A Facile Synthetic Method for Fluorine-Containing 1,7-Phenanthrolines: Pyridine-Ring Formation Reaction of *N*-Propargyl-6,8-bis(trifluoroacetyl)-quinolin-5-amine with Various Nucleophiles

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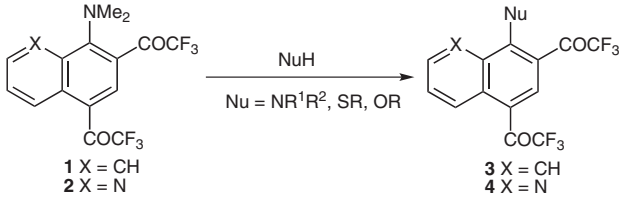
Abstract: Novel fluorine-containing 1,7-phenanthrolines with a variety of substituents at the 3-position were easily synthesized in moderate to high yields by the pyridine-ring formation reaction of *N*-propargyl-6,8-bis(trifluoroacetyl)quinolin-5-amine with various amines, thiols, alcohols, and phenols.

Key words: 1,7-phenanthrolines, fluorine, pyridine-ring formation, propargylamines, 5-quinolines

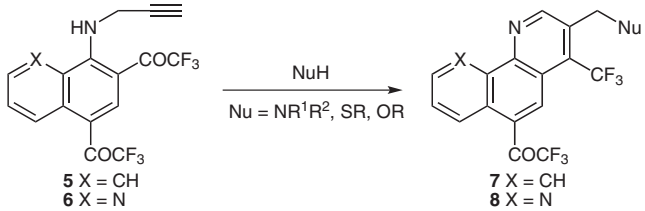
1,7-Phenanthrolines constitute an interesting class of heterocyclic compounds because of their biological properties. For example, they have demonstrated potential applications as topoisomerase I inhibitors with cytotoxic properties towards L1210 murine leukemia cells,[1] antimalarials,[2] and telomerase inhibitors.[3] Besides, their application in host–guest chemistry has also been demonstrated.[4] 1,7-Phenanthroline skeletons are usually elaborated by a similar method of quinoline synthesis, for instance Skraup and Friedländer syntheses. There are three main types of synthetic approaches. One of the routes uses phenylene-1,3-diamine as the starting material and thus allows the construction of two pyridine rings at the same time.[5] The other routes start from quinolin-5-amine[1,2a,6] and quinolin-7-amine.[7]

In recent years considerable attention has been paid to the development of new methodologies for the synthesis of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities and for their potential use in medicinal and agricultural scientific fields.[8] Fluorinated 1,7-phenanthroline derivatives are scarce, and therefore it is of synthetic value to develop convenient and mild approaches for the synthesis of fluorine-containing 1,7-phenanthrolines, which would be expected to exhibit new activities or functionalities.

So far, we have found that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)naphthalen-1-amine (**1**)[9] and *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)quinolin-8-amine (**2**)[10] react easily with various amines, thiols, and alcohols under mild conditions to afford the corresponding N–N-, N–S-, and N–O-exchanged products **3** and **4**, respectively, in excellent yields (Scheme 1). Moreover, we succeeded in extending this type of aromatic nucleophilic substitution to the simple syntheses of various trifluoromethyl-containing heterocycles with naphthalene[11] and quinoline[12] skeletons. During the course of our studies, we have recently revealed that propargylamino derivatives **5** and **6**, which were readily prepared through a dimethylamino–propargylamino exchange reaction, undergo the pyridine-ring formation reaction with N-, S-, and O-nucleophiles to give the corresponding novel fluorine-containing benzo[*h*]quinolines **7**[13] and 1,10-phenanthrolines **8**[14] (Scheme 2).



Scheme 1



Scheme 2

In connection with this work, we now wish to present a facile synthetic method for novel fluorine-containing 1,7-phenanthrolines **10**–**13**, which are not easily accessible by other methods and are greatly expected to show interesting biological activities, by the pyridine-ring formation reaction of *N*-propargyl-6,8-bis(trifluoroacetyl)quinolin-

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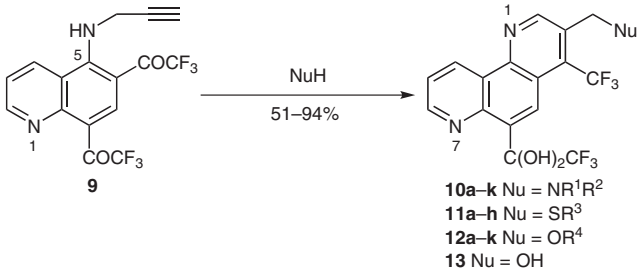
5-amine (**9**) with various nucleophiles (Scheme 3). The results of this study make it possible to clarify the differences in reactivities of the naphthalene,[13] 8-quinoline,[14] and 5-quinoline systems, which are caused by the different effects of the benzene and pyridine rings in the three kinds of substrates (**5**,[13] **6**,[14] and **9**).



Scheme 3

The requisite starting material **9** was easily prepared in moderate yields by a dimethylamino–propargylamino exchange reaction of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine, which was prepared by bis(trifluoroacetylation) of *N*,*N*-dimethylquinolin-5-amine,[15,16] with propargylamine.

The reaction of **9** with various amines was initially examined (Scheme 3), and the results are summarized in Table 1. The cyclization of **9** with dimethylamine proceeded rapidly at 50 °C in acetonitrile to give the corresponding fluorine-containing 1,7-phenanthrolines **10a** in 94% yield (entry 1). Secondary and primary aliphatic amines such as diethylamine, pyrrolidine, piperidine, isopropylamine, and *tert*-butylamine also reacted cleanly to provide the desired phenanthrolines **10b–f** in 68–89% yield (entries 2–6). When the reaction with benzylamine was performed, *N*-benzyl-6,8-bis(trifluoroacetyl)quinolin-5-amine was obtained by propargylamino–benzylamino exchange at the 5-position of **9**. Interestingly, it was found that the addition of triethylamine (5 equiv) prevents the amine–amine exchange reaction, and the desired pyridine-ring formation reaction proceeds selectively to afford the corresponding **10g** in 82% yield (entry 7). In the presence of triethylamine, less nucleophilic aromatic amines (*p*-anisidine, *p*-toluidine, aniline, and *p*-chloroaniline) reacted similarly and cleanly to provide 3-[(arylamino)methyl]-1,7-phenanthrolines **10h–k** in 63–82% yield (entries 8–11). The 6-trifluoroacetyl group of 1,7-phenanthrolines **10** was found to exist in the hydrate form, a phenomenon also observed in the case of 1,10-phenanthrolines **8**,[14] but not in the case of benzo[*h*]quinolines **7**.[13]

