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2,4-Diaryl-5,6-dihydro-1,10-phenanthrolines with Furyl or Thienyl Moiety at 4-Position: Synthesis, Topoisomerase I and II Inhibitory Activity, and Cytotoxicity

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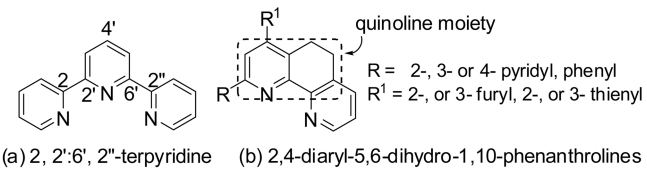
With a goal to discover new anticancer agents, our research group studied various terpyridine derivatives for their topoisomerase (topo) I and II inhibitory activity, and cytotoxicity. Previously, only flexible derivatives were studied for the anticancer activity.[1] To determine the effect of rigid structure on anticancer activity, various rigid analogues of 2,4,6-trisubstituted pyridines were synthesized and evaluated for their topoisomerase I and II inhibitory activity as well as cytotoxicity.[2] In continuation of our previous work,[2c] here we have designed and synthesized various phenanthroline derivatives possessing quinoline core and five membered ring, furyl or thienyl at the 4-position (Figure 1(b)). They were evaluated for their topoisomerase I and II inhibitory activity, and cytotoxicity against several human cancer cell lines.

Phenanthroline derivatives and their metal complexes have been used as intercalating or groove binding agents for DNA and RNA.[3] Some metal complexes are also able to efficiently cleave the DNA backbone, and nowadays the complex $[Cu(phen)_2]^+$ is commonly used in molecular biology as DNA cleaving reagents.[4] Quinoline core present in our synthesized compounds (Figure 1(b)), is in fact one of the important pharmacophores. Many compounds with quinoline core were reported to have wide range of biological activity such as antiviral,[5] antibacterial and antituberculosis,[6] antimalarial,[7] antifungal,[8] and anticancer.[9]

Rigid structures are commonly considered to have little conformational entropy compared to flexible structures, and can be more efficiently fitted into the active site of a receptor.[10] It is reported that planar molecules are able to intercalate into DNA helix and stabilize the topo-DNA covalent cleavage converting topo into a lethal DNA-damaging agent. Anticancer agents such as topotecan (topo I inhibitor) and etoposide (topo II inhibitor) exert their anticancer action by the similar mechanism.[11] In addition, from our previous study, we have observed that [2,2';6',2"]-terpyridine skeleton (Figure 1(a)) has an important role for the cytotoxicity.[1c,2c]



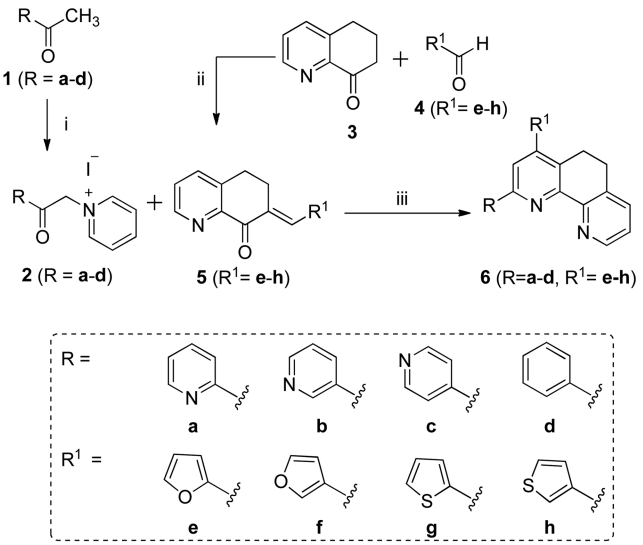
(a) 2, 2':6', 2"-terpyridine (b) 2,4-diaryl-5,6-dihydro-1,10-phenanthrolines

Figure 1. Structure of (a) 2,2':6',2"-terpyridine, and (b) phenanthroline derivatives.

Results and Discussion

Synthetic Chemistry. Pyridinium iodide salts **2** (R=**a-d**) were synthesized by refluxing aryl methyl ketones **1**(R=**a-d**) with iodine and pyridine at 140 °C for 3 h in 64.2-99.4% yields. Starting material 6,7-dihydro-5*H*-quinolin-8-one (**3**) was prepared according to previously reported method.[12] On the basis of Claisen-schmidt KOH catalyzed condensation reaction,[13] 6,7-dihydroquinolin-8(5*H*)-one derivatives **5** (R^1=**e-h**) were synthesized as illustrated in Scheme 1. Compound **3** was reacted with appropriate aryl aldehydes **4** (R^1=**e-h**) in the presence of KOH using a solution of methanol and water at 0 °C for 2.5-3 h to obtain **5** (R^1=**e-h**) in 78.2-90.4% yield as light yellow solids.

