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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In vitro antiproliferative activity of 11-aminoalkylamino-substituted 5*H*-indolo[2,3-*b*]quinolines; improving activity of neocryptolepines by installation of ester substituent

Wen-Jie Lu · Marta Świtalska · Li Wang · Mizuki Yonezawa · Ibrahim El-Tantawy El-Sayed · Joanna Wietrzyk · Tsutomu Inokuchi

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Abstract The research article describes the effect of an ester group on the in vitro antiproliferative activity in SAR studies of 5-methyl-5*H*-indolo[2,3-*b*]quinoline (neocryptolepine) derivatives. The C-2 and/or C-9 ester-substituted neocryptolepines were synthesized starting from indole-3-carboxylates and *N*-methylanilines, which were bearing an ester group. To these ester-substituted neocryptolepines, various aminoalkylamino substituents were further attached at the C-11, and an in vitro antiproliferative assay was performed by varying the substituents at the C-11 and the position of the ester group in the A and/or D ring of neocryptolepines. Results indicated that the antiproliferative activities of the agents could be improved by introducing an ester substituent at the C-9 position. Among them, the methyl 11-(3-aminopropylamino)-5-methyl-5*H*-indolo[2,3-*b*]quinoline-9-carboxylate (**8b**) was the most potent agent with an IC_{50} value of 0.044 μM against the human leukemia MV4-11 cell line. The selective cytotoxicity of the agents between the cancer cell lines and normal cell lines were also described. The antiproliferative potency of dimethyl 11-(3-aminopropylamino)-5-methyl-5*H*-indolo[2,3-*b*]quinoline-2,9-dicarboxylate (**9a**) against the human colon cancer cell line HCT116 is 28 times higher than against the normal mice fibroblast cell line BALB/3T3.

Keywords 5*H*-indolo[2,3-*b*]quinoline · Anti-proliferative agent · C9-ester substituted necryptolepine · MV4-11 · HCT116

W.-J. Lu · L. Wang · M. Yonezawa · I. E.-T. El-Sayed · T. Inokuchi (✉)
Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
e-mail: inokuchi@cc.okayama-u.ac.jp

M. Świtalska · J. Wietrzyk (✉)
Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 12, R. Weigl Street, 53-114 Wroclaw, Poland

I. E.-T. El-Sayed
Chemistry Department, Faculty of Science, El Menoufeia University, Shebin El Koom, Egypt

Introduction

Indoloquinolines isolated from the root of *Cryptolepis sanguinolenta*, the climbing shrub growing in some African countries, are attracting the constant attention of pharmacologists, since an aqueous macerate or decoction of this root is used in traditional medicine for the treatment of infectious diseases like malaria and various disorders of the body (Alexandra *et al.*, 2000; Cimanga *et al.*, 1996a, b). Among the various isolated products with indoloquinoline structures, cryptolepine **i** (5-methylindolo[3,2-*b*]quinoline), and the minor alkaloid neocryptolepine **ii** (5-methylindolo[2,3-*b*]quinoline) (Fig. 1) have been intensively studied, which showed broad spectrum of biological activities including antibacterial (Cimanga *et al.*, 1996a, b, 1997, 1998), antifungal (Cimanga *et al.*, 1996a, b, 1997, 1998), and antimalarial (Philippe *et al.*, 1996; Kirby *et al.*, 1995; Wright *et al.*, 1996).

Since cryptolepine **i** and neocryptolepine **ii** possess linearly arranged tetracyclic planar structures, they behave as a DNA intercalating agent and inhibit topoisomerase II thus revealing a high level of cytotoxicity (Guittat *et al.*, 2003; Jonckers *et al.*, 2002; Bailly *et al.*, 2000). Consequently, SAR studies on these structures as a lead to search for more active drug candidates have been extensively

undertaken (Kumar *et al.*, 2008; Lavrado *et al.*, 2010; Parvatkar *et al.*, 2011).

Our previous research on 5-Me-indolo[2,3-*b*]quinolines revealed that the 11-amino group is important for their activity, especially the 3-aminopropylamino group, which could increase the activity against MV4-11 about 67 times compared to its 11-chloro precursor (Wang *et al.*, 2012). The antiproliferaive test indicated that the 5-methylated derivatives are usually more cytotoxic than their respective 6-methylated congeners. A synergistic effect of the substituents at the C-2 position was also observed. For example, the C-2-Br derivative was 5 times more active compared to the non-halogenated derivative on 11-(3-aminopropylamino)neocryptolepine, and the 2-chloro-11-(4-methyl-1,4-diazepane-1-yl)neocryptolepine was 65 times more active than its corresponding agent with no substituent at C-2.

On the other hand, a recent publication describing effect of substituents on the anticancer activity indicated that the introduction of an ester group to the core structures affects the activity of other plant-derived anticancer agents such taxol (Ojima *et al.*, 1997), camptothecin (Yang *et al.*, 2002), bryostatin (Wender and Hinkle, 2000), and 5-fluorouracil (Xiong *et al.*, 2009). Such an improvement in the anticancer activity is believed to be due to increasing both the lipophilicity and bioavailability of the drug by introducing the ester group into the core structure. Encouraged by these significant information, we examined the introduction of an ester group to the core and checked its influence on the antiproliferative activity. In this study, we report the further investigation of the anticancer potential of the neocryptolepine core. An ester group was introduced at the C-2 position of the A-ring and/or the C-9 position of the D-ring to establish or extend the structure-activity relationship (SAR) study for these regions.

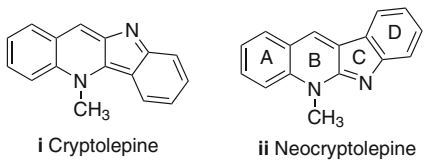
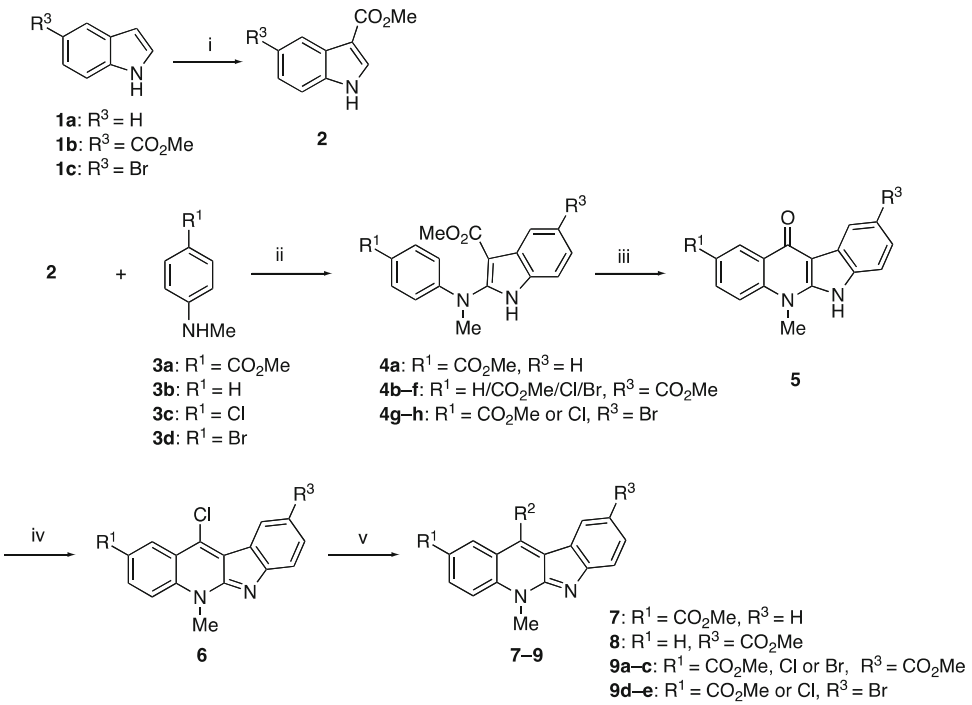


