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Synthesis of 2,4,6-Tripyridyl Pyridines, and Evaluation of Their Antitumor Cytotoxicity, Topoisomerase I and II Inhibitory Activity, and Structure-activity Relationship

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A series of 2,4,6-tripyridyl pyridines were synthesized, and evaluated for their antitumor cytotoxicity, topoisomerase I and II inhibitory activity. From the eighteen prepared compounds, compounds **10**-**12** have shown better or similar cytotoxicity against several human cancer cell lines as compared to 2,2':6',2"-terpyridine and doxorubicin. Especially, compound **10** exhibited the most potent cytotoxicity better than positive controls. Structure-activity relationship study indicated that 2,2':6',2"-terpyridine skeleton has an important role in displaying significant cytotoxicity against several human cancer cell lines.

Key Words : Terpyridine, 2,4,6-Tripyridyl pyridine, Topoisomerase inhibition, Cytotoxicity, SAR study

Introduction

In the past several years, our research group has been studying terpyridine derivatives for their topoisomerase inhibitory activity and cytotoxicity against several human cancer cell lines for the development of novel anticancer agents. As a result, it has been reported that various terpyridine derivatives, as bioisosteres of α-terthiophene (potent protein kinase C inhibitor),[1] has significant topoisomerase I and/or II inhibitory activity, and cytotoxicity against several human cancer cell lines.[2] Early reports on ability of α-terpyridine to form metal complex[3] and to bind with DNA/RNA[4] has been the base for the study on terpyridine derivatives as antitumor agents. Topoisomerases help in unwinding of DNA thereby releasing the torsional stress induced during various cellular processes such as DNA replication, transcription, recombination, repair, and chromatin assembly.[5] Inhibition of these enzymes has been one of the strategies to treat cancer.[6]

From our previous studies involving terpyridines or 4-aryl-2,6-dipyridyl pyridines, where hydrogen on 4'-position of terpyridine was replaced with various aryl moieties (phenyl, 2- or 3-thienyl, 2- or 3-furyl), it has been found that 2,2':6',2"-terpyridine skeleton has an important role in displaying significant cytotoxicity against several human cancer cell lines,[2a,c] as well as 2,2':6',3"- and 2,2':6',4"-terpyridine skeleton showed potent topoisomerase I inhibitory activity[2a] (Figure 1). In connection with the previous study, a series of 2,4,6-tripyridyl pyridine derivatives, where hydrogen on 4'-position of terpyridine was replaced with 2-, 3- or 4-pyridyl moiety, were synthesized, and evaluated for their topoisomerase inhibitory activity, and cytotoxicity against several human tumor cell lines for the purpose of development of novel antitumor agents. In addition, it would be interesting to investigate the role of terpyridine skeleton for cytotoxicity and/or topoisomerase inhibitory activity. It was observed that 2,2':6',2"-terpyridine skeleton was responsible for displaying significant cytotoxicity, and 2,2':6',3"- or 2,2':6',4"-terpyridine skeleton responsible for topoisomerase I inhibitory activity on the studies for 4-aryl-2,6-dipyridyl pyridines.[2a] We were very interested in whether the same prediction would be applied for the study of 2,4,6-tripyridyl pyridines. Total of the eighteen compounds were prepared, and structure-activity relationship study was also performed.

Experimental Section

Compounds used as starting materials and reagents were obtained from Aldrich Chemicals Co., Junsei, Fluka and used without further purification. HPLC grade acetonitrile

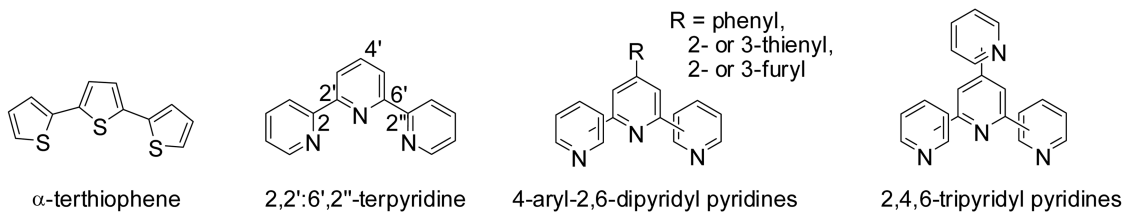


Figure 1. Structure of α-terthiophene, α-terpyridine (2,2':6',2"-terpyridine), 4-aryl-2,6-dipyridyl pyridines, and 2,4,6-tripyridyl pyridines.

