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Synthesis, Topoisomerase I and II Inhibitory Activity, Cytotoxicity, and Structure-activity Relationship Study of Rigid Analogues of 2,4,6-Trisubstituted Pyridine Containing 5,6-Dihydrobenzo[*h*]quinoline Moiety

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DNA topoisomerases are nuclear enzymes that transiently break one or two strands of DNA, passing a single or double stranded DNA through the break and again resealing the breaks which allow to solve various DNA topological problems generated during vital cellular processes such as replication, transcription, recombination, repair, chromatin assembly and chromosome segregation.[1,2] Because of the crucial role of topoisomerase for the maintenance and replication of DNA during proliferation, topoisomerase inhibition has been an important therapeutic strategy for the design of various anticancer agents.[3,4]

Previously, our research group has reported that terpyridine derivatives showed a strong cytotoxicity against several human cancer cell lines and considerable topoisomerase I (topo I) and II (topo II) inhibitory activities.[5] From the previous study it was found that number of aryl groups in terpyridine derivatives has important role in determining the antitumor cytotoxicity.[5e] In connection with the previous results, it would be very interesting to observe the difference of biological activities by introduction of conformationally constrained rigid molecule in terpyridine skeleton. Compounds containing 5,6-dihydrobenzo[*h*]quinoline moiety has been reported to possess various biological activities such as anticancer cytotoxicity,[6,7] antibacterial and antifungal.[8] In this study, twenty-four rigid analogues of 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*]quinoline moiety, were designed and synthesized as shown in Figure 1 and Scheme 1.

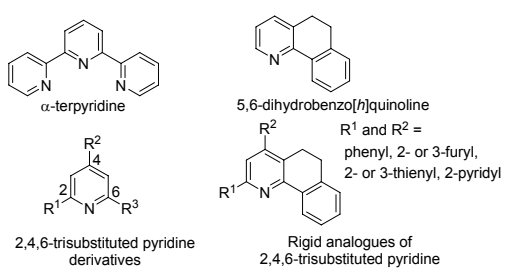


Figure 1. Structures of α-terpyridine, 5,6-dihydrobenzo[*h*]quinoline, 2,4,6-trisubstituted pyridine and rigid analogues of 2,4,6-trisubstituted pyridine (2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo [*h*]quinoline).

They were evaluated for cytotoxicity, topo I and II inhibitory activity, and studied for structure-activity relationships.

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 (ACN) was 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. 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 and ESI LC/MS analyses were performed using the same methods which were previously reported.[5j]

General Method for Preparation of 2. A mixture of aryl acetyls **1** (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 compound **2** in 76.8 to 99.2% yield. Following the same procedure, four compounds were synthesized.

General Method for Preparation of 4. α-Tetralone (30 mmol) was added to methanol (20 mL) followed by aryl aldehydes **3** (30 mmol) at 20 °C. The aqueous solution of NaOH (0.5 mL, 30 mmol) was slowly added at 0 °C, and stirred for 3 h at 20 °C. Precipiate formed was washed with H_2O (30 mL) and cold methanol (20 mL) to receive compound **4** in 69.1 to 87.3% yield. Following the same procedure, six compounds were synthesized.

General Method for Preparation of 5 (6-29). A mixture of **2** (2.0 mmol), **4** (2.0 mmol), and anhydrous ammonium acetate

(20.0 mmol) in glacial acetic acid (2.0 mL) was heated to 100 °C for 16 h. The residue was extracted with methylene chloride (100 mL), washed with water (60 mL × 3), saturated NaCl solution (30 mL), and dried over $MgSO_4$. After filtration, the filtrate was concentrated and purified by silica gel column chromatography with a gradient elution of ethyl acetate/*n*-hexane to afford a white solid compound **5** in 28.8 to 72.0% yield. Following the same procedure, twenty-four compounds were synthesized.