In addition, the present cyclization reaction was applied to thiols (Scheme 3, Table 2). Reactions of **9** with aliphatic thiols such as ethanethiol, butane-1-thiol, 2-methylpropane-2-thiol, and phenylmethanethiol took place at 50 °C in acetonitrile within four to eight hours in the presence of triethylamine as a base to afford the desired 3-[(alkylsulfanyl)methyl]-1,7-phenanthrolines **11a–d** in about 70% yield (entries 1–4). Aromatic thiols such as *p*-substituted benzenethiols also easily underwent the pyridine-ring formation reaction under almost the same mild conditions as in the case of aliphatic thiols to give the corresponding 3-[(arylsulfanyl)methyl]-1,7-phenanthrolines **11e–h** in 65–82% yield (entries 5–8).

We also attempted to accomplish the ring formation reactions of **9** with alcohols and phenols to obtain fluorine-containing 1,7-phenanthrolines with alkoxymethyl or (aryloxy)methyl substituents at the 3-position (Scheme 3, Table 3). The cyclization reactions with methyl, ethyl, *n*-butyl, allyl, and propargyl alcohols occurred as expected to give the corresponding 1,7-phenanthrolines **12a–c**, **12e**,

Table 1 Pyridine-Ring Formation Reactions of **9** with Amines (R^1R^2NH) in Acetonitrile[a]

Entry	R^1	R^2	Base (equiv)	Temp (°C)	Time (h)	Product	Yield[b] (%)
1[c]	Me	Me	none	50	2	**10a**	94
2	Et	Et	none	50	2	**10b**	76
3	$(CH_2)_4$		none	50	1	**10c**	68
4	$(CH_2)_5$		none	50	1	**10d**	89
5	*i*-Pr	H	none	50	16	**10e**	74
6	*t*-Bu	H	none	50	4	**10f**	73
7	Bn	H	Et_3N (5)	reflux	2	**10g**	82
8	4-$MeOC_6H_4$	H	Et_3N (1.5)	50	2	**10h**	82
9	4-MeC_6H_4	H	Et_3N (1.5)	50	2	**10i**	66
10	Ph	H	Et_3N (1.5)	50	4	**10j**	63
11	4-ClC_6H_4	H	Et_3N (1.5)	50	4	**10k**	63

[a] Molar ratio **9**/R^1R^2NH = 1:3.
[b] Isolated yields.
[c] A 50% aq soln of Me_2NH was used.

Table 2 Pyridine-Ring Formation Reaction of **9** with Thiols (R^3SH) in the Presence of Triethylamine at 50 °C in Acetonitrile

Entry	R^3	Thiol, Et_3N (equiv)	Time (h)	Product	Yield[a] (%)
1	Et	1.2	4	**11a**	72
2	*n*-Bu	1.2	4	**11b**	74
3	*t*-Bu	1.2	4	**11c**	72
4	Bn	3	8	**11d**	72
5	4-$MeOC_6H_4$	1.2	2	**11e**	76
6	4-MeC_6H_4	1.2	2	**11f**	65
7	Ph	1.2	2	**11g**	82
8	4-ClC_6H_4	1.2	8	**11h**	75

[a] Isolated yields.

and **12f** in 51–65% yield (entries 1–3, 5, and 6). It was interesting to find that the reaction of **9** with potassium *tert*-butoxide in tetrahydrofuran led to the novel 1,7-phenanthrolin-3-ylmethanol **13** (Nu = OH in Scheme 3) in 39% yield instead of **12d** (Table 3, entry 4). A tentative explanation for the formation of **13** is that the hydrolysis of **12d** occurred immediately in situ due to the presence of a good leaving group. The reactions with phenols such as *p*-methoxyphenol, *p*-cresol, phenol, and *p*-chlorophenol went to completion within two hours in the presence of triethylamine as a base in acetonitrile to afford the corresponding 3-[(aryloxy)methyl]-1,7-phenanthrolines **12g–j** in 53–71% yield (entries 7–10). In the case of *p*-nitrophenol, a prolonged reaction time (24 h) was required for complete conversion, and (*p*-nitrophenoxy)methyl derivative **12k** was obtained in 51% yield together with hydroxymethyl derivative **13** in 19% yield (entry 11). Interestingly, increasing the amount (5 equiv) of *p*-nitrophenol inhibited the formation of **13**, and **12k** was obtained exclusively in 67% yield (entry 12).

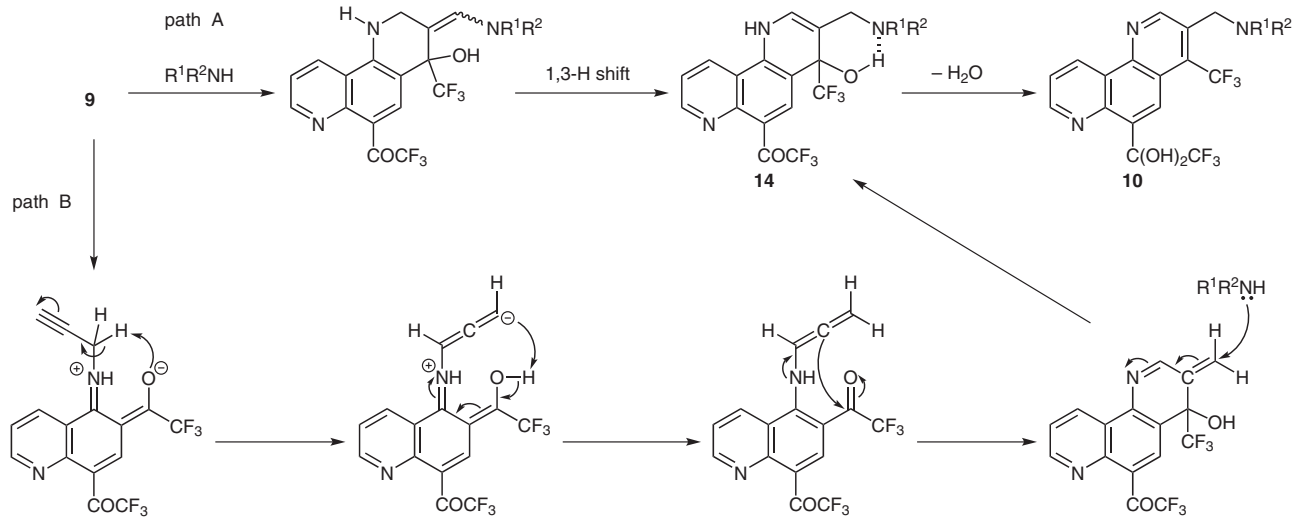
Two possible mechanistic pathways (paths A and B) for the formation of 1,7-phenanthrolines **10** are depicted in Scheme 4. In path A, the addition of amines as nucleophiles to the terminal acetylenic carbon and the attack of the carbonyl carbon at the internal acetylenic carbon occur concertedly to give a cyclization product with an *exo*-methylene moiety. Subsequent 1,3-shift of the allylic hydrogen takes place to afford the intermediate 1,4-dihydro-1,7-phenanthrolin-4-ol **14**, which undergoes dehydration to give 1,7-phenanthroline **10**. In path B, the tautomerization of the keto to the enol form causes the isomerization of the propargyl to an allenyl group, and subsequent intramolecular cyclization gives a 3-methylene-1,7-phenanthroline derivative. This product then reacts with amines to give **14**, leading to **10**. More studies are underway to elucidate the mechanism more clearly.