Fig. 1 Structures of cryptolepine and neocryptolepine

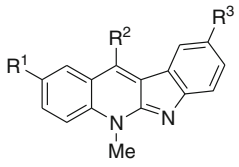
Synthesis and biological evaluation

The preparations of the ester substituted 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolines **6** were carried out according to the method we previously described (Wang *et al.*, 2012). Since the dimethyl 1*H*-indole-3,5-dicarboxylate (**2b**), a key starting compound, was not commercially available, it was synthesized by installation of an ester group at the C-3 position to the methyl 1*H*-indole-5-carboxylate **1** using the reaction with trichloroacetyl chloride in the presence of pyridine, followed by successive alkaline treatment with KOH at reflux in MeOH and MeI

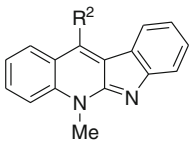


Scheme 1 Preparation of ester substituted 11-amino-neocryptolepines **7–9**. Reagents and conditions: (i) a. Pyridine, trichloroacetyl chloride, THF. b. KOH, MeOH, reflux. (ii) a. *N*-chlorosuccinimide, 1,4-dimethylpiperazine. b. trichloroacetic acid. (iii) diphenyl ether, reflux. (iv) $POCl_3$, toluene, reflux. (v) appropriate amines

Table 1 Compounds **7–8** as anti-proliferative agents against human leukemia cell line MV4-11



7-8



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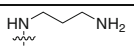
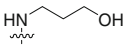
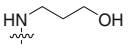
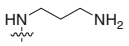
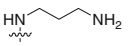
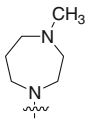
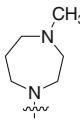
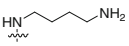
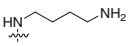
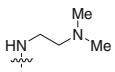
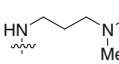
Compound **7–8**	R^1	R^2	R^3	Yield %	IC_{50} (μM) MV4-11	Compound **10**	R^2	IC_{50} (μM) MV4-11
Doxorubicin HCl					0.006 ± 0.002			
7	$-CO_2Me$		H	93	0.086 ± 0.020			
8a	H		$-CO_2Me$	89	0.094 ± 0.030	**10a**[a]		0.170 ± 0.010
8b	H		$-CO_2Me$	92	0.044 ± 0.011	**10b**[a]		0.066 ± 0.023
8c	H		$-CO_2Me$	90	0.797 ± 0.227	**10c**[a]		0.164 ± 0.047
8d	H		$-CO_2Me$	91	0.127 ± 0.035	**10d**[a]		7.171 ± 0.987
8e	H		$-CO_2Me$	95	0.069 ± 0.019	**10e**[a]		0.100 ± 0.035
8f	H		$-CO_2Me$	86	0.811 ± 0.250	**10f**[a]	Cl	1.312 ± 0.262
8g	H		$-CO_2Me$	87	0.051 ± 0.023			

[a] Wang *et al.* (2012)

in DMF (Linton and Kozlowski, 2008). The obtained dimethyl 1*H*-indole-3,5-dicarboxylate (**2b**) was combined with *N*-methylaniline (**3b**) via chlorination with NCS in the presence of 1,4-dimethylpiperazine, giving 2-(*N*-methylanilino)indole-3,5-dicarboxylate (**4b**) in 73 % yield. Heating of **4b** at 250 °C in diphenyl ether induced intramolecular acylation at the C-2 of aniline, forming the tetracyclic indolo[2,3-*b*]quinolinone **5**. The reaction of **5** with $POCl_3$ afforded the 11-chloro-indolo[2,3-*b*]quinoline **6** as a result of dehydrative chlorination. The amination of **6** via an S_{NAr} reaction smoothly proceeded by heating with amines in THF to give various 11-aminoindolo[2,3-*b*]quinolines **7–9** as depicted in Scheme 1.

We introduced an ester group to the indole motif at the C-9 position, and varied the C-11 position with different amines (**8a–8g**). The results of the anti-proliferative evaluation against the human leukemia cell line (MV4-11) are summarized in Table 1. We found that in some cases, their activities were improved compared to those compounds without substituents at C-9. For example, **8a**, **8b**, **8d**, and **8e** were shown to be more active compared to compounds **10a**, **10b**, **10d**, and **10e** which lack a substitutent at the C-2

Table 2 The anti-proliferative activity of agents **9** against human leukemia cell line MV4-11

Compound **9**	R^1	R^2	R^3	Yield%	IC_{50} (μM)
					MV4-11
9a	$-CO_2Me$		$-CO_2Me$	95	0.133 ± 0.057
9b	–Br		$-CO_2Me$	83	0.050 ± 0.016
9c	–Cl		$-CO_2Me$	88	0.056 ± 0.035
9d	$-CO_2Me$		–Br	96	0.118 ± 0.075
9e	–Cl		–Br	91	0.076 ± 0.034

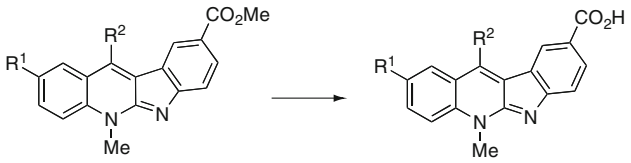
or C-9 position. Their IC_{50} values ranged from 0.044 to 0.811 μM, and the best result was achieved with a 3-aminopropylamino group substituted at C-11 (**8b**, IC_{50} = 0.044 μM). Compared with the agent **7**, which contained an ester group at the C-2 position on the quinoline subunit, the agent **8b** was twice more efficient.

Furthermore, we have synthesized and evaluated agents **9a**–**9e**, bearing the same aminopropylamino group R^2 while varying the ester group at R^1 or R^2 for the SAR study, and a synergistic effect were detected (Table 2). In general, an ester substituent at the C-9 position can efficiently favor the anticancer activity of the agent while the ester substituent at the C-2 position is not as efficient. Comparing compounds **9b** and **9d** for instance, the compound **9b** was twice more active than **9d**, the same trend as observed for the agents **7** and **8b**. Compared with **8b**, the introduction of a substituent at the C-2 position, compounds **9a**, **9b**, and **9c** for instance, has made the compound less active.

The solubility of an agent in an aqueous medium can significantly influence its further application, despite its high anticancer activity. In order to improve the water solubility of the agents, we tried to hydrolyze the 9-ester substituted neocryptolepines into a 9-carboxylic acid analog by treating the methyl 11-amino-5*H*-indolo[2,3-*b*]quinoline-9-carboxylate **8** with NaOH(aq) in MeOH. The mixture was refluxed overnight to afford the 9-carboxylic acid substituted indolo[2,3-*b*]quinoline **11** in good yield, as shown in Scheme 2. The evaluation results of their anti-proliferative activity are summarized in Table 3.

Unfortunately, the anti-proliferative activity of the hydrolyzed derivatives **11** turned out that though the solubility of the agents in an aqueous medium was improved, their anti-proliferative activities dramatically decreased compared to their precursors **8a**–**8d**.

