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New derivatives of 11-methyl-6-[2-(dimethylamino)ethyl]-6*H*-indolo[2,3-b]quinoline as cytotoxic DNA topoisomerase II inhibitors

Wojciech Luniewski [a], Joanna Wietrzyk [b], Joanna Godlewska [b], Marta Switalska [b], Malgorzata Piskozub [b], Wanda Peczynska-Czoch [c], Lukasz Kaczmarek [a,*]

[a] *Pharmaceutical Research Institute, 8 Rydygiera St., Warszawa 01-793, Poland*
[b] *Ludwik Hirszfeld Institute of Immunology and Experimental Therapy of Polish Academy of Science, 12 Weigla St., Wroclaw 53-114, Poland*
[c] *Department of Organic Chemistry, Faculty of Chemistry, Wroclaw University of Technology, 27 Wybrzeze Wyspianskiego St., Wroclaw 50-370, Poland*

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ABSTRACT

Novel indolo[2,3-b]quinoline derivatives substituted at N-6 and C-2 or C-9 positions with (dimethylamino)ethyl chains linked to heteroaromatic core by ether, amide or amine bonds, were manufactured and evaluated in vitro for their cytotoxic activity against several cell lines of different origin including multidrug resistant sublines and tested for their ability to influence the cell cycle and inhibit topoisomerase II activity. It was found, that all compounds show cytotoxic activity against cell lines tested, including multidrug resistant LoVo/DX, MES-SA/DX5 and HL-60 sublines. The tested compounds induce the G_2M phase cell cycle arrest in Jurkat cells, and inhibit topoisomerase II activity.

Synthetic derivatives of indolo[2,3-b]quinolines constitute novel group of compounds with potent in vitro antitumor activity and DNA binding properties. Their structure derive from neocryptolepine, a plant alkaloid isolated from roots of an African shrub *Cryptolepsis sanguinolenta*. Aqueous extracts of this plant (composed of a mixture of isomeric indoloquinolines) have been used for years in folk medicine as antimicrobial and antiplasmodial agents.[1] The first synthesis of indolo[2,3-b]quinoline was performed in 1897 by Gabriel and Eschenbach[2] in the process of o,o′-dinitro-α-cyanodibenzyl reduction. Lawson, Perkin and Robinson[3] and Holt and Petrov[4] obtained some derivatives of this structure by means of Graebe–Ullman reaction (thermal decomposition of adequate triazole). Synthetic analog of neocryptolepine that is 5,11-dimethyl-5*H*-indolo[2,3-b]quinoline (DIMIQ), structurally similar to ellipticine—plant alkaloid with cytotoxic activity[5]—was synthesized by our group in 1988.[6] It was shown that DIMIQ has potent cytotoxic activity in vitro and in vivo against mouse leukemia P388, L1210 and B16 melanoma cell lines.[6,7] However, more advanced studies revealed impaired bioavailability of 5*H*-indolo[2,3-b]quinoline derivatives, which brought about the need for further work on modifications of indoloquinoline ring structure.[8,9] Research on the relationship between structure and cytotoxic activity of indolo[2,3-b]quinoline from series 5*H*- and 6*H*- revealed that the presence, position, and nature of the substituent is crucial for the activity of the derivatives. We found that 6,11-dimethyl-6*H*-indolo[2,3-b]quinoline, an inactive isomer of 5,11-dimethyl-5*H*-indolo[2,3-b]quinoline (DIMIQ), acquires cytotoxic activity after the introduction of proper (alkylamino)alkyl substituents.[10,11] The biological significance of (alkylamino)alkyl substituents introduced into indoloquinoline isomeric cores (indolo [2,3-b] and [3,2-b] quinolines) was also reported by other groups.[12–17]

In this Letter the synthesis and some biological properties of novel series of 11-methyl-6-(2-dimethylamino)ethyl-6*H*-indolo[2,3-b]quinoline derivatives substituted at C-2 or C-9 position with (dimethylamino)alkyl chains linked with ether, amide or amine bonds to heteroaromatic chromophore are presented. These compounds bearing two (alkylamino)alkyl moieties attached to indolo-quinoline core were evaluated in vitro for their cytotoxic activity against several cell lines of different origin, including multidrug resistant sublines: human colon cancer, uterine sarcoma and human promyelocytic leukemia and tested for their ability to influence the cell cycle and inhibit topoisomerase II activity.