(ACN) was purchased from Burdick and Jackson, USA. Thin-layer chromatography (TLC) and column chromatography were performed with Kieselgel 60 F_{254} (Merck) and silica gel (Kieselgel 60, 230-400 mesh, Merck) respectively. Since all the compounds prepared contain aromatic ring, they were visualized and detected on TLC plates with UV light (short wave, long wave or both). 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 TMS (tetramethylsilane). 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 two Shimadzu LC-10AT pumps gradient-controlled HPLC system equipped with Shimadzu system controller (SCL-10A VP) and photo diode array detector (SPD-M10A VP) utilizing Shimadzu Class VP program. Sample volume of 10 μL was injected in Waters X- Terra® 5 μM reverse-phase C_{18} column (4.6 250 mm) with a gradient elution of 60% to 100% of B in A for 15 min followed by 100% to 60% of B in A for 15 min at a flow rate of 1.0 mL/min at 254 nm UV detection, where mobile phase A was double distilled water with 20 mM ammonium formate (AF) and B was 90% ACN in water with 20 mM AF. Purity of compound is described as percent (%).

ESI LC/MS analyses were performed with a Finnigan LCQ Advantage® LC/MS/MS spectrometry utilizing Xcalibur® program. For ESI LC/MS, LC was performed with a 5 μL injection volume on a Waters X Terra® 3.5 μm reverse-phase C_{18} column (2.1 × 100 mm) with a gradient elution from 10% to 90% of B in A for 10 min followed by 90% to 10% of B in A for 15 min at a flow rate of 200 μL/min, where mobile phase A was 100% distilled water and mobile phase B was 100% ACN. MS ionization conditions were: Sheath gas flow rate: 70 arb, aux gas flow rate: 20 arb, I spray voltage: 4.5 KV, capillary temp.: 215°C, capillary voltage: 21 V, tube lens offset: 10 V. Retention time was given in minutes.

General Method for the Preparation of 3. Pyridyl ketone (30 mmol) was added to a solution of 85% KOH (1.2 eq) in MeOH/H_2O (5:1) at 0 °C. After complete dissolution, pyridyl aldehyde (30 mmol) was slowly added at 0 °C. The mixture was stirred for 3 h at 0 °C. The precipitate formed was filtered, washed with cold methanol (20 mL), and dried to yield 51.0-74.8% as a solid.

General Method for the Preparation of 4, 5, 6. A mixture of acetyl pyridines (50 mmol), iodine (50 mmol) and pyridine (100 mL) was refluxed at 140 °C for 3 h. The reaction mixture was cooled to room temperature, precipitate formed was filtered, washed with cold pyridine (10 mL), and dried to obtain solid compounds **4**, **5**, and **6** in quantitative yield.

General Method for the Preparation of 7, 8, 9. A mixture of propenone intermediate **3** (2.0 mmol), pyridinium iodide salt **4**, **5**, or **6** (2.0 mmol), and anhydrous ammonium acetate (10.0 mmol) in glacial acetic acid were heated to 100 °C for 16 h. The residue formed was extracted with ethyl acetate (100 mL), and washed with water (60 mL × 3) and saturated NaCl solution (30 mL). The organic layer was dried with magnesium sulfate and filtered. The filtrate was evaporated at reduced pressure, which was then purified by silica gel column chromatography with the gradient elution of ethyl acetate/*n*-hexane to afford solid compounds **7**, **8**, and **9** in 55.2-85.5% yield.