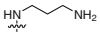
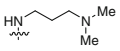
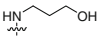
Furthermore, the indoloquinoline derivative compounds bearing an ester substituent (**7**–**9**) were also evaluated against other cell lines to evaluate the selective anticancer properties (Table 4). Two kinds of cancer cell lines



8 **11**

Scheme 2 Preparation of the 9-caboxylic acid substituted indolo[2,3-*b*]quinolines **11**. Reagents and conditions: MeOH/NaOH(aq)

Table 3 The anti-proliferative activity of agents **11** against human leukemia cell line MV4-11

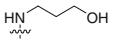
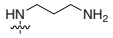
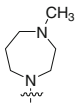
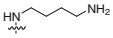
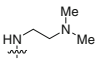
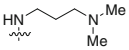
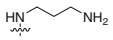
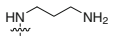
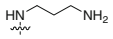
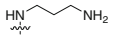
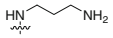
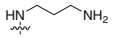
Compound **11**	R^1	R^2	R^3	Yield%	IC_{50} (μM)
					MV4-11
11a	H		$-CO_2H$	82	>25
11b	H		$-CO_2H$	79	9.28 ± 1.74
11c	H		$-CO_2H$	85	>25
11d	H		$-CO_2H$	76	>25

(human lung cancer cell line A549, human colon cancer cell line HCT116) and a kind of normal cell line (normal mice fibroblast cell line BALB/3T3) were chosen for the tests. Most of the tested compounds were cytotoxic against the cancer cell lines, except for the agent **8c** with an IC_{50} value of more than 5 μM. In general, these tested compounds were selectively cytotoxic against the human colon cancer HCT116 cell line, and had a lower cytotoxicity against the A549 or BALB/3T3 cell lines. Their IC_{50} values against the HCT 116 cell line were generally 4–5 times lower than those against the A549 or BALB/3T3 cell lines. The agents **7**, **8a**, **8b**, **8g**, and the **9** series were shown to be more efficient than the wide spectrum anticancer medicine, doxorubicin, against the HCT116 cells. In addition, the agent **9c** revealed a better activity against the A549 cells when compared to doxorubicin.

Spectroscopic characterization of neocryptolepine derivative 8b interacting with salmon fish sperm DNA

The DNA binding studies of compounds **8b** was performed using UV–vis absorption spectroscopy with salmon fish sperm DNA in phosphate buffer of pH 7.0 at 20 °C. The

Table 4 The test of compounds **8** and **9** as anti-proliferative agents against A549, HCT116, and BALB/3T3 cell lines

Compound **8**	R^1	R^2	R^3	IC_{50} (μM)		
				A549[a]	HCT116[a]	BALB/3T3[a]
Doxorubicin HCl				0.329 ± 0.097	0.390 ± 0.098	1.078 ± 0.033
8a	H		$-CO_2Me$	0.587 ± 0.325	0.173 ± 0.047	0.873 ± 0.058
8b	H		$-CO_2Me$	0.820 ± 0.456	0.176 ± 0055	0.933 ± 0.047
8c	H		$-CO_2Me$	5.09 ± 2.96	1.31 ± 0.155	>25
8d	H		$-CO_2Me$	3.39 ± 0.800	0.672 ± 0.400	8.21 ± 0.453
8e	H		$-CO_2Me$	0.712 ± 0.112	0.308 ± 0.112	0.936 ± 0.024
8f	H		$-CO_2Me$	0.797 ± 0.125	0.444 ± 0.321	1.09 ± 0.319
8g	H		$-CO_2Me$	0.664 ± 0.154	0.151 ± 0.026	0.876 ± 0.023
9a	$-CO_2Me$		$-CO_2Me$	0.864 ± 0.221	0.295 ± 0.112	8.40 ± 0.286
9b	–Br		$-CO_2Me$	0.302 ± 0.138	0.164 ± 0.070	0.773 ± 0.023
9c	–Cl		$-CO_2Me$	0.194 ± 0.063	0.116 ± 0.078	0.833 ± 0.030
9d	$-CO_2Me$		–Br	0.461 ± 0.123	0.163 ± 0.073	0.743 ± 0.016
9e	–Cl		–Br	0.464 ± 0.111	0.284 ± 0.142	0.834 ± 0.067
7	$-CO_2Me$		H	0.649 ± 0.080	0.130 ± 0.014	0.768 ± 0.155

[a] *A549* human lung cancer cell line, *HCT116* human colon cancer, *BALB/3T3* normal mice fibroblast cell line

hypochromic effect was observed in the absorption spectra while the DNA solution was gradually added to the solution of the compound **8b**. The results in Fig. 2 showed that the absorption band at 298 nm for the **8b** decreased while increasing the DNA concentration. It illustrated that there is a strong interaction between **8b** and DNA. Then the binding constant of **8b**-DNA was calculated as 2.77×10^5 L mol^{-1} according to double-reciprocal equation.

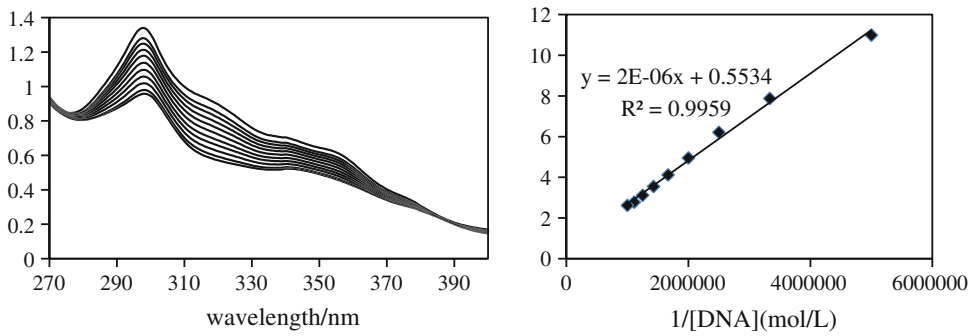


Fig. 2 UV–Vis absorption spectra of compound **8b** and **8b**-DNA at 20 °C. $C_{\mathbf{8b}} = 50$ μmol/L, $C_{DNA} = 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0$ μmol/L for curve 1–11 in pH 7.0 phosphate buffer solution; (b) the plot of 1/ΔA vis 1/[DNA] for **8b**-DNA

Conclusion

To summarize, we have synthesized a series of C-2 and/or C-9 ester substituted 11-amino-5-methyl-5*H*-indolo[2,3-*b*]quinolines and evaluated their antiproliferative activity for an SAR study. The results indicated that the activities of the agents could be improved by introducing an ester substituent at the C-9 position. Among them, the methyl 11-(3-aminopropylamino)-5-methyl-5*H*-indolo[2,3-*b*]quinoline-9-carboxylate (**8b**) was the most potent with an IC_{50} value of 0.044 μM against the human leukemia MV4-11 cell line. While compound **9a** showed 28 times more selective cytotoxic activity against the human colon cancer cell line than normal mice fibroblast cell line, BALB/3T3.

Experimental

Chemistry

General

The commercially obtained reagents were directly used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were measured on the Varian INOVA-600 or Varian INOVA-400 spectrometer. High resolution mass spectra were obtained on a Bruker micrOTOF II-SKA spectrometer. Melting points were determined on a J-Science RFS-10 hot stage microscope. The scaffolds **7**–**8** and were prepared by the method we previously mentioned (Wang *et al.*, 2013).

*General procedure for the synthesis of Dimethyl 1H-indole-3,5-dicarboxylate **2b***

Pyridine (0.30 mL, 3.54 mmol) was added to a suspension of methyl 1*H*-indole-5-carboxylate (0.48 g, 2.72 mmol) in anhydrous THF (6 mL) at 0 °C. A solution of trichloroacetyl chloride (0.40 mL, 3.54 mmol) in THF (6 mL) was added dropwise via an addition funnel over 1 h. The reaction mixture was then allowed to warm to room temperature to stir over night. The reaction mixture was quenched in 1 M HCl, dried over Na_2SO_4, and concentrated under vacuum. The resulting solid was then dissolved in MeOH (54 mL), and KOH(s) was added. The reaction mixture was heated to reflux for 5 h, then stirred at ambient temperature for 1 h, followed by concentration under vacuum. The solid was purified by chromatography (SiO_2, 25 % EtOAc/Hexane) in 75 % yield.