4-(Furan-2-yl)-2-(thiophen-2-yl)-5,6-dihydrobenzo[*h*]quinoline (12): White solid (30.3%), TLC (EtOAc/*n*-hexane = 1:15, v/v), R_f = 0.35, mp 135.9 - 138.3 °C, ESI LC/MS: Retention time: 7.17 min, $[MH]^+$: 330.28, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 1.4, 7.7 Hz, 1H, benzo H-10), 7.84 (s, 1H, pyridine H-3), 7.68 (dd, *J* = 1.1, 3.7 Hz, 1H, 2-thiophene H-3), 7.62 (d, *J* = 1.2Hz, 1H, 4-furan H-5), 7.42 (dt, *J* = 1.4, 6.8 Hz, 1H, benzo H-9), 7.40 (dd, *J* = 1.0, 5.0 Hz, 1H, 2-thiophene H-5), 7.34 (dt, *J* = 1.5, 7.3 Hz, 1H, benzo H-8), 7.24 (d, *J* = 7.1 Hz, 1H, benzo H-7), 7.13 (dt, *J* = 3.7, 5.0 Hz, 1H, 2-thiophene H-4), 6.72 (d, *J* = 3.1 Hz, 1H, 4-furna H-3), 6.58 (dd, *J* = 1.8, 3.4 Hz, 1H, 4-furan H-4), 3.17 (m, 2H, -CH_2- H-5), 2.93 (m, 2H, -CH_2- H-6), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.23, 151.31, 150.56, 145.95, 143.59, 138.14, 137.56, 135.06, 129.56, 128.31, 127.74, 127.52, 126.43, 126.11, 124.49, 115.18, 112.22, 112.12, 28.22, 25.84.

4-(Furan-3-yl)-2-(thiophen-2-yl)-5,6-dihydrobenzo[*h*]quinoline (24): Light yellow solid (39.3%), TLC (EtOAc/*n*-hexane = 1:15, v/v), R_f = 0.33, mp 158.6 - 160.8 °C, ESI LC/MS: Retention time: 6.59 min, $[MH]^+$: 330.27, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 1.4, 7.7 Hz, 1H, benzo H-10), 7.61 (br, 1H, 4-furan H-5), 7.61 (dd, *J* = 1.1, 3.8 Hz, 1H, 2-thiophene H-3), 7.55 (t, *J* = 1.7 Hz, 1H, 4-furan H-2), 7.51 (s, 1H, pyridine H-3), 7.40 (dt, *J* = 1.3, 7.3 Hz, 1H, benzo H-9), 7.37 (dd, *J* = 1.1, 5.1Hz, 1H, 2-thiophene H-5), 7.32 (dt, *J* = 1.5, 7.3 Hz, 1H, benzo H-8), 7.21 (dd, *J* = 0.7, 7.1 Hz, 1H, benzo H-7), 7.10 (dd, *J* = 3.7, 5.0 Hz, 1H, 2-thiophene H-4), 6.63 (dd, *J* = 0.8, 1.8 Hz, 1H, 4-furan H-4), 2.98 (m, 2H, -CH_2- H-5), 2.87 (m, 2H, -CH_2- H-6), ^{13}C NMR (62.5MHz, $CDCl_3$) δ 152.73, 150.29, 145.70, 143.45, 141.25, 140.24, 138.10, 138.87, 129.35, 128.08, 128.00, 127.59, 127.31, 125.89, 124.17, 123.60, 117.64, 111.29, 28.17, 25.51.

2-(Thiophen-2-yl)-4-(thiophen-3-yl)-5,6-dihydrobenzo[*h*]quinoline (28): Light yellow solid (31.5%), TLC (EtOAc/*n*-hexane = 1:15, v/v), R_f = 0.37, mp 160.9 - 164.2 °C, ESI LC/MS: Retention time: 7.39 min, $[MH]^+$: 346.26, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 1.3, 7.7 Hz, 1H, benzo H-10), 7.61 (dd, *J* = 1.0, 3.7 Hz, 1H, 2-thiophene H-3), 7.52 (s, 1H, pyridine H-3) 7.45 (dd, *J* = 3.0, 4.9 Hz, 1H, 4-thiophene H-5), 7.39-7.35 (m, 3H, benzo H-9, 2-thiophene H-5, 4-thiophene H-2), 7.32 (dd, *J* = 1.5, 7.3 Hz, 1H, benzo H-8), 7.21 (dd, *J* = 1.2, 5.0 Hz, 1H, 4-thiophene H-4), 7.21 (d, *J* = 6.2 Hz, 1H, benzo H-7), 7.10 (dd, *J* = 3.7, 5.0 Hz, 1H, 2-thiophene H-4), 2.95 (m, 2H, -CH_2- H-5), 2.85 (m, 2H, -CH_2- H-6), ^{13}C NMR (62.5MHz, $CDCl_3$) δ 152.78, 150.22, 145.74, 144.13, 139.58, 138.24, 134.92, 129.37, 128.57, 128.10, 127.61, 127.33, 126.16, 125.91, 124.46, 124.19, 118.14, 28.27, 25.60.