As depicted in Figure 1, it is noteworthy that we succeeded in isolating the 1,4-dihydro-1,10-phenanthrolines **15**, which are the precursors of the stable aromatized final products 1,10-phenanthrolines **8** (Nu = NR^1R^2 in Scheme 2), and which seem to be stable.[14] However, in both the quinolin-5-amine and naphthalenamine systems, this type of intermediate (**14** and **16**, Figure 1) was not isolated and also not detected. Probably, it is reasonable to postulate that in **15** the additional hydrogen bond between H1 and N10, which cannot exist in the quinolin-5-amine and naphthalenamine systems (**14** and **16**), has contribut-

Table 3 Pyridine-Ring Formation Reaction of **9** with Alcohols and Phenols (R^4OH) at 50 °C

Entry	R^4	R^4OH (equiv)	Additive (equiv)	Time (h)	Solvent	Product	Yield[a] (%)
1	Me	excess	Na (1)	8	MeOH	**12a**	56
2	Et	excess	Na (1)	2	EtOH	**12b**	65
3	*n*-Bu	excess	Na (1)	1	*n*-BuOH	**12c**	56
4	*t*-Bu[b]	1	none	2	THF	**12d/13**	0/39
5	$CH_2CH{=}CH_2$	excess	Na (3)	1	$H_2C{=}CHCH_2OH$	**12e**	62
6	$CH_2C{\equiv}CH$	excess	Na (3)	1	$HC{\equiv}CCH_2OH$	**12f**	51
7	4-$MeOC_6H_4$	3	Et_3N (1.5)	2	MeCN	**12g**	62
8	4-MeC_6H_4	3	Et_3N (1.5)	2	MeCN	**12h**	71
9	Ph	3	Et_3N (1.5)	2	MeCN	**12i**	53
10	4-ClC_6H_4	3	Et_3N (1.5)	2	MeCN	**12j**	69
11	4-$O_2NC_6H_4$	3	Et_3N (1.5)	24	MeCN	**12k/13**	51/19[c]
12	4-$O_2NC_6H_4$	5	Et_3N (1.5)	24	MeCN	**12k**	67

[a] Isolated yields.
[b] *t*-BuOK was used.
[c] Not isolated. Determined by ^1H NMR.



Scheme 4

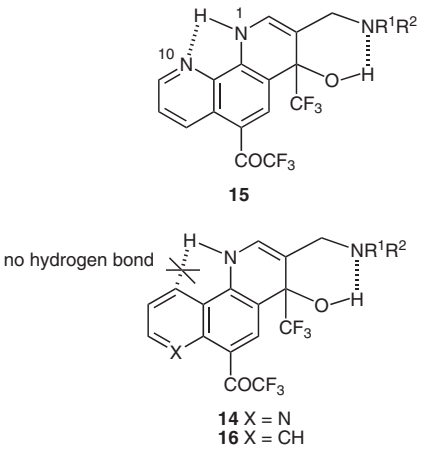


Figure 1

ed to the stability of **15**, namely, has interrupted the dehydration promoted by aromatization.

In summary, we succeeded in developing an efficient synthetic method for trifluoromethyl-containing 1,7-phenanthrolines **10–13**, which are novel and not easily available by other methods, by pyridine-ring formation reactions of *N*-propargylquinolin-5-amine derivative **9** with various nucleophiles. The methodology presented is quite remarkable, since no kind of activation of the propargylamine system was needed to promote addition of the nucleophiles and subsequent ring formation. The mechanism of this reaction is not yet fully established, although two reasonable mechanistic pathways have been presented.

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. NMR spectra were obtained on a Bruker Avance 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 126 MHz) and a Jeol PMX-60SI spectrometer (^{1}H at 60 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.

***N*-Propargyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (9)**
TFAA (1.79 mL, 12.75 mmol) was added dropwise to a stirred soln of *N*,*N*-dimethylquinolin-5-amine (731 mg, 4.25 mmol) and py (1008 mg, 12.75 mmol) in $CHCl_3$ (4.3 mL) with cooling, and stirring was continued at r.t. for 24 h. The solvent was removed under reduced pressure, and EtOAc (100 mL) was added to the residue. The soln was washed with H_2O (100 mL) and sat. aq Na_2CO_3 (100 mL), and then dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude product was dehydrated to give *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine; yield: 1456 mg (94%). Propargylamine (330 mg, 6.0 mmol) was then added to a soln of *N*,*N*-dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (728 mg, 2.0 mmol) in MeCN (16 mL), and the mixture was stirred under reflux for 2 h. After removal of the solvent, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 4:1, for **9**, and *n*-hexane–EtOAc, 2:1, for **10a**).

Yield (**9**): 420 mg (56%); yield (**10a**): 284 mg (34%).