*Dimethyl 1H-indole-3,5-dicarboxylate **2b***

White solids; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 12.28 (s, 1H), 8.69 (d, J = 1.5 Hz, 1H), 8.23 (s, 1H), 7.83 (dd, J = 8.6, 1.7 Hz, 1H), 7.57 (dd, J = 8.6, 0.5 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.34 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.0, 164.4, 139.0, 134.3, 125.2, 123.3, 122.7, 112.5, 107.4, 51.9, 50.9.

*Methyl 5-bromo-1H-indole-3-carboxylate **2c***

White solids; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 8.68 (s, 1H), 8.33 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 3.0 Hz, 1H), 7.37 (dd, J = 8.6, 1.9 Hz, 1H), 7.29 (dd, J = 8.6, 0.4 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 165.1, 134.6, 131.8, 127.4, 126.3, 124.2, 115.7, 112.9, 108.6, 51.3.

*Methyl 2-((4-(methoxycarbonyl)phenyl)(methyl)amino)-1H-indole-3-carboxylate **4a***

White solids, Mp: 217–219 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ_H (ppm) 12.25 (br s, 1 H), 8.00 (d, J = 7.92 Hz, 1 H), 7.81 (d, J = 8.80 Hz, 2 H), 7.39 (d, J = 7.63 Hz, 1 H), 7.29–7.15 (m, 2 H), 6.73 (d, J = 8.80 Hz, 2 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.37 (s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 166.1, 163.5, 151.7, 145.3, 132.6, 130.7, 125.8, 122.7, 121.5, 121.0, 119.0, 112.9, 111.8, 98.4, 51.6, 50.6, 39.1.

*Dimethyl 2-(methyl(phenyl)amino)-1H-indole-3,5-dicarboxylate **4b***

White solids, Mp: 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 9.09 (s, 1H), 8.80–8.75 (m, 1H), 7.85 (dd, J = 8.5, 1.7 Hz, 1H), 7.25–7.19 (m, 3H), 6.96–6.85 (m, 3H), 3.89 (s, 3H), 3.79 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 168.2, 164.3, 149.3, 146.5, 134.9, 129.3, 126.3, 124.0, 123.5(2C), 121.3, 117.1, 110.3, 97.6, 51.9, 51.0, 40.2. ESI-HRMS: *m/z* Calcd. for $C_{19}H_{17}N_2O_4$ $[M–H]^-$ 337.1188. Found 337.1166.

*Dimethyl 2-((4-(methoxycarbonyl)phenyl)(methyl)amino)-1H-indole-3,5-dicarboxylate **4c***

White solids, Mp: 234–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 9.58 (s, 1H), 8.84 (d, J = 1.3 Hz, 1H), 7.96 (dd, J = 8.5, 1.6 Hz, 1H), 7.80–7.73 (m, 2H), 7.38 (d, J = 8.5 Hz, 1H), 6.70–6.63 (m, 2H), 3.93 (s, 3H), 3.82 (d, J = 3.5 Hz, 6H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 168.0, 167.3, 163.9, 150.9, 146.7, 135.0, 131.1, 125.7, 124.7, 124.4, 124.0, 120.6, 113.5, 110.9, 100.8, 52.0, 51.8, 51.2, 39.7. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{20}N_2O_6$ $[M+Na]^+$ 419.1219. Found 419.1217.

*Dimethyl 2-((4-chlorophenyl)(methyl)amino)-1H-indole-3,5-dicarboxylate **4d***

White solids, Mp: 188–189 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 8.79 (s, 1H), 8.70 (s, 1H), 7.92 (dd,

$J = 8.5$, 1.6 Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.21–7.16 (m, 2H), 6.82–6.77 (m, 2H), 3.93 (s, 4H), 3.84 (s, 3H), 3.43 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 168.01, 164.1, 148.4, 145.4, 134.8, 129.1, 126.1, 125.9, 124.3, 123.8(2C), 117.5, 110.4, 98.8, 52.08, 51.1, 40.1. ESI-HRMS: *m/z* Calcd. for $C_{19}H_{18}ClN_2O_4$ $[M+H]^+$ 373.0960. Found 373.0965.

Dimethyl 2-((4-bromophenyl)(methyl)amino)-1H-indole-3,5-dicarboxylate ***4e***

White solids, Mp: 193–194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 8.85 (s, 1H), 8.79 (s, 1H), 7.91 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.34–7.26 (m, 3H), 6.75–6.67 (m, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 168.0, 164.0, 148.1, 145.9, 134.7, 132.1, 126.1, 124.4, 123.9(2C), 117.7, 113.2, 110.4, 99.1, 52.0, 51.1, 40.0. ESI-HRMS: *m/z* Calcd. for $C_{19}H_{18}BrN_2O_4$ $[M+H]^+$ 417.0450. Found 417.0452.

Methyl 5-bromo-2-((4-(methoxycarbonyl)phenyl)(methyl)amino)-1H-indole-3-carboxylate ***4f***

White solids, Mp: 217–218 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 9.08 (s, 1H), 8.29 (d, $J = 1.9$ Hz, 1H), 7.81–7.76 (m, 2H), 7.37 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 1H), 6.69–6.64 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 167.3, 163.8, 151.0, 146.1, 131.1, 130.7, 127.8, 126.4, 124.4, 120.6, 115.7, 113.5, 112.5, 99.7, 51.9, 51.2, 39.7. ESI-HRMS: *m/z* Calcd. for $C_{19}H_{18}BrN_2O_4$ $[M+H]^+$ 417.0450. Found 417.0457.

Methyl 5-bromo-2-((4-chlorophenyl)(methyl)amino)-1H-indole-3-carboxylate ***4g***

White solids, Mp: 193–194 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 8.36 (s, 1H), 8.24 (d, $J = 1.9$ Hz, 1H), 7.31 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.23–7.16 (m, 2H), 7.11 (d, $J = 8.5$ Hz, 1H), 6.79–6.75 (m, 2H), 3.82 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 164.0, 147.9, 145.5, 130.4, 129.2, 128.2, 125.9(2C), 124.1, 117.5, 115.5, 112.0, 97.9, 51.1, 40.1. ESI-HRMS: *m/z* Calcd. for $C_{17}H_{15}BrClN_2O_2$ $[M+H]^+$ 393.0005. Found 393.0006.

Methyl 5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-2-carboxylate ***5a***

Pale gray solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ_H (ppm) 12.21 (s, 1H), 8.96 (d, $J = 2.05$ Hz, 1H), 8.28–8.12 (m, 2H), 7.84 (d, $J = 8.80$ Hz, 1H), 7.48 (d, $J = 7.63$ Hz, 1H), 7.36–7.17 (m, 2H), 3.98 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C (ppm) 171.0, 165.9, 146.9, 142.0, 134.7, 130.9, 127.8, 124.2, 123.7, 123.2, 122.5, 121.5, 120.3, 115.8, 111.0, 102.9, 52.1, 33.7;

Methyl 5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-9-carboxylate ***5b***

Pale gray solids, Mp:>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 12.45 (s, 1H), 8.86–8.81 (m, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 7.94–7.86 (m, 1H), 7.78 (q, $J = 9.1$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.42 (t, $J = 7.1$ Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm) 171.6, 166.9, 147.8, 139.2, 137.9, 131.5, 125.8, 124.7, 124.2, 123.8, 122.5, 122.0, 121.6, 115.5, 110.7, 102.1, 51.9, 33.4. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}N_2O_3$ $[M-H]^-$ 305.0932. Found 305.0867.

