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Indenoindolone derivatives as topoisomerase II–inhibiting anticancer agents

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ABSTRACT

Based on known heterocyclic topoisomerase II inhibitors and anticancer agents, various indenoindolone derivatives were predicted as potential topoisomerase II–inhibiting anticancer agents. They are hydrazones, (thio)semicarbazones, and oximes of indenoindolones, and indenoindolols. These derivatives with suitable substitutions exhibited potent specific inhibition of human DNA TopoIIα while not showing inhibition of topoisomerase I and DNA intercalation, despite the fact that parent indenoindolones are known poor/moderate inhibitors of topoisomerase II. The potent topoisomerase II inhibitor indenoindolone derivatives exhibited good anticancer activities compared to etoposide and 5-fluorouracil, and relatively low toxicity to normal cells. These derivatizations of indenoindolones were found to result in enhancement of anticancer activities.

Topoisomerase II plays key role in transcription, replication, and chromosome segregation. This enzyme maintains topological changes of DNA by creating double-stranded DNA breaks and passage of a second double-stranded DNA through the transiently broken duplex.[1] Its β isozyme expresses almost constant and at relatively low level throughout the cell cycle. However, the expression of α isozyme increases throughout S phase and peaks with 2- to 3-fold at G2/M phase of mitosis. The concentration of α isozyme is even higher in rapidly proliferating tissues than in quiescent cell populations.[2] Some of antitumoral drugs that target topoisomerase II are doxorubicin and daunorubicin (anthracycline class), etoposide and teniposide (epipodophyllotoxin class), mitoxantrone, amonafide, and amsacrine.[3] Topoisomerase II has been recognized as an important target in anticancer drug discovery[4] and the development of its novel inhibitors is recently emerging.[5] Recently, we developed N-fused imidazole as topoisomerase II-targeting novel anticancer agents.[6]

Towards development of novel anticancer agents, the structural modification/hybridization of known natural/synthetic target-specific anticancer agents is a valuable approach.[7] Certain moieties such as functional side chains or monocyclic rings when attached to the key scaffold are known to enhance potency in inhibition of topoisomerase II. They act as minor groove binders to DNA and prevent it to be available in suitable geometry for binding with topoisomerase II. These moieties can also directly bind to topoisomerase II. The presence of such moieties have led to the development of novel therapeutic agents in the form of derivatives of original scaffolds.[8] These derivatizations improve pharmacodyanamic as well as pharmacokinetic properties.[8c-e] Mitoxantrone, which acts as a topoisomerase II poison, on derivatization with incorporation of extended alkylamine shows its enhanced DNA-binding affinity.[8f] The thiosemicarbazone derivatives of α-hererocyclic carboxaldehyde inhibit catalytic activity of topoisomerase IIα. 2-Benzoxazolylhydrazones have been found to be potent anticancer agents.[8g,h] Compared to β-lapachone, its 7-hydroxy derivative have been found to possess higher antiproliferating activity in human solid tumor cell lines.[8i]

As a part of our research on anticancer drug discovery, we have recently explored that indenoindolones possess anticancer activities.[9] Based on the relevance of side chains/moieties towards enhancement of the topoisomerase II-inhibitory and anticancer activities; we considered various indenoindolone derivatives as potential topoisomerase II–inhibiting anticancer agents (Fig. 1).

In this Letter, we present relevant indenoindolone derivatives (hydrazones, (thio)semicarbazones, and oximes of indenoindolones, and indenoindolols) as potent topoisomerase II–inhibiting

