* = 7.0 Hz, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{13}F_6N_3O_2$ (393.1): C, 48.86; H, 3.33; N, 10.68. Found: C, 49.04; H, 3.34; N, 10.29.

2,2,2-Trifluoro-1-(2-isopropyl-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (3c)
Mp 165–166 °C (hexane–EtOAc).

IR (KBr): 3389 cm^{-1}.

^{1}H NMR (DMSO-d_6–CD_3CN): δ = 9.08–8.63 (m, 4 H, H-8, H-10, OH), 8.15 (br s, 1 H, H-5), 7.60 (dd, *J* = 5.0, 9.0 Hz, 1 H, H-9), 6.87–6.42 (br, 1 H, NH), 5.50–5.17 (m, 1 H, H-2), 2.90–1.87 [m, 1 H, C*H*$(CH_3)_2$], 1.07 (d, *J* = 7.0 Hz, 6 H, CH_3).

Anal. Calcd for $C_{17}H_{13}F_6N_3O$ (389.1) (unhydrated form): C, 52.45; H, 3.37; N, 10.79. Found: C, 52.76; H, 3.22; N, 10.63.

2,2,2-Trifluoro-1-[2-(4-methoxyphenyl)-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl]ethane-1,1-diol (3d)
Mp 162–163 °C (*n*-hexane–EtOAc).

IR (KBr): 3264 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 9.02–8.38 (br, 2 H, OH), 8.92 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.63 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 8.27 (br s, 1 H, H-5), 7.70–7.47 (m, 3 H, H-9, H_{arom}), 7.00 (d, *J* = 9.0 Hz, 2 H_{arom}), 6.73 (br s, 1 H, NH), 6.47 (br s, 1 H, H-2), 3.82 (s, 3 H, CH_3).

Anal. Calcd for $C_{21}H_{15}F_6N_3O_3$ (471.1): C, 53.51; H, 3.21; N, 8.91. Found: C, 53.91; H, 3.17; N, 8.55.

2,2,2-Trifluoro-1-(2-*p*-tolyl-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (3e)
Mp 174–175 °C (*n*-hexane–EtOAc).

IR (KBr): 3334 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 9.03 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.72 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 8.33 (br s, 1 H, H-5), 7.80–7.28 (m, 5 H, H-9, H_{arom}), 6.80 (br s, 1 H, NH), 6.58 (br s, 1 H, H-2), 6.00–4.63 (br, 2 H, OH), 2.37 (s, 3 H, CH_3).

Anal. Calcd for $C_{21}H_{15}F_6N_3O_2$ (455.1): C, 55.39; H, 3.32; N, 9.23. Found: C, 55.51; H, 3.37; N, 9.06.

2,2,2-Trifluoro-1-(2-phenyl-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (3f)
Mp 217–218 °C (*n*-hexane–EtOAc).

IR (KBr): 3305 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 9.20–8.40 (br, 2 H, OH), 9.00 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.70 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 8.30 (br s, 1 H, H-5), 7.93–7.33 (m, 6 H, H-9, H_{arom}), 6.80 (br s, 1 H, NH), 6.58 (br s, 1 H, H-2).

Anal. Calcd for $C_{20}H_{13}F_6N_3O_2$ (441.1): C, 54.43; H, 2.97; N, 9.52. Found: C, 54.60; H, 3.18; N, 9.13.

1-(2-(4-Chlorophenyl)-4-trifluoromethyl-1,2-dihydropyrido[2,3-*h*]quinazolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (3g)
Mp 156–157 °C (*n*-hexane–EtOAc).

IR (KBr): 3381 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 8.92 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.63 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 8.22 (br s, 1 H, H-5), 7.72–7.33 (m, 5 H, H-9, H_{arom}), 6.75 (br s, 1 H, NH), 6.48 (br s, 1 H, H-2).

Anal. Calcd for $C_{20}H_{12}ClF_6N_3O_2$ (475.1): C, 50.49; H, 2.54; N, 8.83. Found: C, 50.18; H, 2.72; N, 8.82.

2,2,2-Trifluoro-1-(2-methyl-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (4a)
Mp 201–202 °C (*n*-hexane–EtOAc).

IR (KBr): 3323, 3093 cm^{-1}.

^{1}H NMR (DMSO-d_6–$CDCl_3$): δ = 9.83 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.43 (s, 2 H, OH), 9.27 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.95 (br s, 1 H, H-5), 8.00 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 3.10 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_9F_6N_3O_2$ (377.1): C, 47.76; H, 2.40; N, 11.14. Found: C, 47.71; H, 2.43; N, 11.16.

1-(2-Ethyl-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (4b)
Mp 144–145 °C (*n*-hexane–EtOAc).

IR (KBr): 3350, 3094 cm^{-1}.

