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RESEARCH ARTICLE

Synthesis of novel benzoxanthone analogues as non-Camptothecin topoisomerase I inhibitors

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Abstract

Structure modification of the side chain of the lead compound benzoxanthone provided a series of benzoxanthone analogues and 12 of them were first reported. The results showed that most of these compounds had moderate cytotoxicity against tumour cells with the 50% inhibition concentration in the micromolar range. Furthermore, benzoxanthone derivatives 5, 6c, 7a and 7e, showed potent topoisomerase I (Topo I) inhibitory effect and the results indicated that some compounds had potential for development as non-Camptothecin (CPT) topoisomerase I inhibitors.

Keywords: Benzoxanthone, structural modification, anti-tumour, topoisomerase I inhibitor

Introduction

Xanthone[1], one of the secondary metabolites from higher plants and micro-organisms, shows diverse biological profiles including anti-hypertensive[2], anti-oxidative, anti-thrombotic and anti-cancer activities[3]. Simple structural scaffold and diverse biological spectra of xanthone had led many scientists to synthesize xanthone analogues for the development of prospective drug candidates.

Over the past several decades, DNA topoisomerase I (Topo I) has been recognized as an effective target enzyme for development of chemotherapeutic agents[4]. Among the topoisomerase I inhibitors, two camptothecin (CPT) derivatives topotecan[5] and irinotecan[6] had been approved for ovarian and colon cancers treatment. But the intrinsic instability of the highly electrophilic α-hydroxylactone of CPT leads to rapid hydrolysis of E ring to the biologically inactive carboxylate form under physiological conditions. To overcome the drawbacks of CPTs, the discovery of non-CPT Topo I inhibitors has recently emerged as a promising field to find better anti-tumour agents. Based on our knowledge about topoisomerase I inhibitor, we designed 9,11-substituted benzoxanthones for improving their anti-cancer activities. However, Cho and co-workers[7] had designed a series of new benzoxanthone analogues possessing epoxy or thioepoxy groups during our study about benzoxanthone. They have synthesized 12 oxiranylmethoxy- or thiiranylmethoxy-substituted benzoxanthone analogues and compound 1,3-bis(oxiran-2-ylmethoxy)-*12H*-benzo[b]-xanthen-12-one as potent topoisomerase I and II inhibitor was the most efficient among these compounds. Recently, we carried out structure modification on the side chain of benzoxanthone for finding more potent anti-tumour agents.

Experimental

Chemistry

All reagents and solvents were reagent grade or were purified by standard methods before use. ^{1}H and ^{13}C spectra were recorded at 300 MHz or 500 MHz with a Bruker instrument, and reported with TMS as internal standard and DMSO-d_6 as solvent. Chemical shifts (δ values) and coupling constants (J values) are given

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in ppm and Hz, respectively. The mass spectra were recorded on an Esquire 3000 LC-MS mass spectrometer. Elemental analyses were performed with a MOD-1106 instrument and were consistent with theoretical values within ±0.4%. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Flash column chromatography was carried out on silica gel 300–400 mesh. Anhydrous solvent and reagents were all analytical pure and dried through routine protocols.

General procedure for the synthesis of the benzoxanthone analogues

8,10-dihydroxy-*7H*-benzo[c]xanthen-7-one is synthesized as shown in Scheme 1. We treated 1,3,5-trihydroybenzene with 1 equiv. of 1-naphthol-2-carboxylic acid in phosphorus oxychloride at 70°C. The desired product 1[8] was obtained in 35.8% yield after a reaction time of 6 h. As depicted in Scheme 2, starting from 8,10-dihydroxy-*7-H*-benzoxanthen-7-one (1), we carried out modification to prepare a variety of novel benzoxanthone analogues with different side chain. Treated 1 with Br_2 in acetic acid at room temperature to produce bromide derivative 2 or 4[9]. And treated 1 with NIS in DMF at room temperature to produce iodides derivative 3[10]. Treatment of compound 1 with 2-hydroxybenzyl alcohol and $ZnCl_2$ in dioxane solution at 100°C for 6 h gives derivative 5[11]. On treatment of compound 1 with different acyl chloride provided 6a–c[12]. The target compound 7a was prepared from 1, which was treated with benzyl bromide and K_2CO_3 in the presence of acetone at reflux for 4 h. Then the 8-hydroxyl of 7a was esterified with corresponding acyl chloride to give the compounds 7b–d[13]. And 8,10-dihydroxyl of 1 were esterified with corresponding acyl chloride to give the compound 7e (Scheme 2). The structures of target compounds were confirmed by ^{1}H NMR data and ^{13}C NMR.