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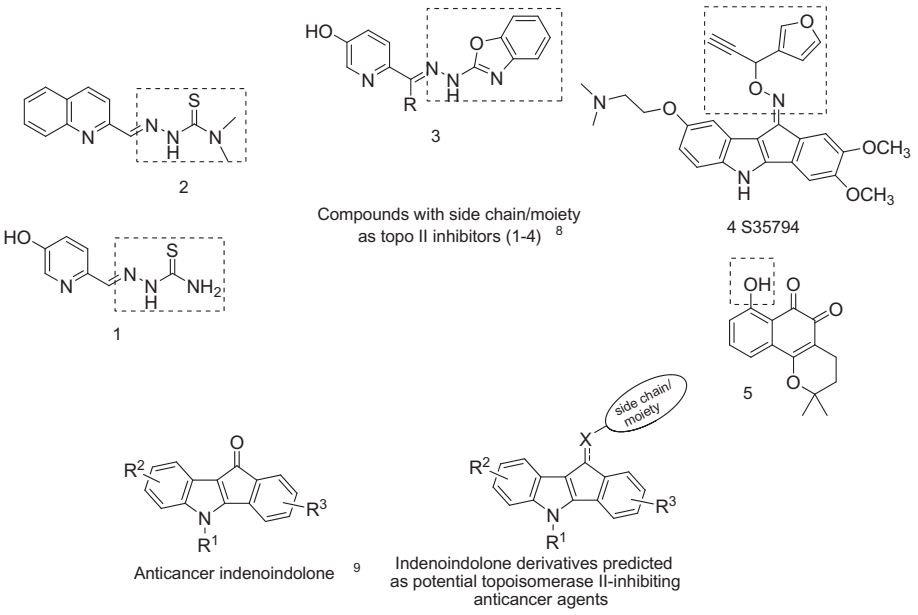
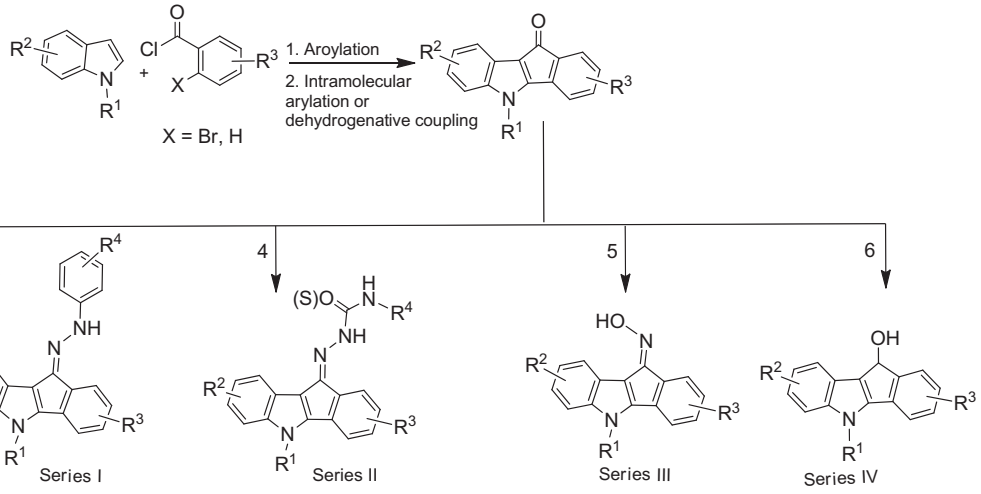


Figure 1. Known Topo II inhibitors and anticancer agents; indenoindolone derivatives (hydrazone, (thio)semicarbazone, and oxime derivatives, and indenoindolols) as potential topoisomerase II–inhibiting anticancer agents.



Series I, Compound 1-16

#[a]	R^1	R^2	R^3	R^4
1	Me	-	-	-
2	Bn	-	-	-
3	Me	8-OMe	-	-
4	Me	-	-	4-Br
5	Me	-	2,3,4-$(OMe)_3$	-
6	Me	-	-	2-Et
7	H	-	-	-
8	Me	-	-	4-Me
9	Me	-	-	4-OMe
10	Me	-	-	2,3-$(Me)_2$
11	Bn	-	-	4-Me
12	Bn	-	-	4-OMe
13	Me	-	2-OMe	-
14	Me	-	2,3-$(OMe)_2$	4-OMe
15	Me	-	2,3,4-$(OMe)_3$	4-OMe
16	H	-	2,3,4-$(OMe)_3$	4-Me

Series II, Compound 17-26

#[a]	R^1	R^2	R^3	R^4
17[b]	H	-	-	H
18	Bn	-	-	Ph
19	Me	-	-	Ph
20	H	-	-	Ph
21	Me	8-OMe	-	Ph
22	H	-	3-F	Ph
23	H	-	3-OMe	Ph
24	H	8-OMe	-	Ph
25[b]	H	-	-	Ph
26	Me	-	2,3,4-$(OMe)_3$	Ph