^{1}H NMR (CD_3CN): δ = 9.85 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.28 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 8.87 (br s, 1 H, H-5), 8.03 (dd, *J* = 5.0, 8.0 Hz, 1 H, H-9), 7.28–5.78 (br, 2 H, OH), 3.38 (q, *J* = 8.0 Hz, 2 H, CH_2), 1.57 (t, *J* = 8.0 Hz, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{11}F_6N_3O_2$ (391.1): C, 49.11; H, 2.83; N, 10.74. Found: C, 49.46; H, 2.86; N, 10.37.

2,2,2-Trifluoro-1-(2-isopropyl-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (4c)
Mp 155–156 °C (*n*-hexane–EtOAc).

IR (KBr): 3350, 3092 cm^{-1}.

^{1}H NMR (DMSO-d_6–$CDCl_3$): δ = 9.95 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.35 (br s, 2 H, OH), 9.23 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.98 (br s, 1 H, H-5), 7.97 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 3.63 (hept, *J* = 7.0 Hz, 1 H, CH), 1.63 (d, *J* = 7.0 Hz, 6 H, CH_3).

Anal. Calcd for $C_{17}H_{13}F_6N_3O_2$ (405.1): C, 50.38; H, 3.23; N, 10.37. Found: C, 50.58; H, 3.32; N, 10.08.

2,2,2-Trifluoro-1-[2-(4-methoxyphenyl)-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl]ethane-1,1-diol (4d)
Mp 208–209 °C (*n*-hexane–EtOAc).

IR (KBr): 3356, 3082 cm^{-1}.

^{1}H NMR (DMSO-d_6–CD_3CN): δ = 10.02 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.62 (s, 2 H, OH), 9.40 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 8.93–8.70 (m, 3 H, H-5, H_{arom}), 8.13 (dd, *J* = 5.0, 8.0 Hz, 1 H, H-9), 7.20 (d, *J* = 9.0 Hz, 2 H_{arom}), 3.95 (s, 3 H, CH_3).

Anal. Calcd for $C_{21}H_{13}F_6N_3O_3$ (469.1): C, 53.74; H, 2.79; N, 8.95. Found: C, 53.92; H, 2.86; N, 9.12.

2,2,2-Trifluoro-1-(2-*p*-tolyl-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (4e)
Mp 205–206 °C (*n*-hexane–EtOAc).

IR (KBr): 3319, 3068 cm^{-1}.

^{1}H NMR (DMSO-d_6–$CDCl_3$): δ = 9.80 (d, *J* = 8.5 Hz, 1 H, H-10), 9.06 (d, *J* = 4.5 Hz, 1 H, H-8), 8.93 (br s, 2 H, OH), 8.84 (s, 1 H, H-5), 8.62 (d, *J* = 8.0 Hz, 2 H_{arom}), 7.81 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 7.37 (d, *J* = 8.0 Hz, 2 H_{arom}), 2.47 (s, 3 H, CH_3).

Anal. Calcd for $C_{21}H_{13}F_6N_3O_2$ (453.1): C, 55.64; H, 2.89; N, 9.27. Found: C, 55.67; H, 2.97; N, 9.16.

2,2,2-Trifluoro-1-(2-phenyl-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl)ethane-1,1-diol (4f)
Mp 189–190 °C (*n*-hexane–EtOAc).

IR (KBr): 3350, 3073 cm^{-1}.

^{1}H NMR (DMSO-d_6–$CDCl_3$): δ = 9.85 (d, *J* = 8.5 Hz, 1 H, H-10), 9.09 (d, *J* = 4.0 Hz, 1 H, H-8), 8.94 (br s, 2 H, OH), 8.87 (s, 1 H, H-5), 7.85 (dd, *J* = 4.0, 8.5 Hz, 1 H, H-9), 7.59 (br s, 5 H_{arom}).

Anal. Calcd for $C_{20}H_{11}F_6N_3O_2$ (439.1): C, 54.68; H, 2.52; N, 9.57. Found: C, 54.65; H, 2.84; N, 9.28.

1-{2-(4-Chlorophenyl)-4-trifluoromethylpyrido[2,3-*h*]quinazolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (4g)
Mp 186–187 °C (*n*-hexane–EtOAc).

IR (KBr): 3352, 3078 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 9.97 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 9.52 (br s, 2 H, OH), 9.35 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 9.00 (br s, 1 H, H-5), 8.78 (d, *J* = 9.0 Hz, 2 H_{arom}), 8.07 (dd, *J* = 5.0, 9.0 Hz, 1 H, H-9), 7.62 (d, *J* = 9.0 Hz, 2 H_{arom}).

Anal. Calcd for $C_{20}H_{10}ClF_6N_3O_2$ (473.0): C, 50.70; H, 2.13; N, 8.87. Found: C, 50.91; H, 2.29; N, 8.50.