The synthesized compounds are listed in Schemes 1 and 2 and the obtained spectral data are as follows:

8,10-dihydroxy-7H-benzo[c]xanthen-7-one(1)

^{1}H NMR (500 MHz, $CDCl_3$), δ 12.91 (s, 1H), 10.24 (s, 1H), 8.62 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.72 (m, 3H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.36 (d, *J* = 1.9 Hz, 1H). ^{13}C NMR (500 MHz, DMSO-d_6), δ 94.79, 99.00, 103.14, 115.86, 120.15, 122.87, 123.29, 124.52, 127.89, 128.61, 130.45, 136.48, 153.29, 157.45, 162.88, 165.89, 179.95. ESI-MS: *m/z*, 277.90 [M - H], 279.95 [M + H]. Anal. calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.47; H, 3.63.

9,11-dibromo-8,10-dihydroxy-7H-benzo[c]xanthen-7-one(2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (m, 3H), 7.91 (m, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 8.74 (m, 1H), 13.97 (s, 1H). ESI-MS: *m/z*, 435.62 [M - H]. Anal. calcd. for $C_{17}H_8Br_2O_4$: C, 46.83; H, 1.85. Found: C, 46.70; H, 1.85.

8,10-dihydroxy-9,11-diiodo-7H-benzo[c]xanthen-7-one(3)

^{1}H NMR (500 MHz, DMSO) δ 7.80 (m, 1H), 7.87 (m, 2H), 8.00 (m, 1H), 8.07 (m, 1H), 8.62 (m, 1H), 10.85 (br s, 1H). ESI-MS: *m/z*, 529.22 [M - H]. Anal. calcd. for $C_{17}H_8I_2O_4$: C, 38.52; H, 1.52. Found: C, 38.64; H, 1.52.

5,9,11-tribromo-8,10-dihydroxy-7H-benzo[c]xanthen-7-one(4)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 1H), 7.73 (m, 1H), 8.08 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 11.93 (s, 1H). ESI-MS: *m/z*, 514.65 [M + H]. Anal. calcd. for $C_{17}H_7Br_3O_4$: C, 39.65; H, 1.37. Found: C, 39.59; H, 1.37.

8,10-dihydroxy-9,11-bis(2-hydroxybenzyl)-7H-benzo[c] xanthen-7-one(5)

^{1}H NMR (500 MHz, DMSO) δ 13.23 (s, 1H),10.02(br s,3H), 8.54 (s, 1H), 8.04 (m,2H), 7.90 (m,1H), 7.80 (m,1H), 7.73 (m,1H), 7.68 (m,2H), 6.90 (m,4H), 6.67 (m,1H), 6.58 (m,1H), 4.29 (s, 2H), 3.96 (s, 2H). ESI-MS: *m/z*, 489.30 [M - H]. Anal. calcd. for $C_{31}H_{22}O_6$: C, 75.91; H, 4.52. Found: C, 75.77; H, 4.53.

8-hydroxy-7-oxo-7H-benzo[c]xanthen-10-yl acetate(6a)

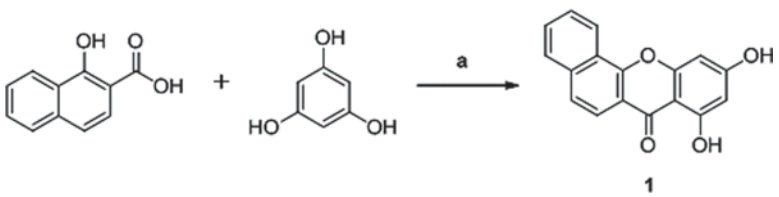
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.63 (d, *J* = 2 Hz, 1H), 7.00 (d, *J* = 2 Hz, 1H), 7.74 (m, 3H), 7.92 (m, 1H), 8.21 (m, 1H), 8.61 (m, 1H), 12.90 (s, 1H). ESI-MS: *m/z*, 319.60 [M - H], 321.25 [M + H]. Anal. calcd. for $C_{19}H_{12}O_5$: C, 71.25; H, 3.78. Found: C, 71.33; H, 3.78.