Finally, on the basis of modified Kröhnke synthesis,[14] rigid analogues of 2,4,6-trisubstituted pyridine **6** (R=**a-d**, R^1=**e-h**) were synthesized by reacting 6,7-dihydroquinolin-8(5*H*)-one derivatives **5** (R^1=**e-h**) and pyridinium iodide salts **2** (R=**a-d**) in the presence of NH_4OAc in MeOH for 12-22 h at 100 °C as illustrated in Scheme 1. Sixteen rigid



Scheme 1. Synthesis of 2,4-diaryl-5,6-dihydro-1,10-phenanthroline, Reagents and conditions; i) I_2, pyridine, 140 °C, 3 h, 64.2-99.4%; ii) KOH (1.2 equiv), MeOH/H_2O (5:1 v/v), 2.5-3 h, 0 °C, 78.2-90.4%; iii) NH_4OAc, MeOH, 12-22 h, 100 °C, 25.3-94.1%.

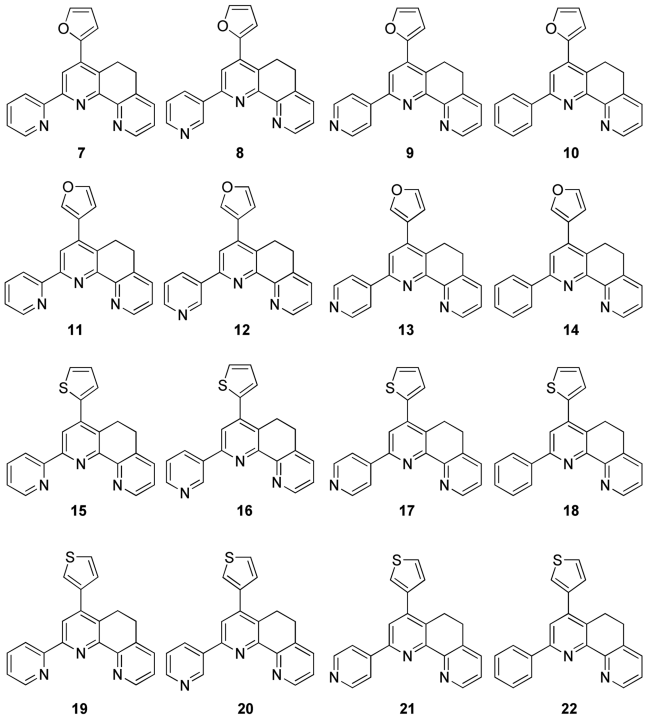


Figure 2. Structure of synthesized 2,4-diaryl-5,6-dihydro-1,10-phenanthrolines.

analogues, 2,4-diaryl-5,6-dihydro-1,10-phenanthrolines (**7-22**), were synthesized in 25.3-94.1% yield as shown in Figure 2.

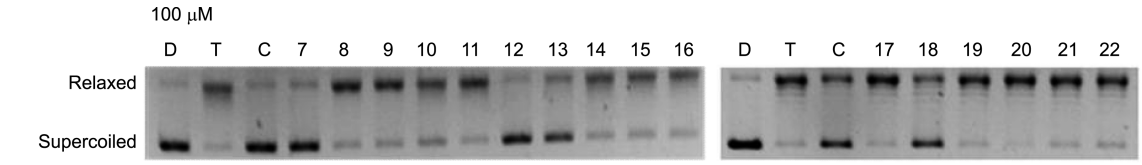
Topo I and II Inhibitory Activity. Synthesized sixteen compounds **7** to **22** were evaluated for their topo I and II inhibitory activities. Topo inhibitory activities of evaluated compounds are displayed in Figure 3, Figure 4, and Table 1. Camptothecin and etoposide, well known topo I and II inhibitors, respectively, were used as positive controls.

All compounds were evaluated for topo I inhibitory activity at 100 μM concentration. It is found that compounds **7** and **12** have shown significant topo I inhibitory activity of 60.9% and 66.5%, respectively at 100 μM, which corresponded 1.25 and 1.36 fold more active than camptothecin, respectively. Compounds **13** and **18** have shown moderate topo I inhibitory activity of 21.4% and 43.5% respectively, as compared to camptothecin (0.44 and 0.63 fold, respectively) at 100 μM. The topo I inhibitory activity of evaluated compounds is summarized in Figure 3, and Table 1.