4'-Pyridin-2-yl-[2,2';6',2"]terpyridine (10). A yellowish solid, Yield: 56.9%; mp 238.4-240.8 °C; R_f (ethyl acetate/*n*-hexane 1:5 v/v in Al_2O_3) 0.15; HPLC retention time: 13.55 min, purity: 97.7%;

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.10 (s, 2H, pyridine H-3', H-5'), 8.80 (d, *J* = 4.1 Hz, 1H, 4'-pyridine H-6), 8.74 (d, *J* = 4.1 Hz, 2H, 2'-pyridine H-6, 6'-pyridine H-6"), 8.67 (d, *J* = 8.0 Hz, 2H, 2'-pyridine H-3, 6'-pyridine H-3"), 8.08 (d, *J* = 7.9 Hz, 1H, 4'-pyridine H-3), 7.91-7.80 (m, 3H, 2'-pyridine H-4, 6'-pyridine H-4", 4'-pyridine H-4), 7.37-7.32 (m, 3H, 2'-pyridine H-5, 6'-pyridine H-5", 4'-pyridine H-5); ^{13}C NMR (62.5 MHZ, $CDCl_3$) δ 156.64, 156.58, 155.48, 150.44, 149.60, 149.04, 137.28, 137.24, 124.24, 124.13, 121.72, 121.69, 119.02.

4'-Pyridin-3-yl-[2,2';6',2"]terpyridine (11). A white solid, Yield: 70.2%; mp 207.5-209.7 °C; R_f (methylene chloride/methanol 40:1 v/v in Al_2O_3) 0.45; HPLC retention time: 11.58 min, purity: 97.5%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.14 (dd, *J* = 2.3, 0.5 Hz, 1H, 4'-pyridine H-2), 8.75-8.70 (m, 3H, 2'-pyridine H-6, 6'-pyridine H-6", 4'-pyridine H-6), 8.74 (s, 2H, pyridine H-3', H-5'), 8.67 (d, *J* = 8.0 Hz, 2H, 2'-pyridine H-3, 6'-pyridine H-3"), 8.19 (dt, *J* = 7.9, 1.7 Hz, 1H, 4'-pyridine H-4), 7.91 (td, *J* = 7.7, 1.8 Hz, 2H, 2'-pyridine H-4, 6'-pyridine H-4"), 7.46 (ddd, *J* = 7.9, 4.8, 0.7 Hz, 1H, 4'-pyridine H-5), 7.38 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 2H, 2'-pyridine H-5, 6'-pyridine H-5"); ^{13}C NMR (62.5 MHZ, $CDCl_3$) δ 156.23, 155.84, 150.12, 149.20, 148.43, 147.27, 136.98, 134.70, 134.27, 124.07, 123.66, 121.38, 118.81.

4'-Pyridin-4-yl-[2,2';6',2"]terpyridine (12). A yellowish solid, Yield: 70.1%; mp 223.8-225.4 °C; R_f (methylene chloride/methanol 40:1 v/v in Al_2O_3) 0.44; HPLC retention time: 13.50 min, purity: 99.5%; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.78-8.72 (m, 4H, 2'-pyridine H-6, 6'-pyridine H-6", 4'-pyridine H-2, H-6), 8.77 (s, 2H, pyridine H-3', H-5'), 8.68 (d, *J* = 7.9 Hz, 2H, 2'-pyridine H-3, 6'-pyridine H-3"), 7.90 (td, *J* = 7.7, 1.7 Hz, 2H, 2'-pyridine H-4, 6'-pyridine H-4"), 7.80 (dd, *J* = 4.5, 1.7 Hz, 2H, 4'-pyridine H-3, H-5), 7.38 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 2H, 2'-pyridine H-5, 6'-pyridine H-5"); ^{13}C NMR (62.5 MHZ, $CDCl_3$) δ 156.40, 155.72, 150.58, 149.21, 147.52, 145.96, 136.99, 124.13, 121.70, 121.37, 118.66.

Pharmacology. The topo I inhibitory activity was carried out as following.[7] The prepared compounds were dissolved in DMSO at 20 mM as stock solution. The activity of DNA topo I was determined by assessing the relaxation of supercoiled DNA pBR322. The mixture of 100 ng of plasmid pBR322 DNA and 0.4 units of recombinant human DNA topo I (TopoGEN INC., USA) was incubated without and with the prepared compounds at 37 °C for 30 minutes in the