The syntheses of the initial indolo[2,3-*b*]quinoline derivatives, which comprise 2-methoxy-11-methyl-6*H*-indolo[2,3-*b*]quinoline (**1**), 9-methoxy-11-methyl-6*H*-indolo[2,3-*b*]quinoline (**2**), 11-methyl-2-nitro-6*H*-indolo[2,3-*b*]quinoline (**7**) and 11-methyl-9-nitro-6*H*-indolo[2,3-*b*]quinoline (**8**) were described elsewhere.[4,11,18]

Compounds **5** and **6** were obtained from 2-methoxy-11-methyl-6*H*-indolo[2,3-*b*]quinoline (**1**) or 9-methoxy-11-methyl-6*H*-indolo[2,3-*b*]quinoline (**2**) which were cleaved in 48% solution of

* Corresponding author. Tel.: +48 22 4563940; fax: +48 22 4563838.
E-mail address: l.kaczmarek@ifarm.eu (L. Kaczmarek).

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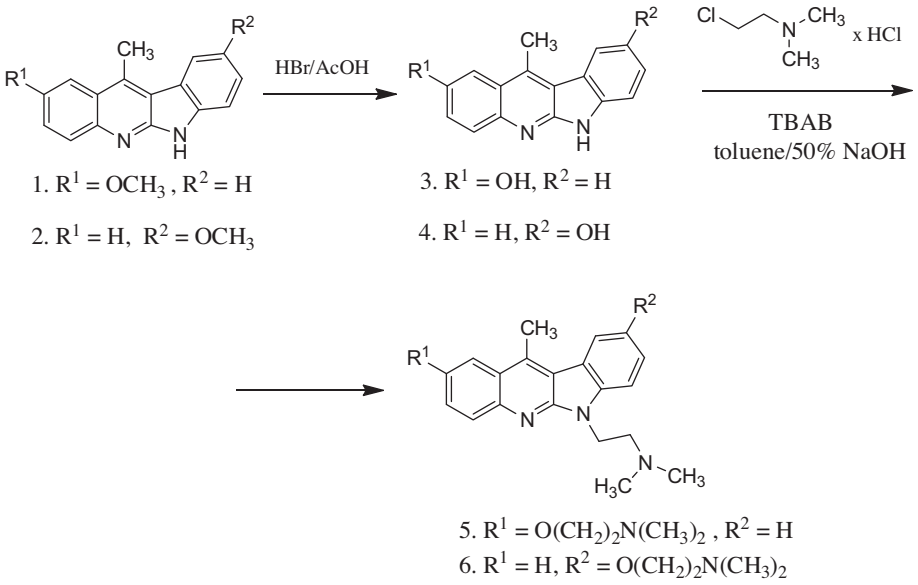
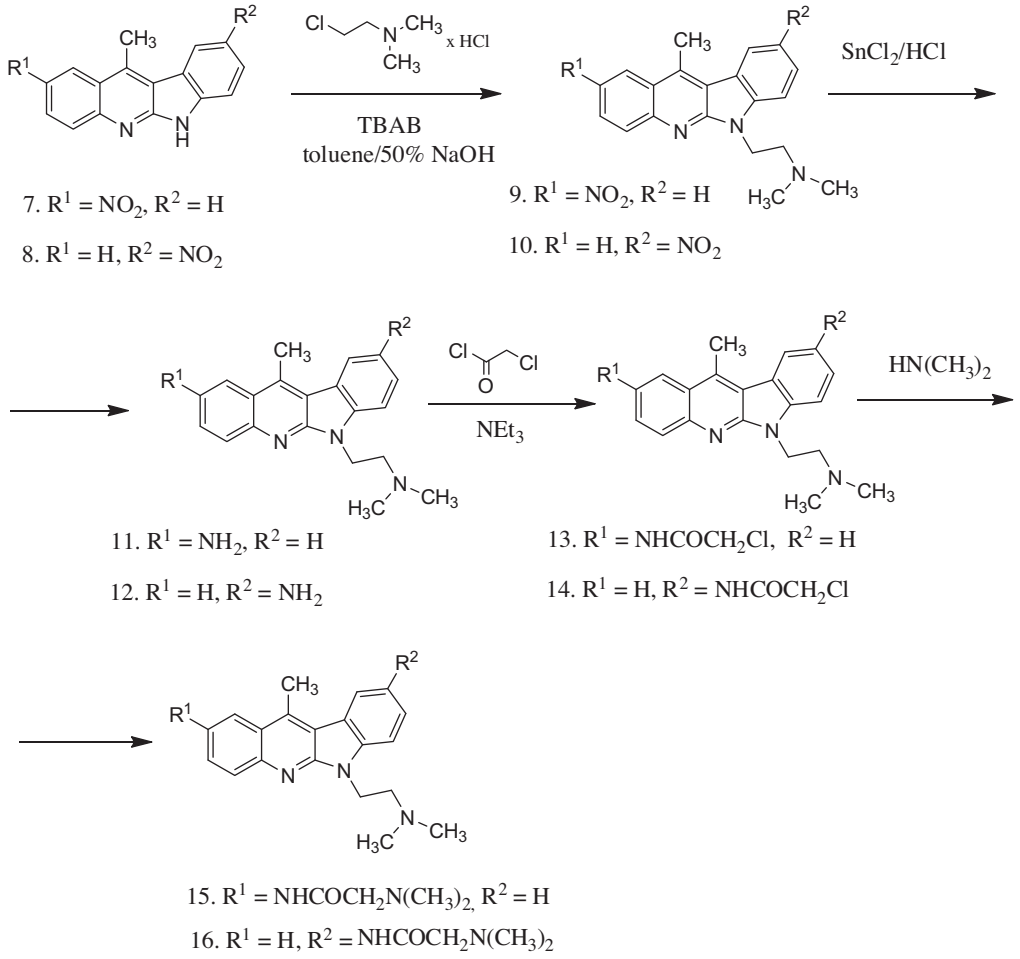
hydrobromic acid in acetic acid to corresponding hydroxyderivatives (**3**, **4**) Both phenols were then substituted with two equivalents of 2-dimethylaminoethyl chloride in phase transfer catalysis (PTC) conditions to yield compounds **5** and **6**. (Scheme 1).