8-hydroxy-7-oxo-7H-benzo[c]xanthen-10-yl isonicotinate(6b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 2 Hz, 1H), 7.12 (d, *J* = 2 Hz, 1H), 7.72 (m, 3H), 7.92 (m, 1H), 8.17 (m, 2H), 8.21 (m, 1H), 8.59 (m, 1H), 8.92 (m, 2H), 12.97 (s, 1H). ESI-MS: *m/z*, 384.60 [M + H]. Anal. calcd. for $C_{23}H_{13}NO_5$: C, 72.06; H, 3.42; N, 3.65. Found: C, 72.11; H, 3.43; N 3.64.

8-hydroxy-7-oxo-7H-benzo[c]xanthen-10-yl nicotinate(6c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 2 Hz, 1H), 7.14 (d, *J* = 2 Hz, 1H), 7.52 (m, 1H), 7.75 (m, 3H), 7.92



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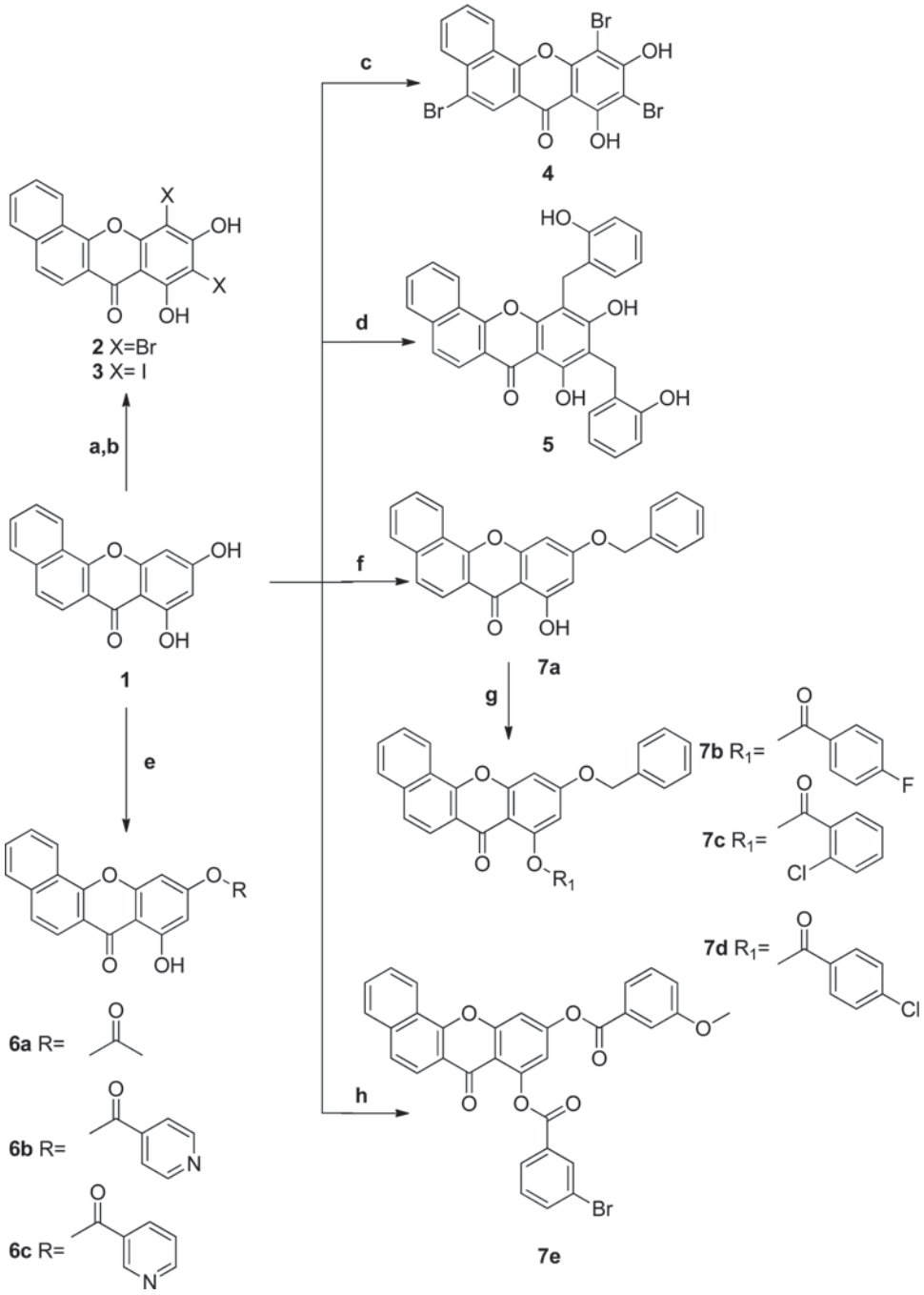
Scheme 1. Reagents and conditions: (a) $POCl_3$, 70°C.