[b] thiosemicarbazones

Series III, Compound 27-36

#[a]	R^1	R^2	R^3
27	H	-	-
28	Bn	-	-
29	Me	-	2-OMe
30	Me	-	3-OMe
31	Me	8-OMe	-
32	Me	-	2,3,4-$(OMe)_3$
33	H	-	3-F
34	H	8-OMe	2-OMe
35	Me	-	2,3-$(OMe)_2$
36	Me	-	-

Series IV, Compound 37-45

#[a]	R^1	R^2	R^3
37	H	-	-
38	Bn	-	-
39	Me	-	2-OMe
40	Me	-	-
41	Me	8-OMe	-
42	Me	-	2,3,4-$(OMe)_3$
43	H	-	3-F
44	H	-	2,3-$(OMe)_2$
45	Me	-	2,3-$(OMe)_2$

[a] compound number

Scheme 1. Step 1: Fridel–Crafts aroylation;[10a] Step 2: intramolecular arylation[10b] or dehydrogenative coupling;[10c] Step 3: indeno[1,2-*b*]indol-10(5*H*)-one (0.5 mmol) and arylhydrazine (0.5 mmol), ethanol, a drop of glacial acetic acid, reflux;[8g,11] Step 4: indeno[1,2-*b*]indol-10(5*H*)-one (0.5 mmol) and (thio)semicarbazides (0.5 mmol), ethanol, a drop of glacial acetic acid, reflux;[8h,11] Step 5: indeno[1,2-*b*]indol-10(5*H*)-one (0.5 mmol), hydroxylamine hydrochloride (1.7 mmol), ethanol/water (7:3), reflux;[12]; Step 6: indeno[1,2-*b*]indol-10(5*H*)-one (0.5 mmol), methanol, sodium borohydride (1.5 mmol), rt.

anticancer agents. Whilst indenoindolones are poor/moderate inhibitors of topoisomerase II,[9] these derivatives with suitable substitutions exhibited potent specific inhibition of hTopoIIα without any effect of topoisomerase I–inhibition and DNA intercalation. The potent topoisomerase II inhibitor indenoindolone derivatives exhibited good anticancer activities in kidney cancer cells (HEK-293), compared to etoposide (a clinically used anticancer drug that targets topoisomerase II) and 5-fluorouracil (5-FU, a widely