2-Phenyl-4-(thiophen-3-yl)-5,6-dihydrobenzo[*h*]quinoline (29): Light yellow solid (32.1%), TLC (EtOAc/*n*-hexane = 1:15, v/v), R_f = 0.38, mp 176.0 - 179.8 °C, ESI LC/MS: Retention time: 7.69 min, $[MH]^+$: 340.31, ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 1.4, 7.6 Hz, 1H, benzo H-10), 8.23-8.20 (m, 2H, 2-phenyl H-2,6), 7.69 (s, 1H, pyridine H-3), 7.57-7.40 (m, 4H, 2-phenyl H-3,4,5, benzo H-9), 7.50 (dd, *J* = 2.8, 4.9 Hz, 1H, 4-thiophene H-5), 7.43 (dd, *J* = 1.3, 3.0 Hz, 1H, 4-thiophene H-2), 7.38 (dt, *J* = 1.5, 7.2 Hz, 1H, benzo H-8), 7.28 (dd, *J* = 1.3, 4.9 Hz, 1H, 4-thiophene H-4), 7.28 (d, *J* = 6.2 Hz, 1H, benzo H-7), 3.07 (m, 2H, -CH_2- H-5), 2.93 (m, 2H, -CH_2- H-6), ^{13}C NMR (62.5MHz, $CDCl_3$) δ 154.69, 152.88, 144.14, 139.85, 139.66, 138.28, 135.35, 129.25, 128.94, 128.86, 128.63, 128.17, 127.65, 127.27, 126.98, 126.11, 125.90, 124.39, 119.88, 28.30, 25.58.

Pharmacology. The topo I inhibitory activity was carried out using the same methods which were previously reported.[9,5k] DNA topo II inhibitory activity of compounds were measured using the same methods which were previously reported.[10,5k]

For the evaluation of cytotoxicity, five different cancer cell lines were used: human breast adenocarcinoma cell line (MCF-7), human prostate tumor cell line (DU145), human cervix tumor cell line (HeLa), chronic myelogenous leukemia cell line (K562), and human colorectal adenocarcinoma cell line (HCT15). Experiments were performed by methods previously described.[10] Cancer cells were cultured according to the supplier's instructions. Cells were seeded in 96-well plates at a density of $2 \sim 4 \times 10^4$ 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 μL 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. Adriamycin, etoposide, and camptothecin were purchased from Sigma and used as positive controls.

Results and Discussion

Synthetic Chemistry. Twenty-four rigid analogues of 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*]quinoline moiety has been synthesized as shown in Scheme 1. At first, using Claisen-Schmidt NaOH catalyzed condensation reaction,[11] six propenone intermediates (**4a-f**) were synthesized in 69.1 to 87.3% yield by the condensation of α-tetralone with six different aryl aldehydes (**3a-f**). Four pyridinium iodide salts (**2a-d**) were prepared in 76.8 to 99.2% yield by refluxing four different aryl acetyls (**1a-d**) with iodine in pyridine. Finally, on the basis of modified Kröhnke synthesis method,[12,13] twenty-four rigid analogues of 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*]quinoline moiety (**6-29**) were synthesized by treating six propenone intermediates (**4a-f**) with four pyridinium iodide salts (**2a-d**) in 28.8 to 72.0% yield.

Figure 2 shows the structure of synthesized twenty-four rigid analogues of 2,4,6-trisubstituted pyridine.

Topo I and II Inhibitory Activity of Compounds 6-29. The conversion of supercoiled plasmid DNA to relaxed DNA by