Scheme 2. Reagents and conditions: (a) Br_2 (2 eq), AcOH, r.t.; (b) NIS, DMF, r.t.; (c) Br_2 (3 eq), AcOH, r.t.; (d) 2-hydroxybenzyl alcohol, $ZnCl_2$, 100°C, dioxane; (e) different acyl chloride, Et_3N, acetone, r.t.; (f) benzyl bromide, K_2CO_3, acetone, ref.; (g) corresponding acyl chloride, NaH, THF (dry), r.t.; (h) 3-methoxybenzoyl chloride, Et_3N, acetone, r.t., then 3-bromobenzoyl chloride, NaH, THF (dry), r.t.

(m, 1H), 8.19 (m, 1H), 8.48 (m, 1H), 8.52 (m, 1H),8.91 (d, J = 4.8 Hz, 1H), 9.44 (s, 1H), 12.97 (s, 1H). ESI-MS: *m/z*, 382.92 [M - H], 384.93 [M + H]. Anal. calcd. for $C_{23}H_{13}NO_5$: C, 72.06; H, 3.42; N, 3.65. Found: C, 72.13; H, 3.42; N 3.66.

10-(benzyloxy)-8-hydroxy-7H-benzo[c]xanthen-7-one(7a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (s, 2H), 6.50 (d, J = 2 Hz, 1H), 6.72 (d, J = 2 Hz, 1H), 7.45 (m, 5H), 7.73 (m, 3H), 7.94(d, J = 7.9 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.62 (d, J = 8 Hz, 1H), 12.95 (s, 1H). ESI-MS: *m/z*, 367.82 [M - H], 369.70 [M + H]. Anal. calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 72.34; H, 4.37.

10-(benzyloxy)-7-oxo-7H-benzo[c]xanthen-8-yl 4-fluorobenzoate(7b)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 2H), 6.87 (d, J = 2.7Hz, 1H), 7.16 (d, J = 2.7 Hz, 1H), 7.23 (m, 2H), 7.45 (m, 1H), 7.48 (m, 4H), 7.68 (m, 3H), 7.92 (m, 1H), 8.13 (m, 1H), 8.34 (m, 1H),8.60 (m,1H). ESI-MS: *m/z*, 491.80 [M + H]. Anal. calcd. for $C_{31}H_{19}FO_5$: C, 75.91; H, 3.90. Found: C, 75.81; H, 3.90.

10-(benzyloxy)-7-oxo-7H-benzo[c]xanthen-8-yl 2-chlorobenzoate(7c)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 2H), 6.90 (d, *J* = 2 Hz, 1H), 7.17 (d, *J* = 2 Hz, 1H), 7.46 (m, 1H), 7.52 (m, 7H), 7.70 (m, 3H), 7.91 (m, 1H), 8.18 (m, 1H), 8.75 (m, 1H), 8.62 (m, 1H). ESI-MS: *m/z*, 507.98 [M + H]. Anal. calcd. for $C_{31}H_{19}ClO_5$: C, 73.45; H, 3.78. Found: C, 73.54; H, 3.77.