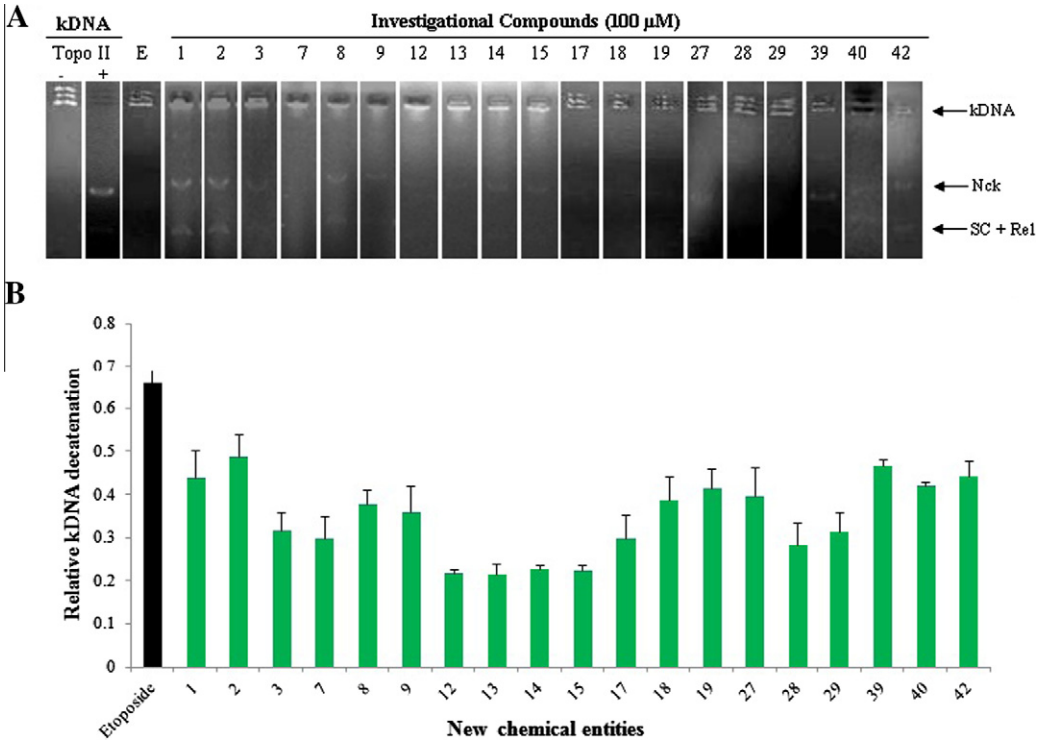


Figure 2. (A) Effect of investigational compounds on catalytic activity of hTopoIIα in kDNA decatenation assay. kDNA was treated with hTopoIIα in the presence of either 100 μM etoposide or investigational compounds. Reaction mixture was incubated at 37 °C for 30 min and electrophoresis was carried out in 1% agarose gel in TAE buffer; (B) quantification of decatenated product formed in kDNA decatenation assay.

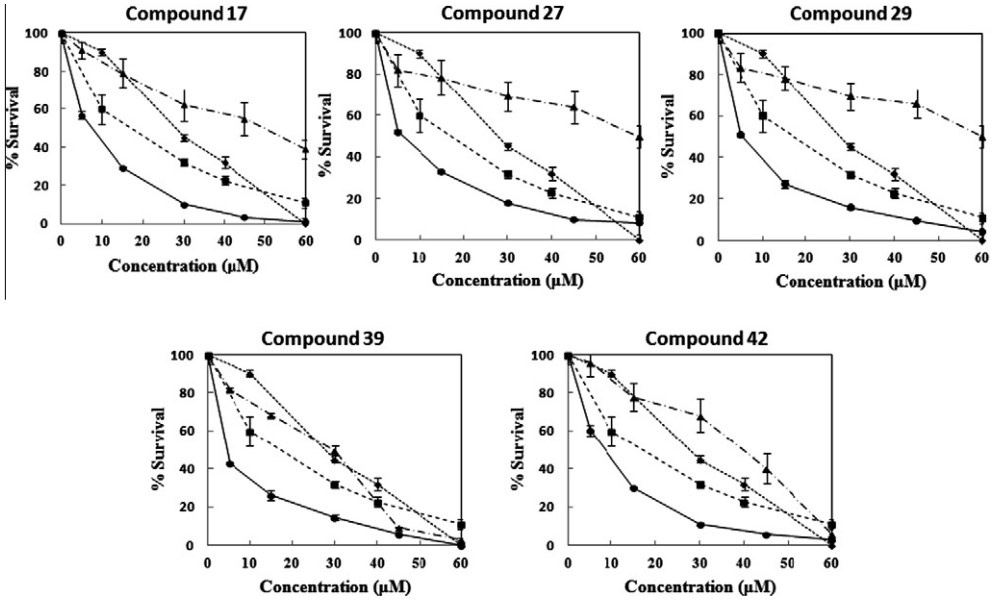


Figure 3. MTT assay: cells after treatment with investigational compounds or etoposide of various concentrations for 48 h. The sign —♦—, —■—, -·-▲-·- and —●— represent for Vero/etoposide, HEK-293/etoposide, Vero /investigational compound and HEK-293/investigational compound, respectively. Data is the mean ± SD of three different experiments.

used anticancer drug), and relatively low toxicity to normal cells. Compared to indenoindolones, their (thio)semicarbazone and oxime derivatives, and indenoindolols were found to possess 3- to 4-fold enhanced anticancer activities.