Dimethyl 5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-2,9-dicarboxylate ***5c***

Pale gray solids, Mp:>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 12.53 (s, 1H), 8.91 (d, $J = 2.1$ Hz, 1H), 8.78 (d, $J = 1.3$ Hz, 1H), 8.17 (dd, $J = 8.9$, 2.2 Hz, 1H), 7.89 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 3.95 (s, 3H), 3.91 (d, $J = 4.7$ Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 171.1, 166.9, 165.9, 147.8, 142.0, 137.8, 131.2 127.7, 124.6, 124.1, 123.4, 122.8(2C), 121.8, 116.1, 111.0, 102.7, 52.2, 52.0, 33.8. ESI-HRMS: *m/z* Calcd. for $C_{20}H_{17}N_2O_5$ $[M+H]^+$ 365.1137. Found 365.1140.

Methyl 2-chloro-5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-9-carboxylate ***5d***

Pale gray solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 12.54 (s, 1H), 8.81 (s, 1H), 8.29 (s, 1H), 7.92 (d, $J = 8.3$ Hz, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 9.0$ Hz, 1H), 7.56 (d, $J = 8.2$ Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 170.3, 166.8, 147.9, 138.0(2C), 131.2, 126.9, 125.9, 124.6(2C), 123.6, 122.7, 121.8, 118.1, 111.0, 102.5, 51.9, 33.8. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{14}ClN_2O_3$ $[M+H]^+$ 341.0693. Found 341.0679.

Methyl 2-bromo-5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-9-carboxylate ***5e***

Pale gray solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 12.57 (s, 1H), 8.82 (d, $J = 1.3$ Hz, 1H), 8.44 (d, $J = 2.4$ Hz, 1H), 7.96–7.87 (m, 2H), 7.81 (d, $J = 9.1$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 3.99 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm)

170.2, 166.9, 147.9, 138.3, 138.1, 133.9, 127.8, 126.3, 124.6, 123.6, 122.7, 121.8, 118.3, 114.8, 111.0, 102.5, 51.9, 33.7. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}BrN_2O_3$ $[M+Na]^+$ 407.0007. Found 407.0009.

Methyl 9-bromo-5-methyl-11-oxo-6,11-dihydro-5H-indolo[2,3-b]quinoline-2-carboxylate ***5f***

Pale gray solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 12.34 (s, 1H), 8.88 (d, $J = 2.1$ Hz, 1H), 8.22 (s, 1H), 8.15 (dd, $J = 8.8$, 2.1 Hz, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.38 (d, $J = 1.7$ Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 171.1, 165.8, 147.2, 142.0, 133.6, 131.2, 127.7, 125.5(2C), 123.9, 122.7, 122.2, 115.9, 113.7, 113.0, 102.0, 52.2, 33.7. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}BrN_2O_3$ $[M+Na]^+$ 407.0007. Found 407.0007.

9-bromo-2-chloro-5-methyl-5H-indolo[2,3-b]quinolin-11(6H)-one ***5g***

Pale gray solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 12.27 (s, 1H), 8.22 (dd, $J = 5.2$, 1.8 Hz, 2H), 7.77 (d, $J = 9.1$ Hz, 1H), 7.73 (dd, $J = 9.0$, 2.6 Hz, 1H), 7.44–7.30 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 170.2, 147.3, 137.8, 133.7, 131.0, 126.7, 125.6(2C), 125.4, 124.6, 122.1, 117.8, 113.5, 112.9, 101.7, 33.6. ESI-HRMS: *m/z* Calcd. for $C_{16}H_{10}BrClN_2O$ $[M+Na]^+$ 382.9563. Found 382.9565.

Methyl 11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-2-carboxylate ***6a***

Orange solids, Mp: 281–283 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ_H (ppm) 8.95 (s, 1H), 8.29 (d, $J = 8.22$ Hz, 2H), 7.74–7.57 (m, 2H), 7.52 (t, $J = 7.48$ Hz, 1H), 7.22 (t, $J = 7.48$ Hz, 1H), 4.24 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C (ppm) 166.0, 155.1, 154.5, 139.2, 135.7, 131.3, 130.1, 128.2, 125.4, 123.9, 123.8,123.5, 120.9, 118.5, 117.8, 114.3, 52.4, 33.4.

Methyl 11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***6b***

Orange solids, Mp: 248–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 9.01 (s, 1H), 8.45 (d, $J = 8.2$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.88 (t, $J = 7.7$ Hz, 1H), 7.81 (d, $J = 8.6$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 4.43 (d, $J = 7.3$ Hz, 3H), 3.98 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 167.4, 157.6, 156.1, 137.1, 136.5, 131.5, 130.9, 126.0, 125.4, 123.4, 122.9(2C), 121.5, 119.2, 116.7, 114.4, 51.9, 33.4. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{14}ClN_2O_2$ $[M+H]^+$ 325.0744. Found 325.0797.

Dimethyl 11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-2,9-dicarboxylate ***6c***

Orange solids, Mp: 278–280 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 9.14 (d, $J = 1.8$ Hz, 1H), 9.03 (d, $J = 1.5$ Hz, 1H), 8.51 (dd, $J = 8.9$, 1.8 Hz, 1H), 8.24 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.91 (d, $J = 9.0$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 4.55 (s, 3H), 4.06 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 167.2, 165.7, 156.4, 155.7, 139.1, 138.0, 132.2, 131.7, 128.6, 125.8, 125.1, 124.4, 123.0, 122.8, 119.2, 117.1, 115.0, 52.7, 52.1, 34.4. ESI-HRMS: *m/z* Calcd. for $C_{20}H_{16}ClN_2O_4$ $[M+H]^+$ 383.0799. Found 383.0799.

Methyl 2,11-dichloro-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***6d***

Orange solids, Mp: 283–284 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 8.90 (d, $J = 1.2$ Hz, 1H), 8.33 (d, $J = 2.3$ Hz, 1H), 8.17 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.73 (dd, $J = 9.1$, 2.3 Hz, 1H), 7.63 (dd, $J = 21.2$, 8.7 Hz, 2H), 4.33 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 167.3, 157.6, 155.9, 135.9, 135.1, 131.8, 131.6, 129.2, 125.7, 125.3, 124.7, 122.8, 122.3, 120.4, 117.0, 116.2, 52.1, 33.9. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}C_{l2}N_2O_2$ $[M+H]^+$ 359.0354. Found 359.0357.

Methyl 2-bromo-11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***6e***

Orange solids, Mp: 289–290 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 9.06 (d, $J = 1.5$ Hz, 1H), 8.60 (d, $J = 2.2$ Hz, 1H), 8.27 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.96 (dd, $J = 9.1$, 2.2 Hz, 1H), 7.74 (dd, $J = 20.0$, 8.7 Hz, 2H), 4.46 (s, 3H), 3.99 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 167.5, 158.5, 156.5, 135.7, 134.4, 131.7, 130.9, 128.8, 128.5, 125.9, 125.2, 123.3, 122.2, 120.8, 117.3, 116.3, 52.1, 33.6. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}BrClN_2O_2$ $[M+H]^+$ 402.9849. Found 402.9848.

Methyl 9-bromo-11-chloro-5-methyl-5H-indolo[2,3-b]quinoline-2-carboxylate ***6f***

Orange solids, Mp: >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 9.14 (d, $J = 1.8$ Hz, 1H), 8.53 (d, $J = 1.9$ Hz, 1H), 8.48 (dd, $J = 8.9$, 1.9 Hz, 1H), 7.84 (d, $J = 9.0$ Hz, 1H), 7.70–7.60 (m, 2H), 4.43 (s, 3H), 4.04 (d, $J = 8.0$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 166.0, 155.4, 153.4, 139.6, 137.9, 137.2, 132.8, 132.0, 128.7, 126.5, 124.7, 124.3, 119.4, 118.7, 114.7, 113.6, 52.6, 33.6. ESI-HRMS: *m/z* Calcd. for $C_{18}H_{13}BrClN_2O_2$ $[M+H]^+$ 402.9849. Found 402.9850.