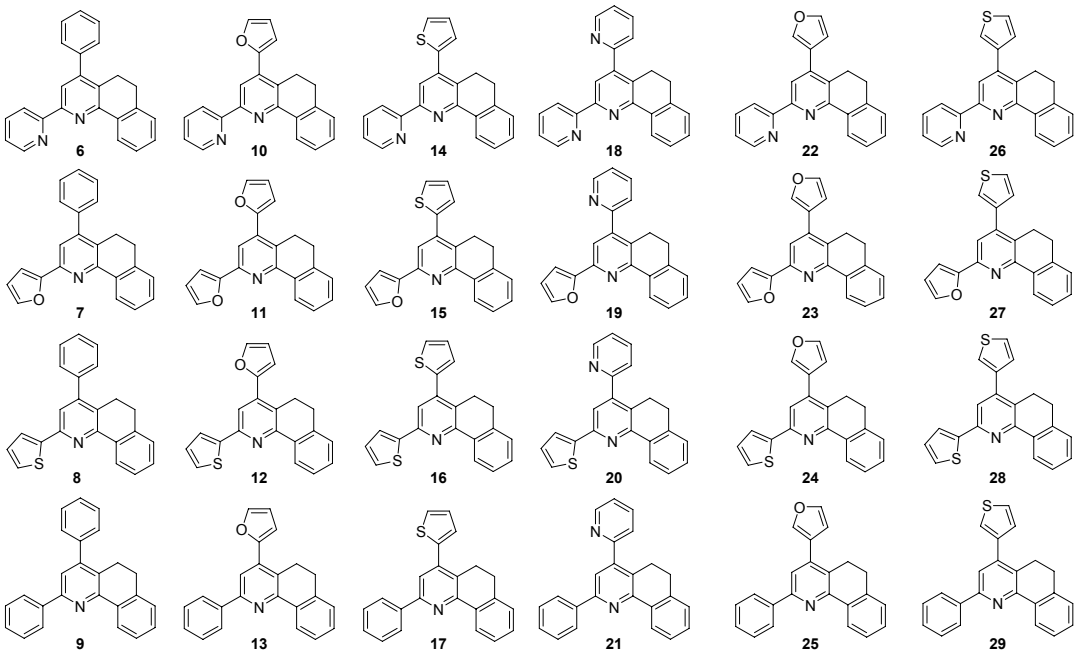
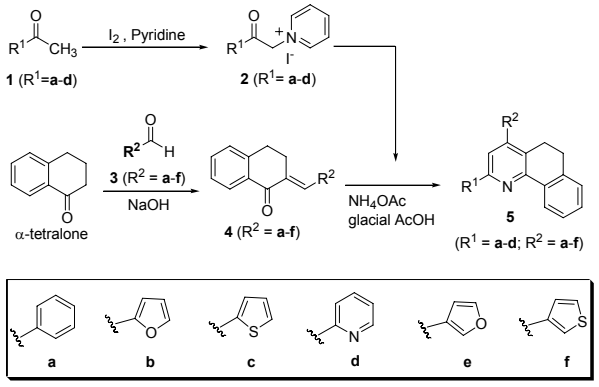
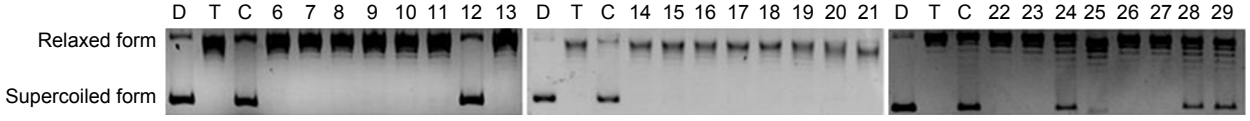


Figure 2. Structures of the synthesized compounds.



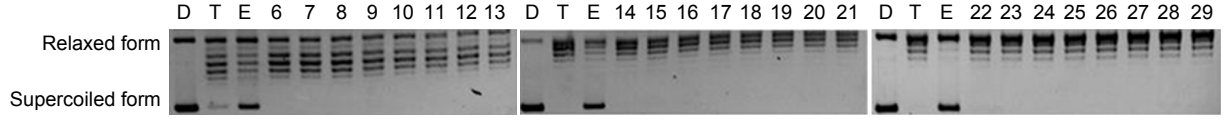
Scheme 1. General synthetic scheme of 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*]quinoline.

topo I and II was examined in the presence of the prepared 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*] quinoline **6-29**. Camptothecin and etoposide, well-known topo I and II inhibitors, respectively, were used as positive controls. The effect of the prepared compounds on human DNA topo I was evaluated by the topo I relaxation assays. The reaction products were analyzed by electrophoretic mobility and developed in ethidium bromide in the presence of UV light. As shown in Figure 3, compounds **12**, **24**, **28**, and **29** exhibited significant topo I inhibitory activity at 100 μM concentration. Especially, compound **12** displayed the most significant topo I inhibitory activity as strong as a positive control, camptothecin (Table 1). The compounds (**12**, **24**, **28**, and **29**) having significant topo I inhibitory activity possess 2-thienyl at 2-position of central pyridine with combination of 2-furyl (**12**), 3-furyl (**24**),



Lane D: pBR322 DNA only
Lane T: pBR322 DNA + Topo I
Lane C: pBR322 DNA + Topo I + Camptothecin (100 μM)
Lane 6-29 (100 μM): pBR322 DNA + Topo I + Compound **6-29** (100 μM)

Figure 3. Human DNA topoisomerase I inhibitory activity of compounds **6-29**.



Lane D: pBR322 DNA only
Lane T: pBR322 DNA + Topo II
Lane E: pBR322 DNA + Topo II + Etoposide (100 μM)
Lane 6-29 (100 μM): pBR322 DNA + Topo II + Compound **6-29** (100 μM)

Figure 4. Human DNA topoisomerase IIα inhibitory activity of compounds **6-29**.