Recently, we developed efficient synthesis of indenoindolones via Friedel–Crafts benzoylation[10a] of indoles and followed by intramolecular direct arylation[10b] or cross dehydrogenative coupling[10c] (Scheme 1, steps 1 and 2). These protocols afford the convenient preparation of diverse substituted/functionalized indenoindolones from easily accessible starting materials in reduced number of reaction steps. Various relevant substituted indenoindolones were prepared by these methods. The indenoindolone derivatives arylhydrazones, (thio)semicarbazones, and oximes of indenoindolones, and indenoindolols were prepared by the reactions of indenoindolones with hydrazines, (thio)semicarbazides, hydroxylamines, and $NaBH_4$, respectively,

Table 1
LC_{50} values of the investigational compounds in VERO and HEK-293 cells at 48 h

Compounds	LC_{50}, 48 h	
	VERO (μM)	HEK-293 (μM)
17	50 ± 2	7 ± 2
27	60 ± 2	6 ± 2
29	60 ± 2	5 ± 2
39	30 ± 2	4 ± 2
42	40 ± 2	8 ± 2
Etoposide	29 ± 2	17 ± 2

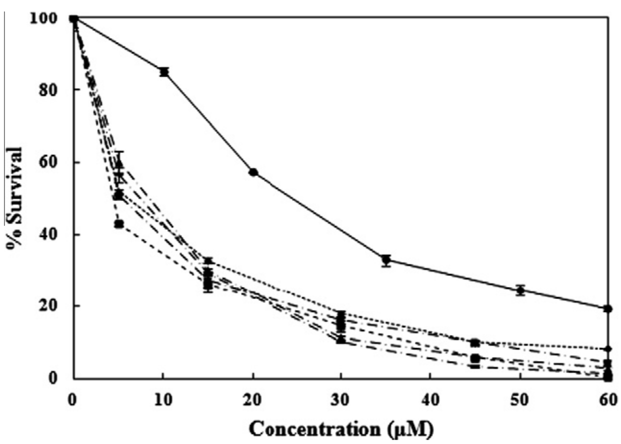


Figure 4. MTT assay: Comparison of anti-cell survival activities of compounds (**17**, **27**, **29**, **39**, **42**) with 5-FU in HEK-293 cells. Data is the mean ± SD of three different experiments. The symbols —●—, -··-··-, —◆—, – – –█– – –, —■—and -·-▲-·- represent 5-FU, compounds **17**, **27**, **29**, **39**, **42**, respectively.

following corresponding conventional methods (Scheme 1, steps 3–6).[8g,h,11,12]

The topoisomerase II–inhibitory activities of investigational indenoindolone derivatives (compounds **1**–**45**, Series I–IV) were investigated against human topoisomerase IIα (hTopoIIα) by in vitro ATP-dependent decatenation assay (agarose gel electrophoresis)[6] using a commercially available topoisomerase drug screening kit purchased from TopoGEN, Inc. (Columbus, OH). Kinetoplast DNA (kDNA) as substrate was used. Etoposide, an anticancer drug that targets topoisomerase II, was used as positive standard. Catenated kDNA appears at the top and cannot enter into the gel because of its overall size, while other decatenated products nicked (Nck), relaxed (Rel), and supercoiled (SC) DNA move into the gel.[13] For many investigational compounds of each class of indenoindolone derivatives, very less or no decatenated products were formed in the assay, compared to that in case of etoposide (Fig. 2A). Compared to parent indenoindolones,[9] the following investigational compounds showed more potent inhibition of topoisomerase II, series I (**1**, **2**, **3**, **7**, **8**, **9**, **12**, **13**, **14**, **15**), series II (**17**, **18**, **19**), series III (**27**, **28**, **29**), and series IV (**39**, **40**, **42**) (Fig. 2 B). Other compounds which exhibited poor or moderate inhibition of topo II compared to etoposide have not been included in the Figure 2. Quantification of decatenation products formed was done by densitometric data obtained using QuantityOne (Bio-Rad) (Fig. 2B). These results indicate that the indenoindolone derivatives with incorporation of relevant side chain/moiety are potent inhibitors of topoisomerase IIα in comparison to etoposide. This activity of indenoindolone derivatives is particularly interesting considering the fact that indenoindolones are poor/moderate inhibitors of topoisomerase II.[9]

The potent topoisomerase II inhibitor indenoindolone derivatives (as in Fig. 2) were considered for the investigation of their anticancer activities using MTT assay[6,9,14] in human embryonic kidney cancer cells (HEK-293, cat. # CRL-1573) and normal monkey kidney cells (Vero, cat. # CCL-81), purchased from ATCC, VA, USA (Fig. 3). Cells were plated in a 96-well tissue culture plate and then treated with the investigational compounds for 48 h.