The subsequent derivatives of indoloquinoline with (dimethylamino)methyl side chain connected to heteroaromatic moiety via amide group (**15** and **16**) were obtained in several steps. The initial nitroderivatives **7** and **8** were substituted at the indole nitrogen

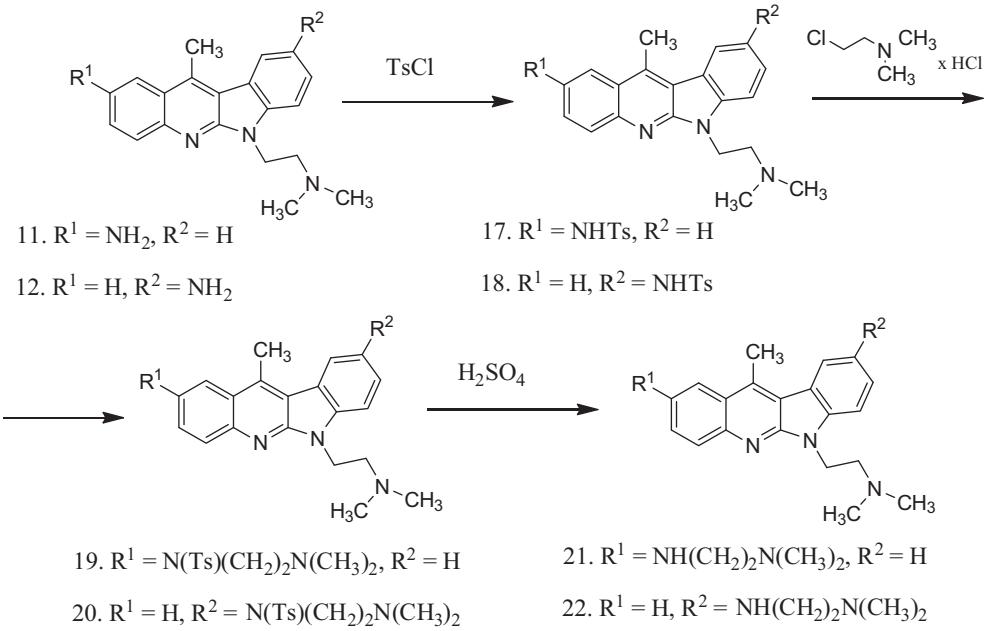


Scheme 1. Synthesis of 11-methyl-2 or 9-[2-(dimethylamino)ethoxy]-6-[(2-dimethylamino)ethyl]-6*H*-indolo[2,3-b]quinolines (**5** and **6**).



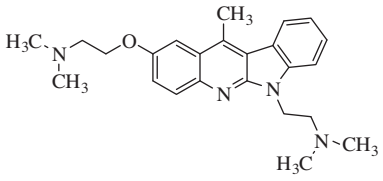
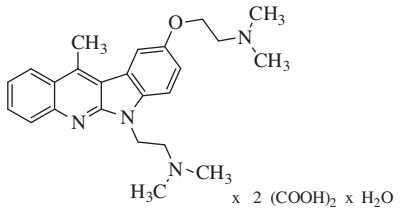
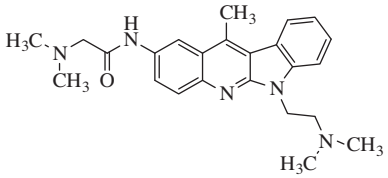
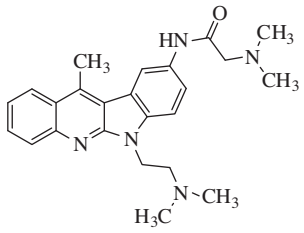
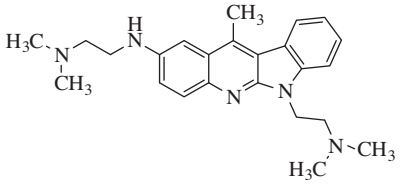
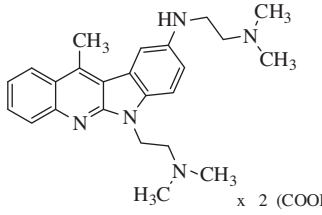
Scheme 2. Synthesis of N-{11-methyl-6-[(2-(dimethylamino)ethyl]-6*H*-indolo[2,3-b]quinolin-2 or 9-yl}-2-(dimethylamino)acetamides (**15** and **16**).

atom with 2-dimethylaminoethyl chain by the reaction with 2-dimethylaminoethyl chloride in PTC conditions, and then the resulted compounds **9** and **10** were reduced with tin (II) chloride in HCl/ethanol. The formed aminoderivatives **11** and **12** were used in the syntheses of amides **15** and **16** (Scheme 2) as well as substituted amine derivatives **21** and **22** (Scheme 3). At first, the amino



Scheme 3. Synthesis of 11-methyl-6-[(2-dimethylamino)ethyl]-2 or 9-[2-(dimethylamino)ethylamino]-6*H*-indolo[2,3-b]quinolines (**21** and **22**).

Table 1
Structures of double substituted indolo[2,3-b]quinoline derivatives

Indolo[2,3-b]quinoline derivatives	
C-2	C-9
	
5 (m.wt. 390.53)	**6** (m.wt. 588.61)
	
15 (m.wt. 403.53)	**16** (m.wt. 403.53)
	
21 (m.wt. 389,54)	**22** (m.w. 587.64)

groups of compounds **11** or **12** were transformed into corresponding chloroamides by reactions with chloroacetyl chloride in the presence of sodium carbonate. Then the side chain chlorine atom of the obtained compound (**13**) or (**14**) was substituted with dimethylamine in the presence of triethylamine as an acid scavenger (Scheme 2).