***N*,*N*-Dimethyl-6,8-bis(trifluoroacetyl)quinolin-5-amine**
Mp 97–98 °C (*n*-hexane–EtOAc).

IR (KBr): 1696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.01 (d, *J* = 4.0 Hz, 1 H, H-2), 8.58 (d, *J* = 8.5 Hz, 1 H, H-4), 8.19 (s, 1 H, H-7), 7.53 (dd, *J* = 4.0, 8.5 Hz, 1 H, H-3), 3.14 (s, 6 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 184.7 (q, J_{CF} = 36.5 Hz), 181.0 (q, J_{CF} = 35.2 Hz), 158.0, 152.9, 149.6, 134.8, 131.6, 125.8, 125.0, 121.5, 119.3, 116.3 (q, J_{CF} = 291.8 Hz), 116.3 (q, J_{CF} = 290.5 Hz), 45.9.

Anal. Calcd for $C_{15}H_{10}F_6N_2O_2$ (364.1): C, 49.46; H, 2.77; N, 7.69. Found: C, 49.22; H, 3.02; N, 7.68.

***N*-Propargyl-6,8-bis(trifluoroacetyl)quinolin-5-amine (9)**
Mp 126–127 °C (*n*-hexane–EtOAc).

IR (KBr): 3302, 3277, 2128, 1653 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.81 (br s, 1 H, NH), 9.03 (d, *J* = 4.0 Hz, 1 H, H-2), 8.76 (d, *J* = 8.5 Hz, 1 H, H-4), 8.40 (s, 1 H, H-7), 7.49 (dd, *J* = 4.0, 8.5 Hz, 1 H, H-3), 4.56 (dd, *J* = 2.0, 6.0 Hz, 2 H, CH_2), 2.58 (br s, 1 H, C≡CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 183.2 (q, J_{CF} = 37.7 Hz), 180.4 (q, J_{CF} = 40.2 Hz), 158.8, 154.0, 150.7, 135.4, 134.4, 121.7, 120.6, 118.5, 117.0 (q, J_{CF} = 290.5 Hz), 116.4 (q, J_{CF} = 291.8 Hz), 106.9, 78.0, 75.2, 38.8.

Anal. Calcd for $C_{16}H_8F_6N_2O_2$ (374.1): C, 51.35; H, 2.15; N, 7.49. Found: C, 51.26; H, 2.46; N, 7.28.

Pyridine-Ring Formation Reaction of 9 with Amines; General Procedure

The appropriate amine R^1R^2NH (3.00 mmol) was added to a soln of **9** (374 mg, 1.00 mmol) in MeCN (10 mL), and the mixture was stirred at 50 °C or under reflux for 1–16 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 2:1) to give the corresponding **10a–k**. In the case of $BnNH_2$ and *p*-substituted anilines, Et_3N (1.50 or 5.00 mmol) was added as a base.

1-{3-[(Dimethylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (10a)

Mp 124–125 °C (*n*-hexane–EtOAc).

IR (KBr): 3038 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.56 (d, *J* = 8.0 Hz, 1 H, H-10), 9.30 (s, 1 H, H-2), 8.84 (s, 1 H, H-5), 8.80 (d, *J* = 4.5 Hz, 1 H, H-8), 8.73–8.29 (br, 2 H, OH), 7.60 (dd, *J* = 4.5, 8.0 Hz, 1 H, H-9), 3.90 (br s, 2 H, CH_2), 2.35 (s, 6 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 148.6, 146.0, 145.7, 134.9, 133.3 (q, J_{CF} = 31.4 Hz), 132.4, 131.5, 128.0, 126.7, 124.3 (q, J_{CF} = 279.2 Hz), 123.3 (q, J_{CF} = 290.5 Hz), 122.2, 120.9, 95.5 (q, J_{CF} = 32.7 Hz), 59.0, 45.6.

Anal. Calcd for $C_{18}H_{13}F_6N_3O$ (401.1) (non-monohydrate form): C, 53.87; H, 3.27; N, 10.47. Found: C, 53.65; H, 3.45; N, 10.51.

1-{3-[(Diethylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (10b)

Mp 125–126 °C (*n*-hexane–EtOAc).

IR (KBr): 3151 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.52 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.40–9.23 (m, 3 H, H-2, OH), 8.93 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.75 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.73 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 3.97 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 2.55 (q, *J* = 7.0 Hz, 4 H, NCH_2CH_3), 1.03 (t, *J* = 7.0 Hz, 6 H, CH_3).

Anal. Calcd for $C_{20}H_{19}F_6N_3O_2$ (447.1): C, 53.69; H, 4.28; N, 9.39. Found: C, 53.76; H, 4.67; N, 9.03.

2,2,2-Trifluoro-1-[3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]ethane-1,1-diol (10c)

Mp 138–139 °C (*n*-hexane–EtOAc).

IR (KBr): 3354 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.73 (dd, *J* = 2.0, 8.5 Hz, 1 H, H-10), 9.40 (s, 1 H, H-2), 8.96 (dd, *J* = 2.0, 4.5 Hz, 1 H, H-8), 8.91 (s, 1 H, H-5), 7.84–7.58 (br, 2 H, OH), 7.76 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 4.12 (br s, 2 H, CH_2), 2.63 (br s, 4 H, NCH_2CH_2), 1.87–1.81 (m, 4 H, NCH_2CH_2).

Anal. Calcd for $C_{20}H_{17}F_6N_3O_2$ (445.1): C, 53.94; H, 3.85; N, 9.44. Found: C, 53.97; H, 3.99; N, 9.26.

2,2,2-Trifluoro-1-[3-(piperidin-1-ylmethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]ethane-1,1-diol (10d)

Mp 135–136 °C (*n*-hexane–EtOAc).

IR (KBr): 3164 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.35 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.20 (br s, 2 H, OH), 9.00 (s, 1 H, H-2), 8.82 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.62 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.62 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 3.75 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 2.48–2.17 (br, 4 H, NCH_2CH_2), 1.43 (br s, 6 H, $NCH_2CH_2CH_2CH_2$).

Anal. Calcd for $C_{21}H_{17}F_6N_3O$ (441.1) (non-monohydrate form): C, 57.15; H, 3.88; N, 9.52. Found: C, 57.54; H, 3.64; N, 9.37.

2,2,2-Trifluoro-1-{3-[(isopropylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (10e)

Mp 122–123 °C (*n*-hexane–EtOAc).