Then, MTT was added for formation of formazan crystal which was dissolved by a detergent solution and the colour intensity was measured at 570 nm using a microplate reader (Berthold, Germany). Compounds **17**, **27**, **29**, **39** and **42** showed relatively higher anticancer activities compared to other derivatives. They caused 50% cell death (LC_{50}) of HEK-293 cells at 7, 6, 5, 4, and 8 μM, respectively while the LC_{50} values in Vero cells were 50, 60, 60, 30 and 40 μM, respectively (Fig. 3 and Table 1). The LC_{50} values for etoposide were 17 μM in HEK-293 cells and 29 μM in Vero cells. Cell death of HEK-293 cells significantly increased in comparison to Vero cells with increase in the concentration of these compounds. After 48 h of treatment, the anti-cell proliferative effect of these investigational derivatives did not further change significantly. The anti-proliferative activities of investigational compounds **17**, **27**, **29**, **39** and **42** were further compared with a clinically used common anticancer drug 5-FU in HEK-293 cells using MTT assay (Fig. 4). The LC_{50} value of 5-FU was found to be 25 μM. Therefore, all these results indicate that the indenoindolone derivatives **17**, **27**, **29**, **39** and **42** are more potent anticancer agents compared to 5-FU and etoposide in HEK-293 cells. The investigational compounds (**17**, **27**, **29**, **39**, **42**) have shown LC_{50} in the range of 4–8 μM for HEK-293 cells, whereas parent indenoindolones have exhibited LC_{50} in the range of 14–24 μM.[9] This indicates that the derivatizations of indenoindolones as (thio)semicarbazones and oximes, and indenoindolols enhance anticancer activities by 3- to 4-fold.

Compounds **17**, **27**, **29**, **39** and **42** showed relatively higher anticancer activities. They were also found to possess significant inhibitory activities of hTopoIIα in decatenation assay, compared to other investigational compounds and etoposide. Therefore, these derivatives were chosen for further studies of their possible specificity in inhibition of the enzyme. In order to check whether compounds are DNA intercalators or non-intercalators, DNA intercalation assay[15] was performed using negatively supercoiled small circular plasmid DNA (isolated from *Escherichia coli*) as substrate. It was found that in the presence of intercalative agent (ethi-

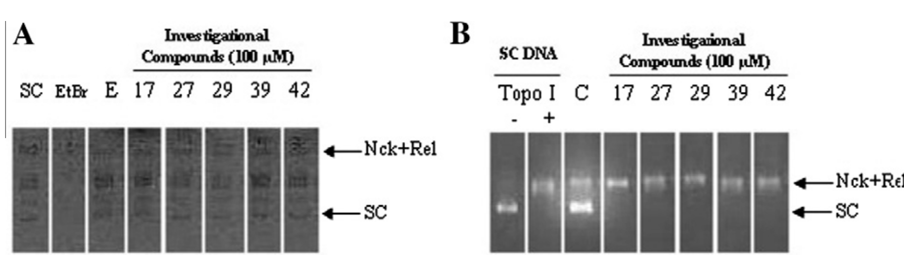


Figure 5. (A) DNA intercalation assay: in this assay, 250 ng of plasmid was incubated with ethidium bromide (EtBr), etoposide or investigational compounds. Reaction mixture was incubated at 37 °C for 20 min and electrophoresis was carried out in 1% agarose gel in TAE buffer; (B) effect of investigational compounds on hTopoI activity in relaxation assay. Negatively supercoiled DNA was treated with TopoI in the presence of either 100 μM camptothecin or investigational compounds. Reaction mixture was incubated at 37 °C for 30 min and electrophoresis was carried out in 1% agarose gel in TAE buffer.

dium bromide), there was retardation in the migration of the DNA, whereas, in the case of etoposide (DNA non-intercalator) and compounds tested, there was no such retardation. These indicate that these derivatives acted as DNA non-intercalators (Fig. 5A).