Most of the tested compounds were devoid of topo II inhibitory activity. Only a few compounds, **8** and **22** has shown very weak inhibitory activity of 12.5% and 10.4%, respectively, at 100 μM. The topo II inhibitory activity of the evaluated compounds is summarized in Figure 4, and Table 1.

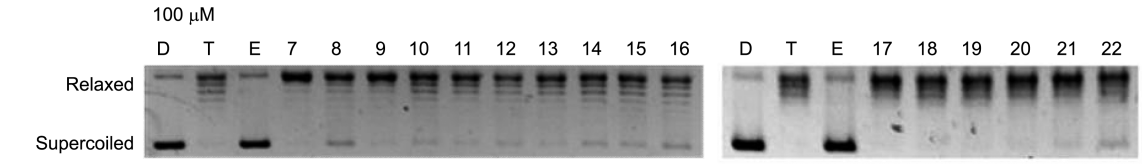
Cytotoxicity. Selected four compounds **7**, **12**, **13**, and **18**, possessing topo I inhibitory activity, were evaluated for cytotoxicity against four different human cancer cell lines: human embryonic kidney cell line (HEK293), human prostate tumor cell line (DU145), human colorectal adenocarcinoma cell line (HCT15), and human breast ductal carcinoma cell line (T47D). Inhibitory activities were presented as micromolar concentrations of the compounds that cause 50% inhibition of cell growth (IC_{50}) under the assay conditions and compared with that of adriamycin. The cytotoxicity results are summarized in Table 2. Among the tested compound, compound **7** has shown the most significant cytotoxicity against all four cancer cell lines. Other three compounds have shown moderate cytotoxicity.

Structure-Activity Relationship (SAR) Study. SAR was performed according to the results of topo I and II inhibitory activity, and cytotoxicity of the evaluated compounds. As



Lane D: pBR322 only,
Lane T: pBR322 + Topo I,
Lane C: pBR322 + Topo I + Camptothecin,
Lane 7-22: pBR322 + Topo I + samples (**7-22**) at 100 μM,

Figure 3. Topo I inhibitory activity of synthesized compounds at 100 μM.



Lane D: pBR322 only,
Lane T: pBR322 + Topo II,
Lane C: pBR322 + Topo II + Etoposide,
Lane 7-22: pBR322 + Topo II + samples (**7-22**) at 100 μM,

Figure 4. Topo II inhibitory activity of synthesized compounds at 100 μM.

Table 1. Topoisomerase I and II inhibitory activity of compounds **7-22**

Compounds	% Inhibition	
	Topo I	Topo II
	100 μM	100 μM
Camptothecin	48.8/69.0*	
E toposide		66.1
7	60.9 (1.25)**	1.4
8	N	12.5
9	0.6	4.6
10	1.4	3.4
11	9.1	N
12	66.5 (1.36)**	0.6
13	21.4 (0.44)**	N
14	N	N
15	3.0	N
16	N	2.6
17	8.1	2.6
18	43.5 (0.63)**	4.0
19	7.0	4.8
20	2.9	6.1
21	4.4	5.7
22	11.4	10.4

*Value for compounds **17-22**. **Relative activity compared to camptothecin. N: no inhibition

Table 2. Cytotoxicity of selected four compounds against four different cancer cell lines

Compounds/ cell	IC_{50} (μM)			
	HEK293	DU145	HCT15	T47D
Adriamycin	2.30±0.95	1.10±0.09	1.05±0.04	1.38±0.19
Etoposide	1.52±0.04	1.21±0.24	1.24±0.20	1.25±0.09
Camptothecin	0.92±0.07	1.06±0.08	0.87±0.03	0.95±0.04
7	4.32±0.17	2.33±0.28	1.92±0.04	1.70±0.38
12	41.73±1.59	46.09±3.08	25.70±2.78	31.65±0.82
13	37.02±3.36	32.68±3.34	24.97±3.76	25.01±4.51
18	40.24±1.54	39.27±7.22	33.82±0.89	44.72±3.64

most of the compounds were devoid of topo I and II inhibitory activity, the concrete correlation of the structure of compounds with topo inhibitory activity could not be determined. However, we observed that several compounds **7**, **12**, **13**, and **18** have shown moderate to significant topo I inhibitory activity which likely suggest the importance of rigid structure for topo I inhibitory activity over topo II inhibitory activity. From the results of cytotoxicity of four tested compounds, it is found that compound **7** with [2,2';6',2"]-terpyridine skeleton has shown the most significant cytotoxic effects. This showed that [2,2';6',2"]-terpyridine skeleton is important for the cytotoxicity against several human cancer cell lines, which further supports the previously reported results.[1c,2c] The inactivity of the compounds, reported here, is believed to be due to the interruption of resonance between five or six membered ring with central pyridine in absence of double bond at 5,6 position as reported in earlier study.[2c,15] This provides a new approach to insert double bond at 5,6 position, which most probably will increase the potency of the compound.