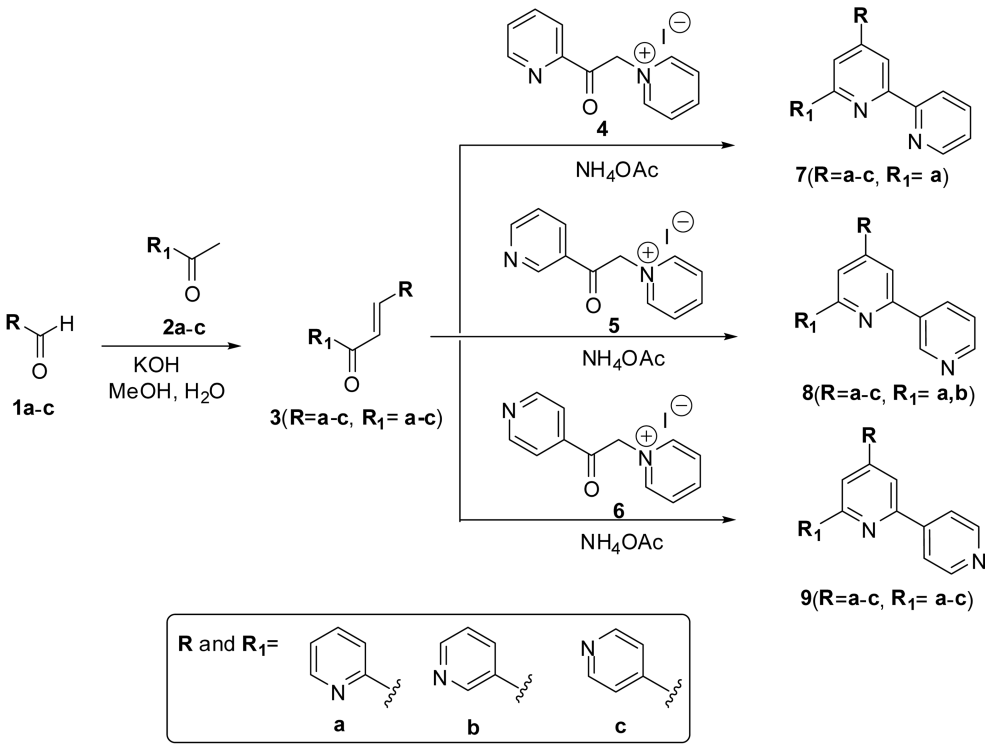
relaxation buffer (10 mM Tris-HCl (pH 7.9), 150 mM NaCl, 0.1% bovine serum albumin, 1 mM spermidine, 5% glycerol). The reaction in the final volume of 10 mL was terminated by adding 2.5 mL of the stop solution containing 5% sarcosyl, 0.0025% bromophenol blue, and 25% glycerol. DNA samples were then electrophoresed on a 1% agarose gel at 15 V for 7 h with a running buffer of TAE. Gels were stained for 30 min in an aqueous solution of ethidium bromide (0.5 μg/mL). DNA bands were visualized by transillumination with UV light and were quantitated using AlphaImager™ (Alpha Innotech Corporation).

DNA topo II inhibitory activity of compounds were measured as follows.[8] The mixture of 200 ng of supercoiled pBR322 plasmid DNA and 1 units of human DNA topo IIα (Amersham, USA) was incubated without and with the prepared compounds in the assay buffer (10 mM Tris-HCl (pH 7.9) containing 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, 1 mM ATP, and 15 μg/mL bovine serum albumin) for 30 min at 30 °C. The reaction in a final volume of 20 μL was terminated by the addition of 3 μL of 7 mM EDTA. Reaction products were analyzed on 1% agarose gel at 25 V for 4 h with a running buffer of TAE. Gels were stained for 30 min in an aqueous solution of ethidium bromide (0.5 μg/mL). DNA bands were visualized by transillumination with UV light and supercoiled DNA was quantitated using AlphaImager™ (Alpha Innotech Corporation).