IR (KBr): 3287, 3025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (non-monohydrate form) = 9.37 (d, *J* = 8.0 Hz, 1 H, H-10), 9.14 (s, 1 H, H-2), 8.97–8.44 (br, 1 H, NH), 8.92 (d, *J* = 4.5 Hz, 1 H, H-8), 8.68 (s, 1 H, H-5), 7.66 (dd, *J* = 4.5, 8.0 Hz, 1 H, H-9), 4.19 (br s, 2 H, CH_2), 3.01 (hp, *J* = 6.5 Hz, 1 H, CH), 1.23 (d, *J* = 6.5 Hz, 6 H, CH_3).

Anal. Calcd for $C_{19}H_{17}F_6N_3O_2$ (433.1): C, 52.66; H, 3.95; N, 9.70. Found: C, 52.61; H, 3.91; N, 9.84.

1-{3-[(*tert*-Butylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (10f)

Mp 140–141 °C (*n*-hexane–EtOAc).

IR (KBr): 3287, 3027 cm^{-1}.

^1H NMR (500 MHz, CD_3CN–$CDCl_3$): δ (non-monohydrate form) = 9.61 (dd, *J* = 1.5, 8.5 Hz, 1 H, H-10), 9.32 (s, 1 H, H-2), 9.04 (dd, *J* = 1.5, 4.5 Hz, 1 H, H-8), 8.90–8.31 (br, 1 H, NH), 8.75 (s, 1 H, H-5), 7.86 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 4.18 (br s, 2 H, CH_2), 1.21 (s, 9 H, CH_3).

Anal. Calcd for $C_{20}H_{17}F_6N_3O$ (429.1) (non-monohydrate form): C, 53.69; H, 4.28; N, 9.39. Found: C, 53.72; H, 4.38; N, 9.26.

1-{3-[(Benzylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (10g)

Mp 207–208 °C (dec.) (*n*-hexane–EtOAc).

IR (KBr): 3348, 3099 cm^{-1}.

^1H NMR (60 MHz, CD_3CN–$CDCl_3$): δ = 8.90 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 8.78 (s, 1 H, H-2), 8.53 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.40 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.43–6.97 (m, 6 H, H-9, Ph), 6.47–5.82 (br, 3 H, NH, OH), 4.02 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 3.78 (br s, 2 H, NCH_2Ph).

Anal. Calcd for $C_{23}H_{17}F_6N_3O_2$ (463.1): C, 57.39; H, 3.56; N, 8.73. Found: C, 57.33; H, 3.79; N, 8.56.

2,2,2-Trifluoro-1-(3-{[(4-methoxyphenyl)amino]methyl}-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl)ethane-1,1-diol (10h)

Mp 95–96 °C (*n*-hexane–EtOAc).

IR (KBr): 3312, 3060 cm^{-1}.

^1H NMR (60 MHz, CD_3CN–$CDCl_3$): δ (non-monohydrate form) = 9.13 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 8.95 (s, 1 H, H-2), 8.67–8.57 (m, 2 H, H-5, H-8), 7.40 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 6.52 (br s, 4 H, H_{arom}), 6.02–5.08 (br, 1 H, NH), 4.63 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 3.53 (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{17}F_6N_3O_3$ (497.1): C, 55.54; H, 3.44; N, 8.45. Found: C, 55.45; H, 3.59; N, 8.73.

2,2,2-Trifluoro-1-{3-[(*p*-tolylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (10i)

Mp 58–59 °C (*n*-hexane–EtOAc).

IR (KBr): 3398, 3044 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.58–8.63 (br, 2 H, OH), 9.42 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.06 (s, 1 H, H-2), 8.84 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.70 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.63 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 6.82 (d, *J* = 7.0 Hz, 2 H, H_{arom}), 6.41 (d, *J* = 7.0 Hz, 2 H, H_{arom}), 5.42–5.00 (br, 1 H, NH), 4.74 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 2.09 (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{17}F_6N_3O_2$ (481.1): C, 57.39; H, 3.56; N, 8.73. Found: C, 57.28; H, 3.93; N, 8.47.

2,2,2-Trifluoro-1-{3-[(phenylamino)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (10j)
Mp 124–125 °C (*n*-hexane–EtOAc).

IR (KBr): 3407, 3030 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.17 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.00 (s, 2 H, OH), 8.87 (s, 1 H, H-2), 8.65 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.55 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.43 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 7.03–6.27 (m, 5 H, Ph), 5.52–4.98 (br, 1 H, NH), 4.67 (q, J_{HF} = 2.0 Hz, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{15}F_6N_3O_2$ (467.1): C, 56.54; H, 3.23; N, 8.99. Found: C, 56.83; H, 3.57; N, 8.99.

1-(3-{[(4-Chlorophenyl)amino]methyl}-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (10k)
Mp 105–106 °C (*n*-hexane–EtOAc).

IR (KBr): 3324, 3088 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.75 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 9.62 (s, 2 H, OH), 9.39 (s, 1 H, H-2), 9.18 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 9.03 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.96 (dd, *J* = 4.0, 9.0 Hz, 1 H, H-9), 7.20 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 6.77 (d, *J* = 8.0 Hz, 2 H, H_{arom}), 6.09 (br t, *J* = 6.0 Hz, 1 H, NH), 5.03–4.73 (m, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{14}ClF_6N_3O_2$ (501.1): C, 52.66; H, 2.81; N, 8.37. Found: C, 52.66; H, 3.17; N, 8.01.

Pyridine-Ring Formation Reaction of 9 with Thiols; General Procedure
The appropriate thiol R^3SH (1.20 or 3.00 mmol) and Et_3N (1.20 or 3.00 mmol) were added to a soln of **9** (374 mg, 1.00 mmol) in MeCN (10 mL), and the mixture was stirred at 50 °C for 2–8 h. Evaporation of the solvent in vacuo gave a crude mixture which was subjected to column chromatography (silica gel, *n*-hexane–EtOAc, 8:1 to 2:1) to give the corresponding **11a–h**.

1-{3-[(Ethylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (11a)
Mp 119–120 °C (*n*-hexane–EtOAc).