To determine whether the tested compounds are selective topoisomerase II inhibitors, topoisomerase I mediated relaxation assay[16] was performed. As compared to camptothecin used as positive standard, it was observed that the investigational compounds did not show any topoisomerase I inhibitory activity (Fig. 5B). These results imply that the investigational derivatives of indenoindolones are selective inhibitors of hTopoIIα while not showing any inhibition of topoisomerase I and DNA intercalation.

In conclusion, the derivatives of indenoindolones as hydrazones, (thio)semicarbazones and oximes, and indenoindolols showed potent topoisomerase II inhibition, while parent indenoindolones are poor/moderate inhibitors of the enzyme. These derivatives were non-intercalating to DNA and non-inhibitors of topoisomerase I, and thus specific for binding to hTopoIIα. Such derivatization of indenoindolones was found to be important for inhibition of topoisomerase II and resulted in improvement of anticancer activities. The compounds **17**, **27**, **29**, **39** and **42** were found to be most potent anticancer agents. They exhibited effective anticancer activities compared to etoposide and 5-FU in kidney cancer cells and low toxicity to normal cells. This work reveals that the incorporation of relevant side chain/moiety in the natural/synthetic scaffolds known for anticancer activity can provide enhanced topoisomerase II inhibition and cytotoxic activity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.12.063.