For the evaluation of cytotoxicity, four different cancer cell lines were used: human lung carcinoma (A-549), human ovary adenocarcinoma (SK-OV-3), human malignant melanoma (SK-MEL-2), and human colon adenocarcinoma cell line (HCT-15). Experiments were performed by methods previously described.[8] Cancer cells were cultured according to the supplier's instructions. Cells were seeded in 96-well plates at a density of 2~4 × 10^4 cells per well and incubated for overnight in 0.1 mL of media supplied with 10% Fetal Bovine Serum (Hyclone, USA) in 5% CO_2 incubator at 37 °C. On day 2, culture medium in each well was exchanged with 0.1 mL aliquots of medium containing graded concentrations of compounds. On day 4, each well was added with 5 mL of the cell counting kit-8 solution (Dojindo, Japan) then incubated for additional 4 h under the same condition. The absorbance of each well was determined by an Automatic Elisa Reader System (Bio-Rad 3550) at 450 nm wavelength. For determination of the IC_{50} values, the absorbance readings at 450 nm were fitted to the four-parameter logistic equation. Doxorubicin, camptothecin, etoposide, and 2,2':6',2"-terpyridine were purchased from Sigma, and used as positive controls.

Results and Discussion

Synthetic Chemistry. Eighteen compounds were synthesized using the synthetic methods as summarized in Scheme 1. Compound **3** (**R**=**a-c**, **R_1**=**a-c**) was synthesized on the basis of KOH catalyzed Claisen Schmidt condensation reaction[9] where pyridyl aldehydes (**1a-c**) were treated with pyridyl ketones (**2a-c**), in the presence of KOH using methanol and water (5:1) as solvents. Nine propenone intermediates **3** (**R**=**a-c**, **R_1**=**a-c**) were synthesized in 51.0-74.8% yield. Compound **4**, **5**, and **6** were synthesized by refluxing 2-, or 3- or 4-acetyl pyridine respectively with I_2 in pyridine at 140 °C for 3 h in quantitative yield. Using modified



Scheme 1. Synthetic route for preparation of 2,4,6-tripyridyl pyridines.

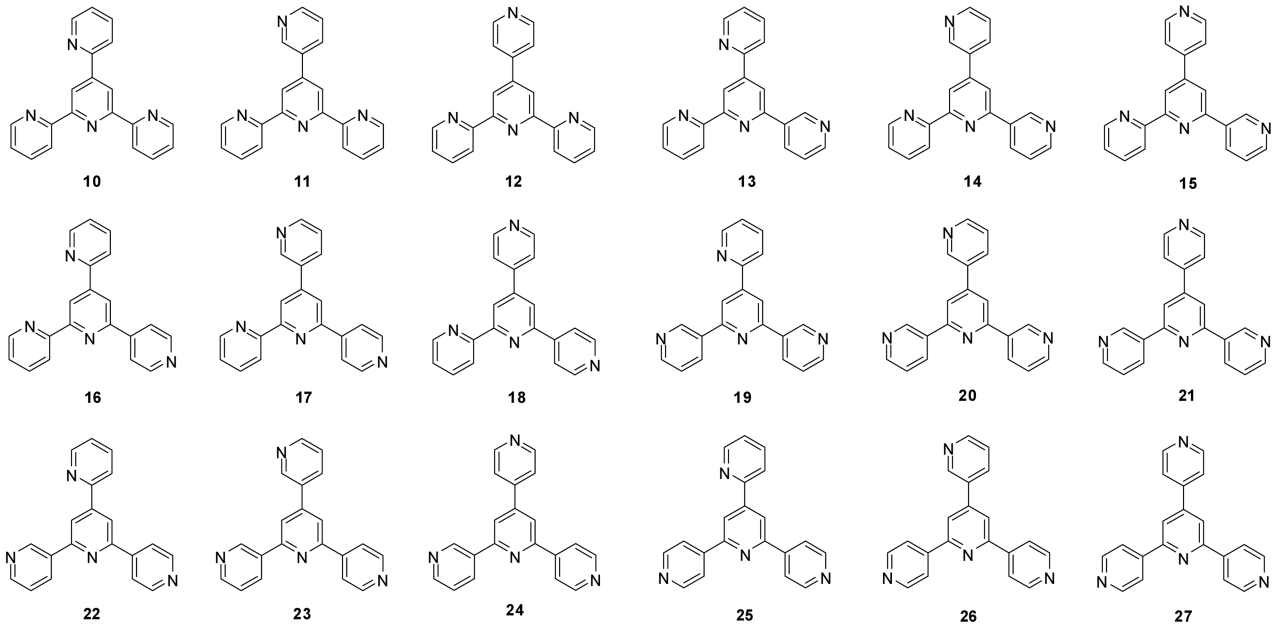


Figure 2. Structures of synthesized 2,4,6-tripyridyl pyridines.