2,2,2-Trifluoro-1-(4-trifluoromethyl-1,7-phenanthrolin-6-yl)ethane-1,1-diol (5a)
Mp 133–134 °C (*n*-hexane–EtOAc).

IR (KBr): 3356 cm^{-1}.

^1H NMR (CD_3CN–$CDCl_3$): δ = 9.82 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.38 (d, *J* = 5.0 Hz, 1 H, H-2), 9.13 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 9.00-8.30 (br, 2 H, OH), 8.87 (br s, 1 H, H-5), 8.13 (d, *J* = 5.0 Hz, 1 H, H-3), 7.90 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9).

Anal. Calcd for $C_{15}H_8F_6N_2O_2$ (362.0): C, 49.74; H, 2.23; N, 7.73. Found: C, 49.55; H, 2.60; N, 7.54.

2,2,2-Trifluoro-1-(3-methyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)ethane-1,1-diol (5b)
Mp 185–186 °C (EtOAc).

IR (KBr): 3366 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 10.07–8.90 (br, 2 H, OH), 9.88 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.33–9.25 (m, 2 H, H-2, H-8), 9.07 (br s, 1 H, H-5), 8.07 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 2.87 (q, $J_{H,F}$ = 4.0 Hz, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{10}F_6N_2O_2$ (376.1): C, 51.07; H, 2.68; N, 7.45. Found: C, 50.73; H, 2.82; N, 7.37.

Three-Component Condensation Reaction of 2 with Ketones in the Presence of Ammonia; General Procedure
The appropriate ketone (3.00 or 5.00 mmol) and 28% (w/w) aq NH_3 (3.00 or 5.00 mmol) were added to a solution of **2** (354 mg, 1.00 mmol) in MeCN (5 mL), and the mixture was stirred at 50 °C for 24–120 h. In the case of diethyl ketone, the mixture was heated 80 °C 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, 5:1 to 1:1) to give the corresponding **6a**–**h** and **7**.

2,2,2-Trifluoro-1-(2-methyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)ethane-1,1-diol (6a)
Mp 142–143 °C (*n*-hexane–EtOAc).

IR (KBr): 3370 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 9.90 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.56 (s, 2 H, OH), 9.15 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.92 (br s, 1 H, H-5), 8.02–7.79 (m, 2 H, H-3, H-9), 2.99 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{10}F_6N_2O_2$ (376.1): C, 51.07; H, 2.68; N, 7.45. Found: C, 51.12; H, 2.92; N, 7.36.

1-(2-Ethyl-3-methyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (6b)
Mp 136–137 °C (*n*-hexane–EtOAc).

IR (KBr): 3336 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 9.90 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.57–8.97 (m, 4 H, H-5, H-8, OH), 7.81 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 3.19 (q, *J* = 7.0 Hz, 2 H, CH_2), 2.70 (q, $J_{H,F}$ = 3.0 Hz, 3 H, CH_3), 1.54 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{18}H_{14}F_6N_2O_2$ (404.1): C, 53.47; H, 3.49; N, 6.93. Found: C, 53.67; H, 3.59; N, 6.53.

1-(2-Ethyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (6c)
Mp 135–136 °C (*n*-hexane–EtOAc).

IR (KBr): 3351 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.76 (dd, *J* = 1.5, 8.5 Hz, 1 H, H-10), 8.93 (dd, *J* = 1.5, 4.8 Hz, 1 H, H-8), 8.75 (br s, 1 H, H-5), 7.80 (br s, 1 H, H-3), 7.79 (br s, 2 H, OH), 7.71 (dd, *J* = 4.8, 8.5 Hz, 1 H, H-9), 3.20 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.53 (t, *J* = 7.5 Hz, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{12}F_6N_2O_2$ (390.1): C, 52.32; H, 3.10; N, 7.18. Found: C, 52.71; H, 3.16; N, 6.81.

2,2,2-Trifluoro-1-(2-isopropyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)ethane-1,1-diol (6d)
Mp 149–150 °C (*n*-hexane–EtOAc).

IR (KBr): 3348 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.71 (dd, *J* = 1.6, 8.4 Hz, 1 H, H-10), 8.89 (dd, *J* = 1.6, 4.4 Hz, 1 H, H-8), 8.73 (br s, 1 H, H-5), 7.90 (br s, 2 H, OH), 7.82 (br s, 1 H, H-3), 7.66 (dd, *J* = 4.4, 8.4 Hz, 1 H, H-9), 3.44 (hept, *J* = 6.9 Hz, 1 H, CH), 1.52 (d, *J* = 6.9 Hz, 6 H, CH_3).