Table 1. Inhibitory activity of selected compounds against topoisomerase I and II (% inhibition ratio of relaxation) and their IC_{50} values against various human cancer cell lines

Compounds	% Inhibition (100μM)		[a]IC_{50} (μM)				
	Topo I	Topo II	[b]MCF-7	[c]DU145	[d]HeLa	[e]K562	[f]HCT15
12	63.0	0.0	37.61 ± 1.68	35.87 ± 1.45	27.67 ± 1.50	13.16 ± 2.02	23.58 ± 2.32
24	34.3	0.0	17.85 ± 0.48	35.59 ± 1.05	40.22 ± 0.21	15.11 ± 3.33	29.14 ± 1.27
28	18.2	0.0	33.44 ± 2.38	24.68 ± 0.72	43.65 ± 0.36	12.85 ± 1.06	63.34 ± 3.05
29	20.8	0.0	26.92 ± 1.50	44.6 ± 1.97	47.14 ± 2.33	18.14 ± 1.75	66.75 ± 0.00
[g]Camptothecin (C)	64.7		2.71 ± 1.59	1.78 ± 0.01	0.93 ± 0.07	3.71 ± 0.34	3.78 ± 0.08
[h]Etoposide (E)		56.1	3.38 ± 0.56	5.69 ± 0.14	2.65 ± 0.45	2.18 ± 0.54	8.99 ± 0.05
[i]Adriamycin			2.37 ± 0.44	1.47 ± 0.16	1.31 ± 0.3	6.10 ± 0.13	9.50 ± 0.17

[a]Each data represents mean ± S.D. from three different experiments performed in triplicate; [b]MCF-7: human breast adenocarcinoma; [c]DU145: human prostate tumor; [d]HeLa: human cervix tumor; [e]K562: chronic myelogenous leukemia; [f]HCT: human colorectal adenocarcinoma; [g]Camptothecin; positive control for topo I and cytotoxicity; [h]Etoposide: positive control for topo II and cytotoxicity; [i]Adriamycin: positive control for cytotoxicity.

or 3-thienyl (**28** and **29**) at 4-position of central pyridine, which supports the idea that 2-thienyl, 2-furyl, 3-furyl, or 3-thienyl at 2- or 4-position on central pyridine play the crucial role for topo I or II inhibitory activity as reported previously.[5b,5d,5g,5h,5i,5k] However all the compounds were devoid of topo IIα inhibitory activity at 100 μM concentration as shown in Figure 4. It is interesting to note that the flexible compounds which do not contain constrained 5,6-dihydrobenzo[*h*]quinoline moiety corresponding to **12**, **24**, **28**, and **29** did not show considerable Topo I or Topo II inhibitory activities.

Cytotoxicity. Cytotoxic evaluation was performed for the compounds (**12**, **24**, **28**, and **29**) having significant topo I inhibitory activity. The IC_{50} values of **12**, **24**, **28**, and **29** against MCF-7, DU145, HeLa, K562, and HCT15 cell lines are shown in Table 1. Most of the compounds showed moderate cytotoxicity, generally IC_{50} values of 10 - 60 μM, which were approximately ten times less potent than positive controls.

In conclusion, we have designed and synthesized 24 compounds by efficient synthetic routes and evaluated them for topo I and II inhibitory activity along with cytotoxicity against several human cancer cell lines. Among them, **12**, **24**, **28**, and **29** displayed significant topo I inhibitory activity. A structure-activity relationship study of 2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[*h*]quinoline for topo I inhibitory activity indicates that 2-thienyl at 2-position of central pyridine with combination of 2-furyl, 3-furyl, or 3-thienyl at 4-position of central pyridine is crucial in displaying topo I inhibitory activity and cytotoxicity. From the results of this study we demonstrated the possibility for the development of potent antitumor agent possessing conformationally constrained rigid molecule such as 5,6-dihydrobenzo[*h*]quinoline moiety in terpyridine skeleton. This study may provide valuable information to researchers working on the development of antitumor agents. In addition, the calculated Log P value of the prepared compounds were within the range of 5 - 7 (Log P of **12**: 5.64, **24**: 5.59, **28**: 6.95, **29**: 6.97, respectively), which indicated somewhat higher value than the standard guide line for the development of new agents according to the Lipinski's rule of five.[14] The effort for the decrease of the Log P value will also perform by introduction of relatively polar constrained skeleton in the molecule.

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