Kröhnke synthesis,[10] eighteen final compounds **7** (**R**=**a-c**, **R**$_1$=**a**), **8** (**R**=**a-c**, **R**$_1$=**a**, **b**), and **9** (**R**=**a-c**, **R**$_1$=**a-c**) were prepared by treating compound **3** (**R**=**a-c**, **R**$_1$=**a-c**) with **4**, **5** or **6** in the presence of ammonium acetate and methanol. For compound **7**, three intermediates **3** (**R**=**a-c**, **R**$_1$=**a**) were treated with **4** to give three final products. For compound **8**, six intermediates **3** (**R**=**a-c**, **R**$_1$=**a**, **b**) were treated with **5** to give six final products. Finally, for compound **9**, nine intermediates **3** (**R**=**a-c**, **R**$_1$=**a-c**) were treated with **6** to give nine final products. Total eighteen final 2,4,6-tripyridyl pyridines were synthesized in 55.2-85.5% yield. The structures of synthesized compounds are as shown in Figure 2.

Pharmacology. The prepared compounds were evaluated for topoisomerase I and II inhibitory activity, and cytotoxicity against several human cancer cell lines following the procedure as described previously.[7,8] For the evaluation of antitumor cytotoxicity, four different human cancer cell lines were used: A-549 (human lung carcinoma), SK-OV-3 (human ovary adenocarcinoma), SK-MEL-2 (human malignant melanoma), and HCT-15 (human colon adenocarcinoma). The IC_{50} value of the evaluated compounds were compared with 2,2':6',2"-terpyridine and doxorubicin as shown in Table 1.

All the prepared compounds were evaluated for topoisomserase I and II inhibitory activities, and cytotoxicities against selected human cancer cell lines. From the results, five compounds showed significant cytotoxicities (**10**, **11**, **12**, **17**, **24**) and three compounds exhibited moderate topoisomerase II inhibitory activity (**15**, **24**, **27**). It has been found that compounds **10-12** have shown better or similar cytotoxicity against all the tested cancer cell lines as compared to 2,2':6',2"-terpyridine and doxorubicin. Especially, compound **10** exhibited the most potent cytotoxicity better than positive controls, doxorubicin and 2,2':6',2"-terpyridine. Similarly, compounds **15**, **17** and **24** have shown the moderate cytotoxicity.

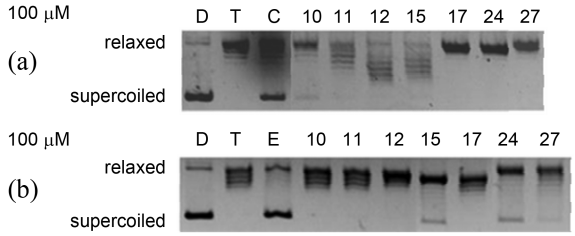
Table 1. Topoisomerase I and II inhibitory activity, and cytotoxicity of the selected 2,4,6-tripyridyl pyridines

Compounds	%Inhibition		IC_{50}[a] (μM)			
	Topo I	Topo II	A-549	SK-OV-3	SK-MEL-2	HCT-15
	100 μM	100 μM				
10	5.8	N	0.02	0.02	0.03	0.03
11	3.6	2.1	0.13	0.03	0.15	0.10
12	6.2	1.8	0.09	0.02	0.11	0.09
15	5.2	10.0	32.62	43.16	59.24	>100
17	N	N	5.81	5.24	12.17	5.36
24	2.8	18.6	9.21	24.73	19.34	32.27
27	3.0	10.6	>100	>100	>100	>100
Terpyridine			0.25	0.08	0.18	0.23
Doxorubicin			0.02	0.09	0.09	0.10
Camptothecin	53.5					
Etoposide		71.7				

[a]Each data represents mean ± SD from three different experiments performed in triplicate. Cell lines used were A-549 (human lung carcinoma), SK-OV-3 (human ovary adenocarcinoma), SK-MEL-2 (human malignant melanoma), and HCT-15 (human colon adenocarcinoma); N: none

Figure 3 and Table 1 shows the topoisomerase I and II inhibitory activity of the selected compounds. It indicates that most of the compounds did not display considerable topoisomerase inhibitory activity. Only few compounds such as **15**, **24** and **27** showed mild topo II inhibitory activity of 10.0, 18.6, and 10.6 %, respectively at 100 μM.