The third group of derivatives was obtained in the three step synthesis. The amino groups of compounds **9** or **10** were transformed into sulfonamides **17** and **18**, then active hydrogen atoms at sulfamoyl functional groups were substituted with 2-dimethylaminoethyl chloride at PTC conditions (compounds **19, 20**). Finally, both sulfonamides were cleaved in the mixture of concentrated sulfuric acid and glacial acetic acid to give the desired compounds **21** and **22** (Scheme 3).

The obtained compounds **5**, **6**, **15**, **16**, **21** and **22** were tested for their biological activity. Compounds **6** and **22** were obtained as oils, which are inconvenient for biological testing. Therefore, prior to tests, they were transformed into crystalline oxalic acid salts. Structures of compounds tested are given in Table 1.

All compounds are substituted with 2-(dimethylamino)ethyl substituents at N-6 and also at C-2 or C-9 positions, where this substituent is connected to a heterocyclic chromophore with an ether (**5**, **6**) or amine (**21**, **22**) linker. However, compounds **15** and **16** are substituted at C-2 or C-9 with (dimethylamino)methyl carbamoyl moiety. The aim of this study was to find whether a character of the linker between chromophore and dialkylaminoalkyl moiety has any impact on the biological activity. Moreover, it was expected that the cytotoxicity in C-2 and C-9 substituted compounds would be higher than in N-6 mono-substituted derivatives.[11] The results of the studies on antiproliferative activity of disubstituted indolo[2,3-b]quinoline derivatives are summarized in Table 2.

All tested compounds were cytotoxic against human cancer cell lines, such as KB (nasopharynx carcinoma), MCF-7 (breast cancer), A549 (lung cancer) and Hs294T(melanoma), but also against normal mice fibroblast BALB/3T3. The IC_{50} were lower than 1 μM and these derivatives were more potent than the referential compound, that is 5,11-dimethyl-indolo[2,3-b]quinoline [DiMIQ] (IC_{50} between 1.0 and 9.7 μM). In general, derivatives substituted in position C-2: **21**, **15** and **5**, exhibited higher cytotoxicity than their C-9 substituted isomers.

Multidrug resistance (MDR) is one of the most important factors affecting the therapy of tumors, and there is still a demand for seeking the novel, anticancer drugs that may overcome this phenomenon. Therefore we examined novel, disubstituted indoloquinolines for their ability to overcome the drug resistance of neoplastic cells. In our research we used three various human cancer cell lines and their drug-resistant sublines: human colon cancer (LoVo) and doxorubicin-resistant LoVo/DX, uterine sarcoma (MES-SA) and MES-SA/DX5 (both showing P-gp-dependent resistance to doxorubicin), human promyelocytic leukemia cell line (HL-60) and HL-60/MX2 (P-gp-independent and topoisomerase II-dependent resistance). The results of these studies are summarized in Table 3.

The results of our investigations showed that—in contrary to the known chemotherapeutics such as doxorubicine and mitoxantron—all indoloquinoline derivatives were active against drug resistant cells and their activity was higher than that of DIMIQ. We calculated the resistance indexes (RI) by dividing the IC_{50} values of the compounds tested against the cells of drug resistant cell subline by the respective values obtained against the cells of drug sensitive cell line. All compounds were capable of overcoming the barrier of drug P-gp-dependent resistance (RI 0.2–1.6). With the exception of the compound **21**, the tested compounds did not overcome the barrier of topoisomerase II-dependent (reduced

Table 2
Antiproliferative activity of disubstituted indolo[2,3-b]quinoline derivatives against human cancer cell lines and normal mice fibroblast (BALB/3T3)

Compound tested	Cell line/IC_{50} ± SD (μM)				
	KB	A-549	MCF-7	Hs294T	BALB/3T3
5	0.08 ± 0.02	0.19 ± 0.07	0.66 ± 0.05	0.76 ± 0.14	0.57 ± 0.05
6[a]	0.31 ± 0.10	0.32 ± 0.03	0.81 ± 0.07	0.91 ± 0.12	0.74 ± 0.05
15	0.15 ± 0.07	0.24 ± 0.07	0.38 ± 0.047	0.62 ± 0.07	0.31 ± 0.05
16	0.15 ± 0.05	0.81 ± 0.10	0.79 ± 0.10	0.64 ± 0.07	0.67 ± 0.05
21	0.64 ± 0.08	0.17 ± 0.05	0.47 ± 0.00	0.35 ± 0.05	0.34 ± 0.02
22[a]	0.36 ± 0.13	0.29 ± 0.05	0.99 ± 0.05	0.72 ± 0.09	0.60 ± 0.02
DIMIQ[b]	1.14 ± 0.61	2.19 ± 0.48	1.50 ± 0.52	9.70 ± 1.42	5.70 ± 0.93