IR (KBr): 3317 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.48 (d, *J* = 8.0 Hz, 1 H, H-10), 9.07 (s, 1 H, H-2), 8.97–7.82 (br, 2 H, OH), 8.79 (s, 1 H, H-5), 8.76 (d, *J* = 4.0 Hz, 1 H, H-8), 7.56 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 4.18 (br s, 2 H, CH_2), 2.64 (q, *J* = 7.5 Hz, 2 H, SCH_2CH_3), 1.33 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 148.6, 145.8, 145.5, 134.8, 132.7, 133.4 (q, J_{CF} = 30.2 Hz), 131.7, 127.8, 126.6, 124.2 (q, J_{CF} = 278.0 Hz), 123.2 (q, J_{CF} = 289.3 Hz), 122.3, 121.0, 95.6 (q, J_{CF} = 34.0 Hz), 32.1, 26.5, 14.4.

Anal. Calcd for $C_{18}H_{14}F_6N_2O_2S$ (436.1): C, 49.54; H, 3.23; N, 6.42. Found: C, 49.24; H, 3.25; N, 6.71.

1-{3-[(Butylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (11b)
Mp 115–116 °C (*n*-hexane–EtOAc).

IR (KBr): 3357 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.93–8.83 (br, 2 H, OH), 9.64 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 9.15–9.05 (m, 2 H, H-2, H-8), 8.92 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.85 (dd, *J* = 4.0, 9.0 Hz, 1 H, H-9), 4.20 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 2.62 (br t, *J* = 7.0 Hz, 2 H, SCH_2CH_2), 1.72–0.75 (m, 7 H, $SCH_2CH_2CH_2CH_3$).

Anal. Calcd for $C_{20}H_{18}F_6N_2O_2S$ (464.1): C, 51.72; H, 3.91; N, 6.03. Found: C, 51.36; H, 4.01; N, 6.08.

1-{3-[(*tert*-Butylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (11c)
Mp 136–137 °C (*n*-hexane–EtOAc).

IR (KBr): 3315 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.71 (d, *J* = 8.0 Hz, 1 H, H-10), 9.19 (s, 1 H, H-2), 9.05 (d, *J* = 4.5 Hz, 1 H, H-8), 8.78 (s, 1 H, H-5), 8.43 (br s, 2 H, OH), 7.89 (dd, *J* = 4.5, 8.0 Hz, 1 H, H-9), 4.24 (br s, 2 H, CH_2), 1.42 (s, 9 H, CH_3).

Anal. Calcd for $C_{20}H_{18}F_6N_2O_2S$ (464.1): C, 51.72; H, 3.91; N, 6.03. Found: C, 51.77; H, 4.00; N, 6.03.

1-{3-[(Benzylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (11d)
Mp 120–121 °C (*n*-hexane–EtOAc).

IR (KBr): 3354 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.68 (dd, *J* = 2.0, 8.5 Hz, 1 H, H-10), 9.05 (dd, *J* = 2.0, 4.5 Hz, 1 H, H-8), 8.99 (s, 1 H, H-2), 8.75 (s, 1 H, H-5), 8.45 (br s, 2 H, OH), 7.88 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 7.30 (d, *J* = 7.0 Hz, 2 H, H_{arom}), 7.23 (t, *J* = 7.0 Hz, 2 H, H_{arom}), 7.14 (t, *J* = 7.0 Hz, 1 H, H_{arom}), 4.16 (br s, 2 H, CH_2), 3.84 (s, 2 H, SCH_2Ph).

Anal. Calcd for $C_{23}H_{16}F_6N_2O_2S$ (498.1): C, 55.42; H, 3.24; N, 5.62. Found: C, 55.60; H, 3.20; N, 5.47.

2,2,2-Trifluoro-1-(3-{[(4-methoxyphenyl)sulfanyl]methyl}-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl)ethane-1,1-diol (11e)
Mp 122–123 °C (*n*-hexane–EtOAc).

IR (KBr): 3357 cm^{-1}.

^1H NMR (60 MHz, CD_3CN–$CDCl_3$): δ = 9.43 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.00 (br s, 2 H, OH), 8.83 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.66 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 8.52 (s, 1 H, H-2), 7.63 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 7.13 (d, *J* = 9.0 Hz, 2 H, H_{arom}), 6.65 (d, *J* = 9.0 Hz, 2 H, H_{arom}), 4.32 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 3.67 (s, 3 H, OCH_3).

Anal. Calcd for $C_{23}H_{16}F_6N_2O_3S$ (514.1): C, 53.70; H, 3.13; N, 5.45. Found: C, 53.77; H, 3.31; N, 5.21.

2,2,2-Trifluoro-1-{3-[(*p*-tolylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (11f)
Mp 135–136 °C (*n*-hexane–EtOAc).

IR (KBr): 3354 cm^{-1}.

^1H NMR (60 MHz, CD_3CN–$CDCl_3$): δ = 9.77 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 9.38–7.88 (br, 2 H, OH), 9.12 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 9.00–8.87 (m, 2 H, H-2, H-5), 7.88 (dd, *J* = 5.0, 9.0 Hz, 1 H, H-9), 7.45–7.12 (m, 4 H, H_{arom}), 4.55 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 2.33 (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{16}F_6N_2O_2S$ (498.1): C, 55.42; H, 3.24; N, 5.62. Found: C, 55.02; H, 3.32; N, 5.93.

2,2,2-Trifluoro-1-{3-[(phenylsulfanyl)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (11g)
Mp 134–135 °C (*n*-hexane–EtOAc).

IR (KBr): 3328 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.64 (d, *J* = 8.5 Hz, 1 H, H-10), 8.94 (d, *J* = 4.0 Hz, 1 H, H-8), 8.86 (s, 1 H, H-5), 8.81 (s, 1 H, H-2), 7.81–7.58 (br, 2 H, OH), 7.73 (dd, *J* = 4.0, 8.5 Hz, 1 H, H-9), 7.36–7.29 (m, 5 H, H_{arom}), 4.50 (br s, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{14}F_6N_2O_2S$ (484.1): C, 54.55; H, 2.91; N, 5.78. Found: C, 54.33; H, 3.16; N, 5.84.

1-(3-{[(4-Chlorophenyl)sulfanyl]methyl}-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl)-2,2,2-trifluoroethane-1,1-diol (11h)
Mp 126–127 °C (*n*-hexane–EtOAc).