In conclusion, we have designed and synthesized sixteen 2,4-diaryl-5,6-dihydro-1,10-phenanthroline derivatives as rigid analogues of 2,4,6-trisubstituted pyridine, and evaluated their topo I and II inhibitory activity, and cytotoxicity against several human cancer cell lines. Compound **7**, **12**, **13**, and **18** showed moderate to significant topo I inhibitory activity. Compound **12** showed the most significant topo I inhibitory activity of 66.5% as compared to camptothecin (48.8%). It is found that compound **7**, having [2,2';6',2"]-terpyridine skeleton has shown the most significant cytotoxicity against all the tested human cancer cell lines.

Experimental Section

Compounds used as starting materials and reagents were obtained from Aldrich Chemicals Co., Junsei or other chemical companies, and utilized without further purification. HPLC grade acetonitrile (ACN) and methanol were purchased from Burdick and Jackson, USA. Thin-layer chromatography (TLC) and column chromatography (CC) were performed with Kieselgel 60 F_{254} (Merck) and silica gel (Kieselgel 60, 230-400 mesh, Merck), respectively. NMR spectra were recorded on a Bruker AMX 250 (250 MHz, FT) for ^{1}H NMR and 62.5 MHz for ^{13}C NMR, and chemical shifts were calibrated to solvent peaks. Chemical shifts (δ) were recorded in ppm and coupling constants (J) in hertz (Hz). Melting points were determined in open capillary tubes on electrothermal 1A 9100 digital melting point apparatus and were uncorrected.

HPLC analyses were performed using previously reported method.[2c] Purity of compound is described as percent (%) and retention time is given in minutes. ESI MS analyses were performed with API 4000 LC-MS/MS system (Applied Biosystems, Foster City, CA, USA) equipped with an electrospray ionization interface. The Turbolon Spray (Applied Biosystems, Foster City, CA, USA) interface was operated in the positive ion mode at 5500 V and 450 °C.

4-(Furan-2-yl)-2-(pyridin-2-yl)-5,6-dihydro-1,10-phenanthroline (7): White solid (74.4%), TLC (EtOAc/*n*-hexane 1:2 v/v, alumina), R_f = 0.19, mp 185.2-186.5 °C, HPLC: purity: 96.8%, retention time: 11.10 min, ESI MS: $[MH]^+$: 326.6, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.66-8.59 (m, 3H, 2-pyridine H-3, H-6, phenanthroline H-9), 8.58 (s, 1H, phenanthroline H-3), 7.73 (td, J = 7.70, 1.83 Hz, 1H, 2-pyridine H-4), 7.50 (d, J = 1.25 Hz, 1H, 4-furan H-5), 7.46 (dd, J = 7.56, 1.48 Hz, 1H, phenanthroline H-7), 7.21 (ddd, J = 7.40, 4.82, 1.11 Hz, 1H, 2-pyridine H-5), 7.15 (dd, J = 7.56, 4.79 Hz, 1H, phenanthroline H-8), 6.68 (d, J = 3.32 Hz, 1H, 4-furan H-3), 6.45 (dd, J = 3.40, 1.80 Hz, 1H, 4-furan H-4), 3.15 (t, J = 7.79 Hz, 2H, 5-CH_2), 2.88 (t, J = 7.72 Hz, 2H, 6-CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.80, 154.62, 151.99, 151.87, 150.84, 148.77, 148.75, 143.29, 137.50, 136.71, 135.32, 133.52, 129.77, 123.55, 123.40, 121.76, 118.49, 111.77, 111.64, 27.13, 24.86.