IC_{50}—compound concentration leading to 50% inhibition of cell proliferation.
[a] Tested as dioxalate hydrates.
[b] DiMIQ—referential compound—5,11-dimethyl-5*H*- indolo[2,3-b]quinoline.

Table 3
Antiproliferative activity of disubstituted indolo[2,3-b]quinoline derivatives against human cancer cell lines and its sublines resistant to chemotherapeutic agents

Compound tested	Cell line/IC_{50} ± SD (μM)								
	LoVo	LoVo/DX	RI_{LoVo}	MESSA	MESSA/DX5	RI_{MESSA}	HL-60	HL-60/MX2	RI_{HL-60}
5	0.64 ± 0.07	0.15 ± 0.05	0.2	0.08 ± 0.01	0.07 ± 0.02	0.9	0.04 ± 0.02	0.32 ± 0.07	8.0
6[a]	0.64 ± 0.10	0.21 ± 003	0.3	0.13 ± 0.07	0.08 ± 0.03	0.6	0.13 ± 0.02	0.51 ± 0.03	3.9
15	0.33 ± 0.10	0.11 ± 0.02	0.4	0.10 ± 0.01	0.07 ± 0.01	0.7	0.06 ± 0.002	0.57 ± 0.14	9.5
16	0.60 ± 0.19	0.14 ± 0.00	0.2	0.09 ± 0.10	0.09 ± 0.02	1.0	0.215±0.012	0.47 ± 0.14	2.2
21	0.12 ± 0.02	0.10 ± 0.01	0.8	0.05 ± 0.01	0.08 ± 0.01	1.6	0.09± 0.02	0.05 ± 0.01	0.6
22[a]	0.27 ± 0.05	0.39 ± 0.02	1.5	0.10 ± 0.01	0.09 ± 0.02	0.9	0,13 ± 0,01	0,61 ± 0,15	4.7
DIMIQ	0.27 ± 0.40	0.80 ± 0.12	3.0	0.31 ± 0.08	0.15 ± 0.28	0.5	1.30 ± 0.04	1.30 ± 0.20	1.0
Doxorubicin	0.04 ± 0.01	5.27 ± 0.02	131.8	0.01 ± 0.002	0.25 ± 0.05	25.0	n.t.	n.t.	—
Mitoxantron	n.t.	n.t.	—	n.t.	n.t.	—	0.0025±0.0008	0.561±0.213	224.4

n.t. not tested.
RI—the resistance indexes were calculated by dividing the ID_{50} values of the compounds tested against the cells of drug resistant cell subline by respective values obtained against the cells of drug sensitive cell line. According to Harker et al.[23] three categories of the cells could be distinguished: (a) the cells are drug-sensitive—if the ratio approaches 0–2; (b) the cells are moderately drug-resistant—if the ratio ranges from 2 to 10; (c) the cells are markedly drug-resistant—if the ratio is higher than 1.
[a] Tested as dioxalate hydrates.

expression of this enzyme[19]) resistance represented by the HL-60/MX2 cells (RI ranged from 2 to 10).

In order to verify the hypothetic mechanism of cytotoxicity of disubstituted indoloquinolines, we studied the ability of the tested compounds to inhibit the human topoisomerase II activity. It was found that these indolo[2,3-b]quinoline derivatives are potent inhibitors of the said enzyme, similar to m-AMSA (aminoacridine derivative) and much more active than daunorubicin (anthracycline aminoglycoside antibiotic), both known as intercalating and inhibiting topoisomerase II antineoplastic agents. However, there was no clear structure–activity relationship among the tested indoloquinolines. (Table 4). In order to find how the novel indoloquinoline derivatives affect the cell cycle, we also performed a cell cycle analysis of the Jurkat cells. The results are summarized in Table 4.