IR (KBr): 3362 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ (non-monohydrate form) = 9.40 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 8.92 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.77–8.60 (m, 2 H, H-2, H-5), 7.71 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 7.20 (s, 4 H, H_{arom}), 4.52 (q, J_{HF} = 2.0 Hz, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{13}ClF_6N_2O_2S$ (518.0): C, 50.93; H, 2.53; N, 5.40. Found: C, 50.63; H, 2.69; N, 5.54.

Pyridine-Ring Formation Reaction of 9 with Alcohols; General Procedure
Compound **9** (374 mg, 1.00 mmol) was added to a soln of alcohol R^4OH (10 mL) containing Na (1.20 or 3.00 mmol), and the mixture was stirred at 50 °C for 1–8 h. The mixture was washed with 1.0 N aq HCl (20 mL), extracted with EtOAc (80 mL), and 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, 13:1 to 2:1); this gave the corresponding **12a**–**c**,**e**,**f**.

2,2,2-Trifluoro-1-[3-(methoxymethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]ethane-1,1-diol (12a)
Mp 113–114 °C (*n*-hexane–EtOAc).

IR (KBr): 3239 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.45–8.50 (br, 2 H, OH), 9.27 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.01 (s, 1 H, H-2), 8.82 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 8.63 (br s, 1 H, H-5), 7.57 (dd, *J* = 5.0, 8.0 Hz, 1 H, H-9), 4.78 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 3.50 (s, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{10}F_6N_2O_2$ (388.1) (non-monohydrate form): C, 52.59; H, 2.60; N, 7.22. Found: C, 52.24; H, 3.00; N, 7.17.

1-[3-(Ethoxymethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]-2,2,2-trifluoroethane-1,1-diol (12b)
Mp 178–179 °C (dec.) (EtOAc).

IR (KBr): 3324 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.38 (d, 1 H, *J* = 8.0 Hz, H-10), 9.31 (s, 1 H, H-2), 9.23–7.86 (br, 2 H, OH), 8.71 (br s, 2 H, H-8, H-5), 7.48 (dd, 1 H, *J* = 4.0, 8.0 Hz, H-9), 4.95 (br s, 2 H, CH_2), 3.75 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 1.38 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.7, 148.5, 145.8, 145.8, 134.8, 132.0 (q, J_{CF} = 30.2 Hz), 131.8, 131.6, 127.6, 126.5, 124.2 (q, J_{CF} = 278.0 Hz), 123.2 (q, J_{CF} = 289.3 Hz), 122.2, 120.4, 95.6 (q, J_{CF} = 34.0 Hz), 68.1, 67.2, 15.1.

Anal. Calcd for $C_{18}H_{12}F_6N_2O_2$ (402.1) (non-monohydrate form): C, 53.74; H, 3.01; N, 6.96. Found: C, 53.38; H, 3.04; N, 7.29.

1-[3-(Butoxymethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]-2,2,2-trifluoroethane-1,1-diol (12c)
Mp 109–110 °C (*n*-hexane–EtOAc).

IR (KBr): 3328 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6–CD_3CN): δ = 9.73 (dd, *J* = 2.0, 9.0 Hz, 1 H, H-10), 9.50 (s, 2 H, OH), 9.43 (s, 1 H, H-2), 9.18 (dd, *J* = 2.0, 5.0 Hz, 1 H, H-8), 8.98 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 7.93 (dd, *J* = 5.0, 9.0 Hz, 1 H, H-9), 5.02 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 3.68 (t, *J* = 6.0 Hz, 2 H, OCH_2CH_2), 1.78–0.83 (m, 7 H, $OCH_2CH_2CH_2CH_3$).

Anal. Calcd for $C_{20}H_{18}F_6N_2O_3$ (448.1): C, 53.58; H, 4.05; N, 6.25. Found: C, 53.20; H, 3.80; N, 5.87.

1-{3-[(Allyloxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (12e)
Mp 91–92 °C (*n*-hexane–EtOAc).

IR (KBr): 3333 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 8.5 Hz, 1 H, H-10), 9.43 (s, 1 H, H-2), 8.95 (d, *J* = 4.5 Hz, 1 H, H-8), 8.87 (s, 1 H, H-5), 7.88–7.62 (br, 2 H, OH), 7.75 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 6.06–5.98 (m, 1 H, $CH_2CH{=}CH_2$), 5.41 (d, *J* = 17.0 Hz, 1 H, $CH{=}CH_2$), 5.30 (d, *J* = 10.0 Hz, 1 H, $CH{=}CH_2$), 5.00 (br s, 2 H, CH_2), 4.22 (d, *J* = 5.5 Hz, 2 H, $OCH_2CH{=}CH_2$).

Anal. Calcd for $C_{19}H_{14}F_6N_2O_3$ (432.1): C, 52.79; H, 3.26; N, 6.48. Found: C, 53.19; H, 3.01; N, 6.33.

2,2,2-Trifluoro-1-{3-[(prop-2-ynyloxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (12f)
Mp 106–107 °C (*n*-hexane–EtOAc).

IR (KBr): 3311, 2121 cm^{-1}.

^1H NMR (60 MHz, CD_3CN): δ = 9.57 (dd, *J* = 2.0, 8.0 Hz, 1 H, H-10), 9.34 (s, 1 H, H-2), 9.02 (dd, *J* = 2.0, 4.0 Hz, 1 H, H-8), 8.82 (q, J_{HF} = 2.0 Hz, 1 H, H-5), 8.61 (br s, 2 H, OH), 7.80 (dd, *J* = 4.0, 8.0 Hz, 1 H, H-9), 5.08 (q, J_{HF} = 2.0 Hz, 2 H, CH_2), 4.45 (d, *J* = 2.0 Hz, 2 H, $OCH_2C{\equiv}CH$), 2.87 (t, *J* = 2.0 Hz, 1 H, CH).

Anal. Calcd for $C_{19}H_{12}F_6N_2O_3$ (430.1): C, 53.03; H, 2.81; N, 6.51. Found: C, 53.11; H, 3.12; N, 6.11.

Pyridine-Ring Formation Reaction of 9 with Potassium *tert*-Butoxide
Compound **9** (374 mg, 1.00 mmol) was added to a THF soln (10 mL) of *t*-BuOK (112 mg, 1.00 mmol), and the mixture was stirred at 50 °C for 2 h. The mixture was washed with 1.0 N aq HCl (20 mL), extracted with EtOAc (80 mL), and 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, 1:1); this gave **13**; yield: 153 mg (39%).