9-Bromo-2,11-dichloro-5-methyl-5H-indolo[2,3-b]quinoline ***6g***

Orange solids, Mp: 288–290 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) 8.45 (d, $J = 1.9$ Hz, 1H), 8.37 (d, $J = 2.3$ Hz, 1H), 7.76 (dd, $J = 9.1$, 2.4 Hz, 1H), 7.66 (d, $J = 9.1$ Hz, 1H), 7.62 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 4.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) 155.0, 153.6, 135.6, 135.5, 132.8, 131.8, 128.6, 126.5, 125.4, 125.0, 124.8, 120.08, 119.1, 115.9, 113.1, 33.5. ESI-HRMS: *m/z* Calcd. for $C_{16}H_{10}BrCl_2N_2$ $[M+H]^+$ 378.9404. Found 378.9406.

General procedure for the synthesis of ester substituted 11-amino-5-methyl-5H-indolo[2,3-b]quinolines ***7–9***

The methyl 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline-2-carboxylate (**6**) or methyl 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline-9-carboxylate (**7**) was heated at reflux with a large excess of an appropriate amine in THF for 3–4 h. The reaction was monitored by TLC. Then the mixture was washed with water and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography using eluent changed from AcOEt to AcOEt-2 N ammonia in MeOH (10: 1) to give the final product.

Methyl 11-(3-aminopropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-2-carboxylate ***7***

Yellow solids, Mp: 149–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 9.12 (d, $J = 1.8$ Hz, 1 H), 8.25 (dd, $J = 9.0$, 1.8 Hz, 1H), 7.99 (d, $J = 7.7$ Hz, 1H), 7.90 (d, $J = 9.1$ Hz, 1H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.09 (t, $J = 7.0$ Hz, 1H), 4.17 (s, 3H), 3.99 (t, $J = 6.5$ Hz, 2H), 3.93 (s, 3H), 2.67 (t, $J = 6.3$ Hz, 2H), 1.78–1.74 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 165.9, 156.2, 151.9, 148.1, 140.2, 130.2, 126.5, 124.5, 124.3, 122.1, 121.3, 118.5, 116.9, 115.3, 115.1, 103.7, 52.2, 47.4, 39.9, 33.1, 32.5. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{21}N_4O_2$ $[M-H]^-$ 361.1670. Found 375.1666.

Methyl 11-(3-hydroxypropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***8a***

Orange solids, Mp: 223–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 8.60–8.50 (m, 2H), 7.94–7.88 (m, 2H), 7.86–7.81 (m, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.50–7.43 (m, 2H), 4.57 (t, $J = 4.7$ Hz, 1H), 4.19 (s, 3H), 3.97 (q, $J = 6.5$ Hz, 2H), 3.87 (s, 3H), 3.47 (dd, $J = 10.8$, 5.9 Hz, 2H), 1.90 (p, $J = 6.4$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 158.3, 155.8, 149.2, 137.4, 131.2, 125.7, 124.0(2C), 123.6, 121.3, 118.4, 116.0, 115.6(d), 103.1, 58.4, 51.6, 45.8, 40.0(overlap with DMSO-*d*6 peaks), 33.6, 32.5. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{20}N_3O_3[M-H]^-$ 362.1492. Found 362.1483.

Methyl 11-(3-aminopropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***8b***

Yellow solids, Mp: 170–171 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 8.63 (d, $J = 1.4$ Hz, 1H), 8.52 (d, $J = 7.7$ Hz, 1H), 7.93–7.87 (m, 2H), 7.83 (t, $J = 7.7$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.46 (t, $J = 7.4$ Hz, 1H), 4.19 (s, 3H), 4.00 (t, $J = 6.6$ Hz, 2H), 3.86 (s, 3H), 2.71 (t, $J = 6.3$ Hz, 2H), 1.84–1.78 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 158.3, 155.7, 149.1, 137.5, 131.1, 125.6, 124.1(2C), 123.6, 121.2, 118.3, 116.0, 115.5(2C), 102.6, 51.6, 47.2, 33.1, 32.5. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{21}N_4O_2[M-H]^-$ 361.1670. Found 361.1639.

Methyl 5-methyl-11-morpholino-5H-indolo[2,3-b]quinoline-9-carboxylate ***8c***

Orange solids, Mp: 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 9.01 (d, $J = 1.6$ Hz, 1H), 8.50 (d, $J = 8.2$ Hz, 1H), 8.20 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.83 (d, $J = 4.1$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.57–7.47 (m, 1H), 4.41 (s, 3H), 4.18–4.09 (m, 4H), 3.98 (s, 3H), 3.75–3.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 167.8, 158.4, 156.7, 151.3, 138.1, 131.0, 129.7, 126.5, 126.0, 122.4, 122.0, 121.0(2C), 120.7, 116.5, 115.1, 67.6, 51.9, 51.0, 33.7. ESI-HRMS: *m/z* Calcd. for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661. Found 376.1662.

Methyl 5-methyl-11-(4-methyl-1,4-diazepan-1-yl)-5H-indolo[2,3-b]quinoline-9-carboxylate ***8d***

Orange solids, Mp: 179–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) 8.93 (s, 1H), 8.47 (d, $J = 8.2$ Hz, 1H), 8.26–8.18 (m, 1H), 7.80 (dd, $J = 3.7$, 1.7 Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.50 (ddd, $J = 8.1$, 4.2, 1.7 Hz, 1H), 4.37 (d, $J = 0.8$ Hz, 3H), 3.97 (d, $J = 0.9$ Hz, 3H), 3.93–3.87 (m, 2H), 3.78 (t, $J = 6.1$ Hz, 2H), 3.14 (d, $J = 4.5$ Hz, 2H), 3.05–2.90 (m, 2H), 2.63 (s, 3H), 2.39–2.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 168.1, 159.5, 157.8, 152.3, 138.5, 130.7, 129.7, 126.8, 125.7, 122.8, 122.0, 121.5, 121.0, 120.8, 116.8, 115.0, 61.3, 57.9, 52.9, 52.2, 51.9, 47.2, 33.3, 29.2. ESI-HRMS: *m/z* Calcd. for $C_{24}H_{27}N_4O_2$ $[M+H]^+$ 403.2134. Found 403.2135.

Methyl 11-(4-aminobutylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***8e***

Yellow oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 8.62 (t, $J = 6.1$ Hz, 1H), 8.53 (s, 1H), 7.92 (dd, $J = 8.3$, 7.0, 2H),

7.85 (t, $J = 7.7$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 1 H), 4.20 (s, 3H), 3.90 (t, $J = 7.1$ Hz, 2H), 3.87 (s, 3H), 2.67 (t, $J = 7.4$ Hz, 2H), 1.85–1.76 (m, 2H), 1.48 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 158.4, 155.9, 149.0, 137.4, 131.2, 125.8, 124.0 (2C), 123.7, 121.4, 118.4, 116.1, 115.7, 115.5, 103.0, 51.7, 47.3, 38.6, 32.5, 27.6, 24.9. ESI-HRMS: *m/z* Calcd. for $C_{22}H_{25}N_4O_2$ $[M + H]^+$ 377.1978. Found 377.1978.

Methyl 11-(2-(dimethylamino)ethylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***8f***

Yellow solids, Mp: 172–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) = 8.70 (s, 1H), 8.54 (d, $J = 8.3$ Hz, 1H), 7.97–7.91 (m, 2H), 7.86 (t, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 7.26 (t, $J = 4.5$ Hz, 1H), 4.21 (s, 3H), 4.00 (dd, $J = 10.8$, 5.5 Hz, 2H), 3.87 (s, 3H), 2.65 (t, $J = 6.1$ Hz, 2H), 2.27 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) = 168.2, 157.4, 155.6, 149.3, 138.3, 130.5, 127.0, 125.3, 123.8, 122.5, 120.6, 119.7, 116.1, 115.6, 114.8, 106.0, 58.2, 51.5, 45.2, 44.7, 32.6. ESI-HRMS: *m/z* Calcd. for $C_{22}H_{23}N_4O_2$ $[M-H]^-$ 375.1826. Found 375.1806.