All of disubstituted indolo[2,3-b]quinoline derivatives showed the ability to inhibit the cell cycle in G2/M phase. The lowest influence on cell cycle inhibition in G2/M phase was exhibited by the compound **6** substituted with 2-(dimethylamino)ethoxy chain at C-2 position, and the highest one was revealed by the compound **15** substituted with carbamoyl chain at C-2. The rest of the derivatives had activity similar to that of the referential compound DIMIQ, with lower sub-toxic concentrations.

In conclusion, the tested 11-methyl-6-(2-dimethylamino)ethyl-6*H*-indolo[2,3-b]quinolines bearing (dimethylamino)alkyl chain at C-2 or C-9 positions, connected to heterocyclic chromophore with ether (**5** and **6**), amine (**15** and **16**) or amide (**21** and **22**) linker, revealed antiproliferative activity against human cancer cell lines KB (nasopharynx carcinoma), A-549 (lung carcinoma), MCF-7 (breast cancer) and Hs294T (melanoma). This activity was considerably higher than that of the reference DIMIQ and, in general, the C-2 substituted derivatives were more active than C-9 ones. Compounds **5, 6, 15, 16, 21** and **22** were also tested for their antiproliferative activity against human cancer cell lines and their sublines, resistant to chemotherapeutic agents, that is LoVo versus LoVo/DX, MESSA versus MESSA/DX5 and HL-60 versus HL-60 /MX2. All compounds showed pronounced ability to overcome the barrier of drug P-gp-dependent resistance (RI 0.2–1.6), however (with the exception of the compound **21**) they did not overcome the barrier of topoisomerase II-dependent resistance represented by the HL-60/MX2 cells (RI ranged from 2 to 10). The presented data suggest that the mechanism of action of these compounds is strongly related to topoisomerase II activity, as it is known for many other indolo[2,3-b]quinoline derivatives.[11,20,21] The study of the ability of the tested compounds to inhibit the human topoisomerase II activity confirmed that they are potent inhibitors of this enzyme, comparable to m-AMSA (aminoacridine derivative) and much more active than daunorubicin (anthracycline aminoglycoside antibiotic), both known as intercalating and inhibiting topoisomerase II antineoplastic agents. On the other hand, the presented results show that the tested compounds are not able to overcome the topoisomerase II-dependent resistance barrier in HL-60/MX2 cells, which supports our earlier observations that their mechanism of action involves more than the inhibition of topoisomerase II activity.[22] Although all tested compounds revealed promising antiproliferative activity against human tumor cell lines and also were able to overcome the barrier of drug resistance, their cytotoxicity to normal cells (mice fibroblast BALB/3T3) is comparable with antineoplastic activity. As we also found, there is no clear structure–activity relationship among the tested indoloquinolines. These results show that further extensive study among indolo[2,3-b]-quinoline derivatives are needed. The aim of the further work is to elucidate their mechanism of action as well as the rational design and manufacturing of the compounds with pronounced bioavailability and reduced toxicity to the normal cells.

Table 4
Inhibition of topoisomerase II activity and the effect on cell cycle of Jurkat cells revealed by disubstituted indolo[2,3-b]quinoline derivatives

Compound tested	Total topoisomerase II inhibition [mM]	Cell cycle inhibiton	
		Subtoxic concentration [μM]	Degree of inhibition in G2M phase
5	0.025	0.38	++
6[*]	0.025	0.17	+
15	0.05	0.10	+++
16	0.025	0.37	++
21	0.025	0.26	++
22[a]	0.05	0.26	++
DIMIQ[b]	0.5	1.02	++
m-AMSA[c]	0.05		
Daunorubicin[d]	0.5		

[a] Tested as dioxalate hydrates; referential compounds.
[b] DiMIQ—5,11-dimethyl-5*H*-indolo[2,3-b]quinoline.
[c] m-AMSA—aminoacridine derivative.
[d] Daunorubicin—anthracycline aminoglycoside antibiotic; both are a potent intercalating and inhibiting topoisomerase II antineoplastic agents.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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