Anal. Calcd for $C_{18}H_{12}F_6N_2O$ (386.1) (unhydrated form): C, 55.97; H, 3.13; N, 7.25. Found: C, 56.09; H, 3.38; N, 6.88.

2,2,2-Trifluoro-1-(2-phenyl-4-trifluoromethyl-1,7-phenanthrolin-6-yl)ethane-1,1-diol (6e)
Mp 213–214 °C (*n*-hexane–EtOAc).

IR (KBr): 3346 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.91 (dd, *J* = 1.6, 8.3 Hz, 1 H, H-10), 9.01 (dd, *J* = 1.6, 4.4 Hz, 1 H, H-8), 8.82 (br s, 1 H, H-5), 8.41 (br s, 1 H, H-3), 8.36 (br s, 2 H, OH), 7.81 (dd, *J* = 4.4, 8.3 Hz, 1 H, H-9), 7.65–7.58 (m, 5 H, C_6H_5).

Anal. Calcd for $C_{21}H_{12}F_6N_2O_2$ (438.1): C, 57.54; H, 2.76; N, 6.39. Found: C, 57.27; H, 2.75; N, 5.99.

2,2,2-Trifluoro-1-(7-trifluoromethyl-9,10-dihydro-8*H*-cyclopenta[*b*][1,7]phenanthrolin-5-yl)ethane-1,1-diol (6f)
Mp 177–178 °C (*n*-hexane–EtOAc).

IR (KBr): 3349 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.75 (dd, *J* = 1.5, 8.4 Hz, 1 H, H-1), 8.95 (dd, *J* = 1.5, 4.4 Hz, 1 H, H-3), 8.80 (br s, 1 H, H-6), 7.90 (br s, 2 H, OH), 7.74 (dd, *J* = 4.4, 8.4 Hz, 1 H, H-2), 3.46–3.42 (m, 2 H, $ArCH_2$), 3.32 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 2.32 (quint, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2$).

Anal. Calcd for $C_{18}H_{12}F_6N_2O_2$ (402.1): C, 53.74; H, 3.01; N, 6.96. Found: C, 53.64; H, 2.92; N, 6.56.

2,2,2-Trifluoro-1-(7-trifluoromethyl-8,9,10,11-tetrahydrobenzo[*b*][1,7]phenanthrolin-5-yl)ethane-1,1-diol (6g)
Mp 149–150 °C (*n*-hexane–EtOAc).

IR (KBr): 3366 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 9.73 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-1), 9.47 (br s, 2 H, OH), 9.17–8.88 (m, 2 H, H-3, H-6), 7.77 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-2), 3.50–3.00 (m, 4 H, $ArCH_2$), 2.20–1.79 [m, 4 H, $CH_2(C_2H_4)CH_2$].

Anal. Calcd for $C_{19}H_{14}F_6N_2O_2$ (416.1): C, 54.81; H, 3.39; N, 6.73. Found: C, 55.20; H, 3.37; N, 6.35.

2,2,2-Trifluoro-1-(7-trifluoromethyl-9,10,11,12-tetrahydro-8*H*-cyclohepta[*b*][1,7]phenanthrolin-5-yl)ethane-1,1-diol (6h)
Mp 159–160 °C (*n*-hexane–EtOAc).

IR (KBr): 3361 cm^{-1}.

^1H NMR (DMSO-d_6–$CDCl_3$): δ = 9.78 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-1), 9.44 (br s, 2 H, OH), 9.17–8.92 (m, 2 H, H-3, H-6), 7.77 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-2), 3.65–3.06 (m, 4 H, $ArCH_2$), 2.14–1.69 [m, 6 H, $CH_2(C_3H_6)CH_2$].

Anal. Calcd for $C_{20}H_{16}F_6N_2O_2$ (430.1): C, 55.82; H, 3.75; N, 6.51. Found: C, 56.09; H, 3.85; N, 6.13.

2,2,2-Trifluoro-1-(4′-trifluoromethylspiro[cyclohexane-1,2′-[1,2]dihydropyrido[2,3-*h*]quinazoline]-6′-yl)ethanone (7)
Mp 167–168 °C (*n*-hexane–EtOAc).

IR (KBr): 3382, 2944, 1662 cm^{-1}.

^1H NMR (CD_3CN): δ = 9.16–8.90 (m, 1 H, H-10′), 8.84–8.53 (m, 1 H, H-8′), 8.14 (br s, 1 H, H-5′), 7.63 (dd, *J* = 4.0, 8.5 Hz, 1 H, H-9′), 6.77–5.78 (br, 1 H, NH), 2.00–1.43 (m, 10 H, C_5H_{10}).

Anal. Calcd for $C_{19}H_{15}F_6N_3O$ (415.1): C, 54.94; H, 3.64; N, 10.12. Found: C, 55.28; H, 3.70; N, 9.73.

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