4-(Furan-3-yl)-2-(pyridin-3-yl)-5,6-dihydro-1,10-phenanthroline (12): White solid (83.9%), TLC (methanol/

dichloromethane 1:15 v/v, silica), R_f = 0.27, mp 220.1-221.3 °C, HPLC: purity: 100.0%, retention time: 9.46 min, ESI MS: $[MH]^+$: 326.9, ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.23 (d, *J* = 1.97 Hz, 1H, 2-pyridine H-2), 8.74 (d, *J* = 3.58 Hz, 1H, phenanthroline H-9), 8.61 (dd, *J* = 4.69, 1.27 Hz, 1H, 2-pyridine H-6), 8.52 (dt, *J* = 7.94, 1.70 Hz, 1H, 2-pyridine H-4), 7.69 (s, 1H, phenanthroline H-3), 7.65 (s, 1H, 4-furan H-2), 7.57-7.55 (m, 2H, 4-furan H-5, phenanthroline H-7), 7.39 (dd, *J* = 7.91, 4.80 Hz, 1H, 2-pyridine H-5), 7.24 (dd, *J* = 7.34, 4.79 Hz, 1H, phenanthroline H-8), 6.63 (d, *J* = 0.75 Hz, 1H, furan H-4), 3.10 (t, *J* = 7.72 Hz, 2H, 5-CH_2), 2.93 (t, *J* = 7.63 Hz, 2H, 6-CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.59, 152.66, 151.90, 149.65, 149.07, 148.16, 143.52, 141.18, 140.69, 135.55, 135.06, 135.03, 133.76, 130.81, 123.67, 123.53, 123.05, 120.87, 110.94, 27.38, 24.82.

4-(Furan-3-yl)-2-(pyridin-4-yl)-5,6-dihydro-1,10-phenanthroline (13): White solid (25.3%), TLC (methanol/dichloromethane 1:15 v/v, silica), R_f = 0.27, mp 253.0-253.7 °C, HPLC: purity: 100.0%, retention time: 9.46 min, ESI MS: $[MH]^+$: 326.8, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.69, 1.43 Hz, 1H, phenanthroline H-9), 8.70 (dd, *J* = 6.12, 1.56 Hz, 2H, 2-pyridine H-2, H-6), 8.02 (dd, *J* = 6.13, 1.57 Hz, 2H, 2-pyridine H-3, H-5), 7.74 (s, 1H, phenanthroline H-3), 7.66 (s, 1H, 4-furan H-2), 7.58-7.57 (m, 2H, phenanthroline H-7, 4-furan H-5), 7.27 (dd, *J* = 7.59, 4.77 Hz, 1H, phenanthroline H-8), 6.64 (d, *J* = 0.89 Hz, 1H, 4-furan H-4), 3.12 (t, *J* = 7.82 Hz, 2H, 5-CH_2), 2.94 (t, *J* = 7.69 Hz, 2H, 6-CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.42, 152.76, 151.83, 150.27, 149.19, 146.39, 143.60, 141.22, 140.81, 135.57, 133.79, 131.84, 123.78, 123.01, 121.43, 121.08, 110.93, 27.35, 24.94.

2-Phenyl-4-(thiophen-2-yl)-5,6-dihydro-1,10-phenanthroline (18): White solid (88.5%), TLC (ethyl acetate/*n*-hexane 15:1 v/v, silica), R_f = 0.42, mp 242.5-243.1 °C, HPLC: purity: 97.2%, retention time: 13.42 min, ESI MS: $[MH]^+$: 341.9, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.74, 1.49 Hz, 1H, phenanthroline H-9), 8.14 (d, *J* = 6.81 Hz, 2H, 2-phenyl H-2, H-6), 7.77 (s, 1H, phenanthroline H-3), 7.55 (dd, *J* = 7.56, 1.32 Hz, 1H, phenanthroline H-7), 7.49-7.35 (m, 4H, 2-phenyl H-3, H-4, H-5, 4-thiophene H-5), 7.23 (dd, *J* = 7.54, 4.96 Hz, 1H, phenanthroline H-8), 7.19-7.14 (m, 2H, 4-thiophene H-3, H-4), 3.15 (t, *J* = 7.90 Hz, 2H, 5-CH_2), 2.93 (t, *J* = 7.79 Hz, 2H, 6-CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.19, 152.49, 152.28, 149.10, 141.98, 139.79, 139.19, 135.38, 133.74, 130.03, 128.82, 128.56, 128.05, 127.61, 127.28, 126.87, 123.48, 121.71, 27.57, 24.94.

Pharmacology. DNA topo I and II inhibition assays were determined following the previously reported method.[2c] Cytotoxicity was determined in four different cancer cell lines: human embryonic kidney cell line (HEK293), human prostate tumor cell line (DU145), human colorectal adenocarcinoma cell line (HCT15) and human breast ductal carcinoma cell line (T47D) by following the previously reported method.[2c]

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