It is interesting to note that all three compounds **10-12** which has shown significant cytotoxicity possess the common 2,2':6',2"-terpyridine skeleton. Therefore, it suggests that linkage between the alpha carbons of terpyridine is



Lane D: pBR322 DNA only
Lane T: pBR322 DNA + Topo I or Topo II
Lane C pBR322 DNA + Topo I + Camptothecin
Lane E: pBR322 DNA + Topo II + Etoposide
Lane **10-27**: pBR322 DNA + Topo I or Topo II + Compound **10-27** at 100 μM

Figure 3. Human DNA topoisomerase I (a) or IIα (b) inhibitory activity of selected compounds.

important for the cytotoxic effects of 2,4,6-tripyridyl pyridine derivatives regardless of 4'-substituents on 2,2':6',2"-terpyridine skeleton. However, most of the prepared compounds did not show significant topoisomerase inhibitory activities. We have been expected strong topoisomerase inhibitory activities for the compounds possessing 2,2':6',3"- or 2,2':6',4"-terpyridine skeleton in accordance with the previous report. Only for the compounds **15**, **24**, and **27** which possess 4-pyridyls at the 2-, 4-, and/or 6-position of the central pyridine showed mild topoismerase II inhibitory activity. This may indicate that 4-pyridyl at 2-, 4-, and/or 6-position of central pyridine would have a role for topo II inhibitory activity of 2,4,6-tripyridyl pyridines.

In conclusion, we have designed and synthesized eighteen 2,4,6-tripyridyl pyridines in an efficient synthetic route. All the compounds were evaluated for their antitumor cytotoxicity, and topoisomerase I and II inhibitory activity. From the structure-activity relationships, it revealed that 2,2':6',2"-terpyridine skeleton is important for the cytotoxicity against several human cancer cell lines which supports the previous results.[2a,c] As most of the compound did not show considerable topoisomerase inhibitory activity, concrete SAR could not be determined in context to topoisomerase inhibitory activity. In addition, there was no direct correlation between antitumor cytotoxicity and topoisomerase inhibitory activity. This study may provide valuable information for the researchers working in the field of development of new anticancer agents, especially those targeting topoisomerase.