10-(benzyloxy)-7-oxo-7H-benzo[c]xanthen-8-yl 4-chlorobenzoate(7d)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 2H), 6.87 (d, *J* = 2 Hz, 1H), 7.16 (d, *J* = 2 Hz, 1H), 7.44 (m, 5H), 7.52 (m, 2H), 7.62 (m, 3H), 7.90 (m, 1H), 8.12 (m, 1H), 8.24 (m, 2H), 8.62 (m, 1H). ESI-MS: *m/z*, 1036.19 [2M + Na]. Anal. calcd. for $C_{31}H_{19}ClO_5$: C, 73.45; H, 3.78. Found: C, 73.52; H, 3.78.

8-(3-bromobenzoyloxy)-7-oxo-7H-benzo[c]xanthen-10-yl 3-methoxybenzoate(7e)

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.17 (d, *J* = 2 Hz, 1H), 7.47 (m, 3H), 7.75 (m, 5H), 7.80 (m, 1H), 7.84 (m, 1H), 7.92 (m, 1H), 8.18 (m, 1H), 8.25 (m, 1H), 8.48 (m, 1H), 8.62 (m, 1H). ESI-MS: *m/z*, 1213.18 [2M + Na]. Anal. calcd. for $C_{32}H_{19}BrO_7$: C, 64.55; H, 3.22. Found: C, 64.52; H, 3.22.

Cytotoxicity

One thousand two hundred cells per well were plated in 96 well plates. After culturing for 24 h, test compounds were added onto triplicate wells with different concentration, and 0.1% DMSO for control. After 3 days of incubation, 20 μL MTT (3-[4,5-dimethylthiazol-2-yl]-2, 5-diphenyl- tetrazolium bromide) solution (5 mg/mL) was added to each well, and after shaking for 1 min, the plate was incubated further for 4 h. Formazan crystals were dissolved with 100 μL DMSO. The absorbance (OD) was quantitated with microplate spectrophotometer at 570 nm. Wells containing no drugs were used as blanks for the spectrophotometer. The survival of the cells was expressed as percentage of untreated control wells.

DNA topoisomerase I activity assays

Camptothecin was obtained from the company of Tianzunzezhong in China. Topo I (calf thymus), buffer, BSA, loading buffer and supercoiled DNA pBR322 were all from TaKaRa Biotechnology CO., Ltd.

All reactions were carried out in 20 μL volumes (16 μL double distilled water, 2 μL DNA Topo I buffer, 2 μL 0.1% BSA) including 0.25 μg supercoiled DNA, 0.5 U Topo I with or without drug. The reactions were incubated at 37°C for 15 min and then stopped by adding SDS (0.5% final concentration). To the reaction mixtures, 3.5 μL 6 × loading buffer (0.1 mM EDTA, 7% Glycerol, 0.01% Xylene Cyanol FF, Bromopenol Blue 0.01%) was added. The mixtures were electrophoresed in 0.8% agarose gel in TAE buffer for 40 min at 120 V. The gel was stained with ethidium bromide at room temperature and photographed with UV transilluminator.

Results and discussion

Chemistry

In the ^{1}H NMR spectra, all non-substituted or mono-substituted on hydroxy benzoxanthones (1–6c) showed single peaks at δ 13.00 corresponding to the hydroxyl hydrogen adjacent to the carbonyl group in the benzoxanthone ring[7]. These single peaks disappeared in the ^{1}H NMR spectra of di-substituted derivatives (7a–e), which indicates the introduction of two substituted groups on two hydroxyl groups. With regard to compounds 2–5, the chemical shifts of 9- and 11-hydrogen of benzoxanthones ring were assigned at δ 6.30–7.20. Due to the benzoxanthone derivatives having several aromatic rings, there are many multiple peaks at δ 7.50–8.50.

Cytotoxicity

Many reports in recent years have shown that the inhibition of DNA topoisomerase by numerous natural and synthetic compounds is closely associated with the cytotoxic potentials of these compounds[14–16]. The anti-tumour activity of benzoxanthone analogues were assayed *in vitro* against human lung adenocarcinoma cell lines (A549), human breast cancer cell lines (MDA-MB-435) and human colon cancer cell lines (HCT-116). TPT was used as the positive drug and the results were shown in Table 1. It appeared that benzoxanthone derivatives with polyhydroxy had broad-spectrum anti-tumour activity and the other compounds had moderate anti-tumour activity against one cell line or two cell lines. Among the 13 compounds, only five showed a significant cytotoxicity with relatively low IC_{50} values of 14.27 μM, 15.80 μM

Table 1. The IC_{50} (μM) values of the synthesized compounds against three tumour cell lines.