References and notes

1. Brown, P. O.; Cozzarelli, N. R. *Science* **1979**, *1081*, 206.
2. (a) Woessner, R. D.; Mattern, M. R.; Mirabelli, C. K.; Johnson, R. K.; Drake, F. H. *Cell Growth Differ.* **1991**, *2*, 209; (b) Issacs, R. J.; Davies, S. L.; Sandri, M. I.; Redwood, C.; Wells, N. J.; Hickson, I. D. *Biochim. Biophys. Acta* **1998**, *1400*, 121; (c) Bromberg, K. D.; Burgin, A. B.; Osheroff, N. A. *J. Biol. Chem.* **2003**, *278*, 7406.
3. (a) Zunino, F.; Capranico, G. *Anti-Cancer Drug Disc.* **1990**, *5*, 307; (b) Nitiss, J. L.; Liu, Y. X.; Harbury, P.; Jannatipour, M.; Wasserman, R.; Wang, J. C. *Cancer Res.* **1992**, *52*, 4467.
4. (a) Nitiss, J. L. *Nat. Rev. Cancer* **2009**, *9*, 338; (b) Wang, H. K.; Morris-Natschke, S. L.; Lee, K. H. *Med. Res. Rev.* **1997**, *17*, 367.
5. Bailly, C. *Chem. Rev.* **2012**, *112*, 3611.
6. (a) Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013; (b) Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Baviskar, A.; Madaan, C.; Agarwal, A.; Preet, R.; Mohapatra, P. Indian Patent 91/DEL/2011, **2011**.
7. (a) Dong, Y.; Shi, Q.; Liu, Y. N.; Wang, X.; Bastow, K. F.; Lee, K. H. *J. Med. Chem.* **2009**, *52*, 3586; (b) Meunier, B. *Acc. Chem. Res.* **2008**, *41*, 69; (c) Müller-Schiffmann, A.; März-Berberich, J.; Andreyeva, A.; Rönicke, R.; Bartnik, D.; Brener, O.; Kutzsche, J.; Horn, A. H. C.; Hellmert, M.; Polkowska, J.; Gottmann, K.; Reymann, K. G.; Funke, S. A.; Nagel-Steger, L.; Moriscot, C.; Schoehn, G.; Sticht, H.; Willbold, D.; Schrader, T.; Korth, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8743; (d) Lenhart, J. A.; Ling, X.; Gandhi, R.; Guo, T. L.; Gerk, P. M.; Brunzell, D. H.; Zhang, S. *J. Med. Chem.* **2010**, *53*, 6198; (e) Solary, E.; Leteurtre, F.; Paull, K. D.; Scudiero, D.; Hamel, E.; Pommier, Y. *Biochem. Pharmacol.* **1993**, *45*, 2449.
8. (a) Bal, C.; Baldeyrou, B.; Moz, F.; Lansiaux, A.; Colson, P.; Kraus-Berthier, L.; Léonce, S.; Pierré, A.; Boussard, M.-F.; Rousseau, A.; Wierzbicki, M.; Bailly, C. *Biochem. Pharmacol.* **1911**, *2004*, 68; (b) Wierzbicki, M.; Boussard, M. F.; Rousseau, A.; Boutin, J. A.; Delagrange, P. U.S. Patent 6844445 B2, **2005**.; (c) Ferlin, M. G.; Gatto, B.; Chiarelotto, G.; Palumbo, M. *Bioorg. Med. Chem.* **1843**, *2001*, 9; (d) Zagotto, G.; Oliva, A.; Guano, F.; Menta, E.; Capranico, G.; Palumbo, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 121; (e) Auclair, C.; Pierre, A.; Voisin, E.; Pepin, O.; Cros, S.; Colas, C.; Saucier, J. M.; Verschuere, B.; Gros, P.; Paoletti, C. *Cancer Res.* **1987**, *47*, 6254; (f) Mansour, O. C.; Evison, B. J.; Sleebs, B. E.; Watson, K. G.; Nudelman, A.; Rephaeli, A.; Buck, D. P.; Collins, J. G.; Bilardi, R. A.; Phillips, D. R.; Cutts, S. M. *J. Med. Chem.* **2010**, *53*, 6851; (g) Easmon, J.; Pürstinger, G.; Thies, K.-S.; Heinisch, G.; Hofmann, J. *J. Med. Chem.* **2006**, *49*, 6343; (h) Huang, H.; Chen, Q.; Ku, X.; Meng, L.; Lin, L.; Wang, X.; Zhu, C.; Wang, Y.; Chen, Z.; Li, M.; Jiang, H.; Chen, K.; Ding, J.; Liu, H. *J. Med. Chem.* **2010**, *53*, 3048; (i) Ríos-Luci, C.; Bonifazi, E. L.; León, L. G.; Montero, J. C.; Burton, G.; Pandiella, A.; Misico, R. I.; Padrón, J. M. *Eur. J. Med. Chem.* **2012**, *53*, 26.
9. Kashyap, M.; Das, D.; Preet, R.; Mohapatra, P.; Satapathy, S. R.; Siddharth, S.; Kundu, C. N.; Guchhait, S. K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2474.
10. (a) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4753; (b) Guchhait, S. K.; Kashyap, M. *Synthesis* **2012**, 619; (c) Guchhait, S. K.; Kashyap, M.; Kandekar, S. *Tetrahedron Lett.* **2012**, *53*, 3919.
11. Wang, J. B.; Ji, Q. G.; Xu, J.; Wu, X. H.; Xie, Y. Y. *Synth. Commun.* **2005**, *35*, 581.
12. Ni, S.; Yuan, Y.; Huang, J.; Mao, X.; Lv, M.; Zhu, J.; Shen, X.; Pei, J.; Lai, L.; Jiang, H.; Li, J. *J. Med. Chem.* **2009**, *52*, 5295.
13. Jimenez-Alonso, S.; Orellana, H. C.; Braun, A. E.; Ravelo, A. G.; Sacau, E. P.; Machin, F. *J. Med. Chem.* **2008**, *51*, 6761.
14. (a) Mohapatra, P.; Preet, R.; Choudhuri, M.; Choudhuri, T.; Kundu, C. N. *Oncol. Res.* **2011**, *19*, 311; (b) Preet, R.; Mohapatra, P.; Mohanty, S.; Sahu, S. K.; Choudhuri, T.; Wyatt, M. D.; Kundu, C. N. *Int. J. Cancer* **2012**, *130*, 1660.
15. (a) Besterman, J. M.; Elwell, L. P.; Cragoe, E. J.; Andrews, C. W.; Cory, M. *J. Biol. Chem.* **1989**, *265*, 2324; (b) Burres, N. S.; Sazesh, S.; Gunawardana, G. P.; Clement, J. J. *Cancer Res.* **1989**, *49*, 5267.
16. Haung, H.; Chen, Q.; Ku, X.; Meng, L.; Lin, L.; Wang, X.; Zhu, C.; Wang, Y.; Chen, Z.; Li, M.; Jiang, H.; Chen, K.; Ding, J.; Liu, H. *J. Med. Chem.* **2010**, *53*, 3048.