Methyl 11-(3-(dimethylamino)propylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***8g***

Yellow solids, Mp: 105–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H (ppm) = 8.65 (d, $J = 1.4$ Hz, 2H), 8.07 (dd, $J = 8.4$, 1.5 Hz, 1H), 8.00 (d, $J = 8.3$ Hz, 1H), 7.70 (dd, $J = 11.9$, 4.4 Hz, 2H), 7.65 (d, $J = 8.6$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 4.23 (d, $J = 1.2$ Hz, 3H), 4.20–4.10 (m, 2H), 3.94 (s, 3H), 2.72–2.64 (m, 2H), 2.39 (s, 6H), 1.95–1.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm) = 168.4, 158.3, 155.5, 149.0, 137.5, 130.3, 126.2, 124.1, 123.6, 123.4, 120.7, 119.1, 115.9, 115.8, 114.5, 103.0, 59.5, 51.5, 50.1, 45.4, 32.5, 26.3. ESI-HRMS: *m/z* Calcd. for $C_{23}H_{25}N_4O_2[M-H]^-$ 389.1983. Found 389.1949.

Dimethyl 11-(3-aminopropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-2,9-dicarboxylate ***9a***

Yellow solids, Mp: 75–76 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 9.17 (s, 1H), 8.63 (s, 1H), 8.28 (d, $J = 8.1$ Hz, 1H), 7.97–7.89 (m, 2H), 7.55 (d, $J = 8.4$ Hz, 1H), 4.20 (s, 3H), 4.02 (t, $J = 6.6$ Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 2.75 (t, $J = 6.3$ Hz, 2H), 1.87–1.82 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 165.9, 158.2, 155.4, 148.9, 140.2, 130.7, 126.6, 125.7, 124.1, 123.7, 122.0, 119.0, 116.4, 115.8, 115.2, 102.5, 52.3, 51.6(2C), 47.1, 32.8, 32.5. ESI-HRMS: *m/z* Calcd. for $C_{23}H_{25}N_4O_4$ $[M+H]^+$ 421.1876. Found 421.1877.

Methyl 11-(3-aminopropylamino)-2-chloro-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***9b***

Yellow solids, Mp: 185–186 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 8.59 (d, $J = 2.0$ Hz, 1H), 8.54 (s, 1H), 7.89 (dd, $J = 8.4$, 1.4 Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.79 (dd, $J = 9.1$, 2.1 Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 4.12 (s, 3H), 3.93 (t, $J = 6.7$ Hz, 2H), 3.86 (s, 3H), 2.67 (t, $J = 6.4$ Hz, 2H), 1.86–1.77 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 158.1, 155.8, 147.9, 136.1, 130.7, 125.8(2C), 123.9, 123.2, 118.6, 117.5, 116.7, 116.2, 104.6, 103.1, 51.8, 46.8, 39.9(overlap with DMSO-*d*6 peaks), 33.3, 32.6. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{22}ClN_4O_2$ $[M+H]^+$ 397.1431. Found 397.1432.

Methyl 11-(3-aminopropylamino)-2-bromo-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylate ***9c***

Yellow solids, Mp: 109–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 8.76 (s, 1H), 8.57 (s, 1H), 7.97–7.88 (m, 2H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 4.16 (s, 3H), 3.95 (t, $J = 6.7$ Hz, 2H), 3.86 (s, 3H), 2.67 (t, $J = 6.4$ Hz, 2H), 1.82 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 158.1, 155.8, 147.9, 136.4, 133.4, 126.1, 125.9, 123.9(2C), 118.6, 117.7, 117.3, 116.2, 113.5 103.1, 51.7, 46.6, 39.3, 33.1, 32.6, 32.3. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{22}BrN_4O_2$ $[M+H]^+$ 441.0926. Found 441.0927.

Methyl 11-(3-aminopropylamino)-9-bromo-5-methyl-5H-indolo[2,3-b]quinoline-2-carboxylate ***9d***

Yellow solids, Mp: 162–163 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 9.10 (d, $J = 1.6$ Hz, 1H), 8.24 (dd, $J = 8.9$, 1.7 Hz, 1H), 8.10 (d, $J = 1.9$ Hz, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.39 (dd, $J = 8.4$, 1.9 Hz, 1H), 4.14 (s, 3H), 3.97 (t, $J = 6.6$ Hz, 2H), 3.92 (s, 3H), 2.71 (t, $J = 6.2$ Hz, 2H), 1.83–1.77 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 165.8, 156.5, 150.5, 149.0, 140.4, 130.7, 126.7(2C), 126.2, 124.0, 121.5, 118.5, 115.6, 114.9, 110.4, 102.3, 52.2, 47.5, 39.9(overlap with DMSO-*d*6 peaks), 32.9, 32.6. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{22}BrN_4O_2$ $[M+H]^+$ 441.0926. Found 441.0927.

N-(3-aminopropyl)-9-bromo-2-chloro-5-methyl-5H-indolo[2,3-b]quinolin-11-amine ***9e***

Yellow solids, Mp: 152–154 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 8.59 (d, $J = 1.8$ Hz, 1H), 8.03 (d, $J = 1.7$ Hz, 1H), 7.86 (d, $J = 9.2$ Hz, 1H), 7.82 (dd, $J = 9.1$, 2.0 Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.39 (dd, $J = 8.4$, 1.9 Hz, 1H), 4.12 (s, 3H), 3.91 (t, $J = 6.6$ Hz, 2H), 2.63 (t, $J = 6.3$ Hz, 2H), 1.77 (p, $J = 6.5$ Hz, 2H).

^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 156.6, 150.9, 148.1, 136.3, 130.7, 126.9, 126.1, 125.2, 124.2, 123.3, 118.3, 117.3, 116.5, 109.9, 102.9, 46.9, 39.5(overlap with DMSO-*d*6 peaks), 33.3, 32.5. ESI-HRMS: *m/z* Calcd. for $C_{19}H_{19}BrClN_4$ $[M+H]^+$ 417.0482. Found 417.0480.

General procedure for the synthesis of 11-amino-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylic acid ***11***

Methyl 11-amino-5-methyl-5*H*-indolo[2,3-*b*]quinoline-9-carboxylate was dissolved in MeOH and refluxed with 20 % NaOH (aq.) over night. The reaction was monitored by TLC. Then the mixture was neutralized with 1 N HCl (aq.) and concentrated to remove the MeOH under vacuum. The crude product was purified by reverse-phase chromatography using eluent changed from H_2O to H_2O/CH_3CN (50:1) to give carboxylic acid.

11-(3-aminopropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylic acid ***11a***

White solids, Mp: >300 °C; ^{1}H NMR (600 MHz, D_2O) δ_H (ppm) 8.10 (d, $J = 8.2$ Hz, 1H), 7.90 (t, $J = 7.5$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.58 (dd, $J = 9.9$, 4.9 Hz, 2H), 7.53 (s, 1H), 7.17 (dd, $J = 7.9$, 4.8 Hz, 1H), 3.69–3.57 (m,5H), 2.93–2.83 (m, 2H), 2.06–1.91 (m, 2H). ^{13}C NMR (150 MHz, D_2O) δ_C (ppm) 168.9, 151.6, 146.9, 139.0, 135.8, 133.7, 127.4, 125.1, 123.7, 123.3, 122.4, 118.8, 116.2, 115.4, 111.0, 97.9, 44.8, 36.4, 34.3, 27.9. ESI-HRMS: *m/z* Calcd. for $C_{20}H_{19}N_4O_2$ $[M-H]^-$ 347.1513. Found 347.1505.