2,2,2-Trifluoro-1-[3-(hydroxymethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]ethane-1,1-diol (13)
Mp 130–131 °C (*n*-hexane–EtOAc).

IR (KBr): 3384 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.75 (d, *J* = 8.5 Hz, 1 H, H-10), 9.46 (s, 1 H, H-2), 9.06 (d, *J* = 4.5 Hz, 1 H, H-8), 8.80 (s, 1 H, H-5), 8.45 (br s, 2 H, OH), 7.90 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9), 5.10 (br s, 2 H, CH_2), 3.78 (t, *J* = 6.0 Hz, 1 H, CH_2OH).

Anal. Calcd for $C_{16}H_{10}F_6N_2O_3$ (392.1): C, 48.99; H, 2.57; N, 7.14. Found: C, 49.03; H, 2.49; N, 7.18.

Pyridine-Ring Formation Reaction of 9 with Phenols; General Procedure
The appropriate phenol R^4OH (3.00 or 5.00 mmol) and Et_3N (1.50 mmol) were added to a soln of **9** (374 mg, 1.00 mmol) in MeCN (10 mL), and the mixture was stirred at 50 °C for 2 or 24 h. Evaporation of the solvent in vacuo gave a crude mixture which was purified by washing with an *n*-hexane–EtOAc mixture (2:1, 120 mL); this gave the corresponding **12g**–**k**.

2,2,2-Trifluoro-1-{3-[(4-methoxyphenoxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (12g)
Mp 118–119 °C (*n*-hexane–EtOAc).

IR (KBr): 3396 cm^{-1}.

^1H NMR (500 MHz, CD_3CN–$CDCl_3$): δ = 9.74 (d, *J* = 8.5 Hz, 1 H, H-10), 9.40 (s, 1 H, H-2), 9.00 (d, *J* = 4.5 Hz, 1 H, H-8), 8.88 (s, 1 H, H-5), 8.13 (br s, 2 H, OH), 7.81 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-9),

6.98 (d, J = 9.0 Hz, 2 H, H_{arom}), 6.88 (d, J = 9.0 Hz, 2 H, H_{arom}), 5.51 (br s, 2 H, CH_2), 3.78 (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{16}F_6N_2O_4$ (498.1): C, 55.43; H, 3.24; N, 5.62. Found: C, 55.74; H, 2.90; N, 5.66.

2,2,2-Trifluoro-1-{3-[(*p*-tolyloxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (12h)
Mp 111–112 °C (*n*-hexane–EtOAc).

IR (KBr): 3326 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.73 (d, J = 8.0 Hz, 1 H, H-10), 9.41 (s, 1 H, H-2), 9.07 (d, J = 4.5 Hz, 1 H, H-8), 8.82 (s, 1 H, H-5), 8.45 (br s, 2 H, OH), 7.89 (dd, J = 4.5, 8.0 Hz, 1 H, H-9), 7.15 (d, J = 8.5 Hz, 2 H, H_{arom}), 6.97 (d, J = 8.5 Hz, 2 H, H_{arom}), 5.54 (br s, 2 H, CH_2), 2.28 (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{16}F_6N_2O_3$ (482.1): C, 57.27; H, 3.34; N, 5.81. Found: C, 57.27; H, 3.73; N, 5.93.

2,2,2-Trifluoro-1-[3-(phenoxymethyl)-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl]ethane-1,1-diol (12i)
Mp 121–122 °C (*n*-hexane–EtOAc).

IR (KBr): 3313 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.74 (dd, J = 1.5, 8.5 Hz, 1 H, H-10), 9.43 (s, 1 H, H-2), 9.07 (dd, J = 1.5, 4.5 Hz, 1 H, H-8), 8.83 (s, 1 H, H-5), 8.45 (br s, 2 H, OH), 7.90 (dd, J = 4.5, 8.5 Hz, 1 H, H-9), 7.38–7.34 (m, 2 H, H_{arom}), 7.10–7.02 (m, 3 H, H_{arom}), 5.58 (br s, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{14}F_6N_2O_3$ (468.1): C, 56.42; H, 3.01; N, 5.98. Found: C, 56.41; H, 3.35; N, 5.62.

1-{3-[(4-Chlorophenoxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}-2,2,2-trifluoroethane-1,1-diol (12j)
Mp 153–154 °C (EtOAc).

IR (KBr): 3330 cm^{-1}.

^1H NMR (500 MHz, CD_3CN): δ = 9.75 (d, J = 8.5 Hz, 1 H, H-10), 9.41 (s, 1 H, H-2), 9.08 (d, J = 4.5 Hz, 1 H, H-8), 8.83 (s, 1 H, H-5), 8.45 (br s, 2 H, OH), 7.91 (dd, J = 4.5, 8.5 Hz, 1 H, H-9), 7.35 (d, J = 8.5 Hz, 2 H, H_{arom}), 7.08 (d, J = 8.5 Hz, 2 H, H_{arom}), 5.56 (br s, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{13}ClF_6N_2O_3$ (502.1): C, 52.55; H, 2.61; N, 5.57. Found: C, 52.52; H, 2.71; N, 5.56.

2,2,2-Trifluoro-1-{3-[(4-nitrophenoxy)methyl]-4-(trifluoromethyl)-1,7-phenanthrolin-6-yl}ethane-1,1-diol (12k)
Mp 221–222 °C (EtOAc).

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

^1H NMR (500 MHz, $CDCl_3$): δ = 9.77 (d, J = 8.0 Hz, 1 H, H-10), 9.40 (s, 1 H, H-2), 9.03 (d, J = 4.0 Hz, 1 H, H-8), 8.94 (s, 1 H, H-5), 8.29 (d, J = 9.0 Hz, 2 H, H_{arom}), 7.83 (dd, J = 4.0, 8.0 Hz, 1 H, H-9), 7.55 (br s, 2 H, OH), 7.13 (d, J = 9.0 Hz, 2 H, H_{arom}), 5.64 (br s, 2 H, CH_2).

Anal. Calcd for $C_{22}H_{13}F_6N_3O_5$ (513.1): C, 51.47; H, 2.55; N, 8.19. Found: C, 51.07; H, 2.61; N, 7.95.

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