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References and Notes

1. (a) Kim, D. S. H. L.; Ashendel, C. L.; Zhou, Q.; Chang, C.-T.; Lee E.-S.; Chang, C.-J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2695. (b) Xu, W.-C.; Zhou, Q.; Ashendel, C. L.; Chang, C.-T.; Chang, C.-J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2279.
2. (a) Zhao, L. X.; Kim, T. S.; Ahn, S. H.; Kim, T. H.; Kim, E. K.; Cho, W. J.; Choi, H. S.; Lee, C. S.; Kim, J. A.; Jeong, T. C.; Chang, C.-J.; Lee, E.-S. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2659. (b) Zhao, L. X.; Moon, Y. S.; Basnet, A.; Kim, E. K.; Jahng, Y.; Park, J. G.; Jeong, T. C.; Cho, W. J.; Choi, S. U.; Lee, C. O.; Lee, S. Y.; Lee, C. S.; Lee, E.-S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1333. (c) Zhao, L. X.; Sherchan, J.; Park, J. K.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E.-S. *Arch. Pharm. Res.* **2006**, *29*, 1091. (d) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E.-S. *Bioorg. Med. Chem.* **2007**, *15*, 4351. (e) Son, J. K., Zhao, L. X.; Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, T. C.; Jeong, B. S.; Lee, C. S.; Lee, E.-S. *Eur. J. Med. Chem.* **2008**, *43*, 675. (f) Thapa, P.; Karki, R.; Basnet, A.; Thapa, U.; Choi, H. Y.; Na, Y.; Jahng, Y.; Lee, C. S.; Kwon, Y.; Jeong, B. S.; Lee, E.-S. *Bull. Korean Chem. Soc.* **2008**, *29*, 1605. (g) Basnet, A.; Thapa, P.; Karki, R.; Choi, H. Y.; Choi, J. H.; Yun, M.; Jeong, B. S.; Jahng, Y.; Na, Y.; Cho, W. J.; Kwon, Y.; Lee, C. S.; Lee, E.-S. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 42. (h) Thapa, P.; Karki, R.; Thapa, U.; Jahng, Y.; Jung, M. J.; Nam, J. M.; Na, Y.; Kwon, Y.; Lee, E.-S. *Bioorg. Med. Chem*. **2010**, *18*, 377. (i) Thapa, P.; Karki, R.; Choi, H. Y.; Choi, J. H.; Yun, M.; Jeong, B. S.; Jung, M. J.; Nam, J. M.; Na, Y.; Cho, W. J.; Kwon, Y.; Lee, E.-S. *Bioorg. Med. Chem*. **2010**, *18*, 2245. (j) Karki, R.; Thapa, P.; Kang, M. J.; Jeong, T. C.; Nam, J. M.; Kim, H. L.; Na, Y.; Cho, W. J.; Kwon, Y.; Lee, E.-S. *Bioorg. Med. Chem.* **2010**, *18*, 3066. (k) Karki, R.; Thapa, P.; Kwon, Y.; Lee, E.-S. *Bull. Korean Chem. Soc.* **2010**, *31*, 1747. (l) Jeong, B. S.; Choi, H. Y.; Thapa, P.; Karki, R.; Lee, E.; Nam, J. M.; Na, Y.; Ha, E.-M.; Kwon, Y.; Lee, E.-S. *Bull. Korean Chem. Soc.* **2011**, *32*, 303.
3. (a) Eryazici, I.; Moorefield, C. N.; Newkome, G. R. *Chem. Rev.* **2008**, *108*, 1834. (b) Heller, M.; Schubert, U. S. *Macromol. Rapid. Comm.* **2002**, *23*, 411. (c) Lowe, G.; Droz, A. S.; Park, J. J.; Weaver, G. W. *Bioorg. Chemistry* **1999**, *27*, 477.
4. (a) Patel, K. K.; Plummer, E. A.; Darwish, M.; Rodger, A.; Hannon, M. J. *J. Inorg. Biochem.* **2002**, *91*, 220. (b) Carter, P. J.; Cheng, C. C.; Thorp, H. H. *J. Am. Chem. Soc.* **1998**, *120*, 632. (c) Jennette, K. W.; Lippard, S. J.; Vassiliades, G. A.; Bauer, W. R. *Proc. Nat. Acad. Sci. USA* **1974**, *71*, 3839. (d) McCoubrey, A.; Latham, H. C.; Cook, P. R.; Rodger, A.; Lowe, G. *FEBS Lett.* **1996**, *380*, 73.
5. (a) Wang, J. C. *Annu. Rev. Biochem.* **1996**, *65*, 635. (b) Nitiss, J. L. *Biochim. Biophys. Acta* **1998**, *1400*, 63.
6. (a) Haglof, K. J.; Popa, E.; Hochster, H. S. *Update Cancer Ther.* **2006**, *1*, 117. (b) Hande, K. R. *Update Cancer Ther.* **2008**, *3*, 13. (c) Holden, J. A. *Curr. Med. Chem.-Anti-Cancer Agents* **2001**, *1*, 1.
7. Fukuda, M.; Nishio, K.; Kanzawa, F.; Ogasawara, H.; Ishida, T.; Arioka, H.; Bonjanowski, K.; Oka, M.; Saijo, N. *Cancer Res.* **1996**, *56*, 789.
8. Kang, D. H.; Kim, J. S.; Jung, M. J.; Lee, E.-S.; Jahng, Y.; Kwon, Y.; Na, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1520.
9. Jahng, Y.; Zhao, L. X.; Moon, Y. S.; Basnet, A.; Kim, E. K.; Chang, H. W.; Ju, H. K.; Jeong, T. C.; Lee, E.-S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2559.
10. (a) Kröhnke, F. *Angew. Chem. Internat. Edit*. **1963**, *2*, 380. (b) Kröhnke, F. *Synthesis* **1976**, 1.