Compounds	A549	MDA-MB-435	HCT116
1	151.58	179.54	26.8
2	102.23	127.87	72.51
3	56.99	121.57	59.65
4	87.75	86.18	60.47
5	14.27	15.8	5.17
6a	>200	>200	117.17
6b	96.02	>200	>200
6c	57.85	>200	28.66
7a	42.8	>200	>200
7b	>200	153.19	>200
7c	>200	59.65	153.61
7d	>200	171.6	>200
7e	50.2	>200	28.94
TPT	3.16	0.448	1.1

Note: Cancer cells: A549: Lung cancer cell, HCT116: Colon cancer cell, MDA-MB-435: Breast cancer cell.

and 5.17 μM against A549, MDA-MB-435 and HCT-116 cells, respectively.

Structure-activity relationships

Base on the above data, we found that polyhydroxy derivatives exhibited higher activity than hydroxyl-substituted compounds. Among the halogen-substituted derivatives, bromine-substituted compound (2) are less active than iodine-substituted compound (3). And the tri-substituted derivative (4) showed improved anti-tumour activity compared with the di-bromine substituted compound (2). For the position of halogen, the *o*-position substituted derivative, such as compound 7c, exhibited higher inhibitory activity than *p*-position substituted derivatives (compounds 7b and 7d). Interestingly, compared with the mono-phenol ester compounds (e.g., compounds 7b, 7c and 7d), the di-phenol ester-substituted derivative (7e) lost anti-tumour activity against MDA-MB-435, while maintaining anti-tumour activity against A549 and HCT-116. In addition, the ether compound (7a), heterocyclic derivatives (6b and 6c) displayed moderate cytotoxicity against A549, while they were not sensitive to MDA-MB-435.

DNA topoisomerase I activity assays

The most frequently employed method for monitoring DNA topoisomerase activity utilizes an *in vitro* Topo I-mediated DNA cleavage assay using plasmid substrates. We employed this method to identify whether the synthesized derivatives interfere with Topo I. This assay employed supercoiled plasmid DNA (sc DNA) and relied on the ability of Topo I to relax sc DNA, which can be separated as discrete bands using gel electrophoresis. The inhibition of relaxation activity due to the presence of a particular inhibitor is monitored in the form of an accumulated faster-migrating sc DNA. A representative assay using 100 μM concentration of the test compounds in Topo I reactions is given in Figure 1. The sc DNA was fully relaxed (Figure 1, lane 2) and the CPT as the positive control was found to interfere with the Topo I activity (Figure 1, lane 3). Relaxation of sc DNA substrate was inhibited upon incubation with compounds 5, 6c, 7a and 7e to different extends (Figure 1, lanes 4–7). The compound **5** was found to exert the strongest interference (Figure 1, lane 4), while compounds 6c, 7a and 7e showed a potent inhibitory effect (Figure 1, lanes 6, 7 and 8, respectively).

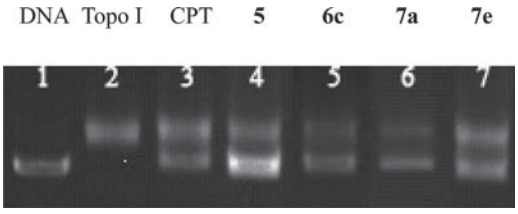


Figure 1. Effect of the selected compounds on topoisomerase-I-mediated DNA relaxation in single concentration. Topo I was Topoisomerase I and DNA without drugs. The samples were reacted with 100 μM drugs at 37°C for 15 min. Reactions were then stopped by adding 0.5% SDS. Gels were photographed under UV transilluminator.

In conclusion, all the benzoxanthone analogues exhibited moderate cytotoxicity against A549, MDA-MB-435 and HCT-116 cell lines. Among these compounds, compound **5** was the most effective in the tested cancer cell lines. Compounds 5, 6c, 7a and 7e also showed potent inhibitory activities against DNA relaxation by topoisomerase I. According to the biological activities, benzoxanthone derivatives indicated potential for development as non-CPT topoisomerase I inhibitors by means of elaborate structure optimization.

Declaration of interest

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