11-(2-(dimethylamino)ethylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylic acid ***11b***

White solids, Mp: 276–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) = 9.03 (d, $J = 8.0$ Hz, 2H), 8.57 (s, 1H), 8.15 (dd, $J = 19.0$, 8.6 Hz, 2H), 8.04 (t, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 4.37 (dd, $J = 11.4$, 5.7 Hz, 2H), 4.30 (s, 3H), 3.55 (t, $J = 5.5$ Hz, 2H), 2.78 (s, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.6, 152.5, 149.3, 140.71, 136.7, 133.3, 127.7, 125.2, 124.9, 124.5 (2C), 120.6, 116.9, 112.2, 99.5, 56.0, 43.1, 42.8, 35.7, 34.4. ESI-HRMS: *m/z* Calcd. for $C_{21}H_{21}N_4O_2$ $[M-H]^-$ 361.1670. Found 361.1653.

11-(3-(Dimethylamino)propylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylic acid ***11c***

Pale Yellow solids, Mp: 280–282 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) 8.97 (s, 1H), 8.89 (d, $J = 8.5$ Hz, 1H), 8.52 (s, 1H), 8.12 (dd, $J = 16.6$, 8.6 Hz, 2H), 8.05–7.98 (m, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.70 (t, $J = 7.7$ Hz, 1H), 4.26 (s, 3H), 4.01 (dd, $J = 12.9$, 6.5 Hz, 2H), 3.15–3.04 (m, 2H), 2.70 (s, 6H), 2.31 (dt, $J = 14.0$, 7.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm)167.7, 152.4, 149.3, 136.8, 133.2, 127.3, 124.9, 124.5 (2C), 124.2, 120.8, 116.9, 116.7, 112.2, 98.6, 53.7, 45.3, 42.1, 35.6, 25.1. ESI-HRMS: *m/z* Calcd. for $C_{22}H_{23}N_4O_2$ $[M-H]^-$ 375.1826. Found 375.1828.

11-(3-Hydroxypropylamino)-5-methyl-5H-indolo[2,3-b]quinoline-9-carboxylic acid ***11d***

White solids, Mp: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) 8.86–8.72 (m, 2H), 8.59 (s, 1H), 8.10 (d, $J = 8.5$, 1H), 8.05 (d, $J = 8.3$, 1H), 7.99 (t, $J = 7.6$, 1H), 7.76 (d, $J = 8.3$, 1H), 7.66 (t, $J = 7.5$, 1H), 4.24 (s, 3H), 4.04 (dd, $J = 11.8$, 6.0, 2H), 3.46 (t, $J = 5.6$, 2H), 2.07–1.82 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm) 167.4, 152.4, 148.7, 140.2, 136.7, 132.9, 127.0, 124.8, 124.4, 124.1, 123.9, 120.6, 116.8, 116.5, 111.9, 98.2, 58.0, 46.1, 35.6, 32.8. ESI-HRMS: *m/z* Calcd. for $C_{20}H_{18}N_3O_3$ $[M-H]^-$ 348.1354. Found 348.1327.

Antitumor screening test

Cell lines

Established in vitro, human cell line: MV4-11 (leukemia), A549 (lung cancer), HCT116 (colon cancer), and normal mice fibroblast (Balb/3T3) were used. These lines were obtained from American Type Culture Collection (Rockville, Maryland, USA) and were being maintained at the Institute of Immunology and Experimental Therapy, Wroclaw, Poland.

MV4-11 cells were cultured in the RPMI 1640 supplemented with 2 mM L-glutamine, 1.0 mM sodium pyruvate and 10 % fetal bovine serum (all from Sigma-Aldrich Chemie GmbH, Steinheim, Germany), HCT 116, and A549 cells were cultured in the RPMI 1640 + OptiMEM (50:50) medium (Gibco, Scotland, UK) supplemented with 2 mM L-glutamine and 5 % fetal bovine serum (all from Sigma-Aldrich Chemie GmbH, Steinheim, Germany), BALB/3T3 cells were cultured in Dulbecco medium (IIET) supplemented with 2 mM L-glutamine and 1.0 mM sodium pyruvate, 10 % fetal bovine serum (all from Sigma-Aldrich Chemie GmbH, Steinheim, Germany). All culture medium was supplemented with 100 units/ml penicillin and 100 μg/ml streptomycin (both from Polfa, Tarchomin S.A., Poland). All cell lines were grown at 37 °C with 5 % CO_2 humidified atmosphere.

Antiproliferative assay in vitro

Test solutions of the compounds tested (1 mg/ml) were prepared by dissolving the substances in 100 μl of DMSO

completed with 900 µl of tissue culture medium. Afterward, the tested compounds were diluted in culture medium to reach the final concentrations of 10, 1, 0.1, 0.01, and 0.001 µg/ml.

Twenty-four hours before the addition of the tested compounds, the cells were plated in 96-well plates (Sarstedt, Germany) at a density of 1×10^4 cells per well. The assay was performed after 72 h of exposure to varying concentrations of the tested agents. The in vitro cytotoxic effect of all agents was examined using the MTT (MV4-11) or SRB (A549, HCT116 and Balb/3T3) assay.

The results were calculated as an IC50 (inhibitory concentration 50)—the dose of tested agent which inhibits proliferation of 50 % of the cancer cell population. IC values were calculated for each experiment separately and mean values ± SD are presented in the Table 1, 2, 3 and 4. Each compound in each concentration was tested in triplicate in a single experiment, which was repeated 3–5 times.

MTT assay

This technique was applied for the cytotoxicity screening against leukemia cells growing in suspension culture. An assay was performed after 72 h exposure to varying concentrations (from 0.001 to 10 µg/ml) of the tested agents. For the last 3–4 h of incubation 20 µl of MTT solution were added to each well (MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; stock solution: 5 mg/ml, Sigma-Aldrich, Germany). The mitochondria of viable cells reduce the pale yellow MTT to a navy blue formazan: the more viable cells are present in well, the more MTT will be reduced to formazan. When incubation time was completed, 80 µl of the lysing mixture were added to each well (lysing mixture: 225 ml dimethylformamide, POCh, Gliwice, Poland, 67.5 g sodium dodecyl sulfate, Sigma-Aldrich, Germany, and 275 ml of distilled water). After 24 h, when formazan crystals had been dissolved, the optical densities of the samples were read on an Multiskan RC photometer (Labsystems, Helsinki, Finland) at 570 nm wavelength. Each compound in given concentration was tested in triplicates in each experiment, which was repeated 3–5 times.

SRB assay

This technique was applied for the cytotoxicity screening against cells growing in adherent culture. The details of this technique were described by Skehan (Skehan *et al.*, 1990). The cytotoxicity assay was performed after 72 h exposure of the cultured cells to varying concentrations (from 0.01 to 10 µg/ml) of the tested agents. The cells attached to the plastic were fixed by gently layering cold 50 % TCA (trichloroacetic acid, Aldrich-Chemie, Germany) on the top of the culture medium in each well. The plates were incubated at 4 °C for 1 h and then washed five times with tap water. The background optical density was measured in the wells filled with culture medium, without the cells. The cellular material fixed with TCA was stained with 0.4 % sulforhodamine B (SRB, Sigma, Germany) dissolved in 1 % acetic acid (POCh, Gliwice, Poland) for 30 min. Unbound dye was removed by rinsing (4*x*) with 1 % acetic acid. The protein-bound dye was extracted with 10 mM unbuffered Tris base (Sigma, Germany) for determination of optical density (at 540 nm) in a computer-interfaced, 96-well microtiter plate reader Multiskan RC photometer (Labsystems, Helsinki, Finland).

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