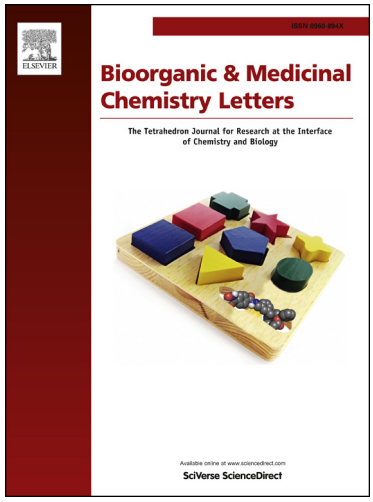

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PII: S0960-894X(13)00843-3
DOI: http://dx.doi.org/10.1016/j.bmcl.2013.07.009
Reference: BMCL 20674

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 23 April 2013
Revised Date: 28 June 2013
Accepted Date: 2 July 2013

Please cite this article as: Chen, H., Li, S., Yao, Y., Zhou, L., Zhao, J., Gu, Y., Wang, K., Li, X., Design, synthesis, and anti-tumor activities of novel triphenylethylene-coumarin hybrids, and their interactions with Ct-DNA, *Bioorganic & Medicinal Chemistry Letters* (2013), doi: http://dx.doi.org/10.1016/j.bmcl.2013.07.009

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

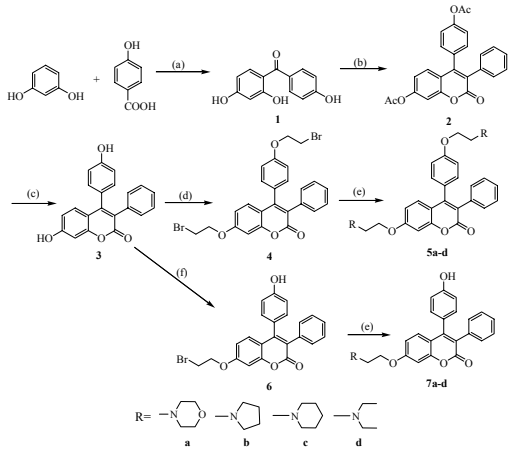
Article history:
Received
Revised
Accepted
Available online

Keywords:
Coumarin
Triphenylethylene
Anti-tumor activities
DNA binding property

ABSTRACT

Novel triphenylethylene-coumarin hybrid derivatives containing different amounts of amino side chains were designed and synthesized in good yields under microwave radiation. The derivatives **5b-d** which possessed two amino side chains (except morpholinyl) showed a broad-spectrum and good anti-proliferative activity against five tumor cells and low cytotoxicity in osteoblast. UV-Vis, fluorescence, and circular dichroism (CD) spectroscopies and thermal denaturation exhibited that compounds **10c**, **5c**, and **13c** bearing amino side chain (except morpholinyl) on 4-phenyl had significant interactions with Ct-DNA by the intercalative mode of binding. Structure activity relationships (SARs) analysis suggested that the amino alkyl chain would play an important role both in the compounds against tumor cells proliferation and their interactions with DNA.

Cancer is at present one of the most leading causes of death in the world. Many novel chemotherapeutic agents derived from natural products have been well developed for cancer treatment.[1] Coumarins are a wide group of naturally occurring compounds and represent a significant source of inspiration for the new anti-cancer agents.[2] They have a variety of biological activities such as anti-cancer, anti-HIV, antimicrobial, and anti-inflammatory.[3] As the anti-tumor agents, they can act on the cancer formation by interfering the cellular proliferation.[3a,3b,4] Due to their potential applications in cancer therapy, extensive studies have been carried out on the design and synthesis of coumarin derivatives with improved anticancer activity.[5] Based on the combination principle of drug design,[6] coupling coumarin with different bioactive molecules is one of the effective ways. Adopting this approach, stilbene-, chalcone- and pyrazole-commarin hybrid compounds[2,5a,5c] have exhibited significant anti-tumor activities. On the other hand, triphenylethylene derivatives such as tamoxifen have been successfully used in the treatment of breast cancer.[7] However, the triphenylethylene-coumarin hybrids in which the 3,4-double bond of the coumarin nucleus fix the disposition of the double bond of ethylene are less explored for the anti-tumor drug discovery. To the best of our knowledge, there was only one report of such 3,4-diphenyl coumarin derivatives[8] which were studied as the new selective estrogen receptor modulator (SERMs).[9] The promising anti-cancer activities of coumarin and triphenylethylene prompted us to explore their structural hybrids for the development of new anti-tumor drug. Herein, we would like to report the design and synthesis of the novel triphenylethylene-coumarin hybrid derivatives containing different amounts of amino side chains which were generally introduced to the fused heterocycles to improve their solubility and biological activity.[10] The anti-proliferative activity against tumor cells and the cytotoxicity towards normal cell (osteoblast) of the new compounds were preliminary evaluated. Since many coumarins as DNA binders exhibited their antitumor efficacy by inhibiting DNA replication,[11] in order to seek for the potential anti-tumor target of our coumarin derivatives, the interactions of the compounds with Ct-DNA were also tested by UV-Vis, fluorescence, and circular dichroism (CD) spectroscopies and thermal denaturation experiment.



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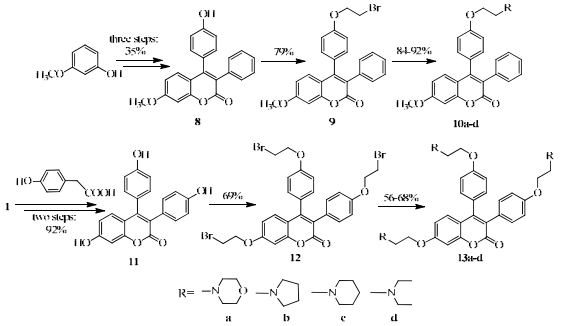
Scheme 1 Synthesis of compounds **5a-d** and **7a-d**. *Reagents and conditions*: (a) $POCl_3$, $ZnCl_2$, sulfolane, 65 ºC, 2 h, 66%; (b) phenyl acetic acid, Ac_2O, Et_3N, M.W., 130 ºC, 30 min, 82%. (c) 3N HCl, acetone, reflux, 99%; (d) $BrCH_2CH_2Br$ (20.0 equiv.), dry acetone, K_2CO_3 (6.0 equiv.), M.W., 130 ºC, 30 min, 73%; (e) RH, THF, M.W., 120 ºC, 30 min, 80% - 91%; (f) $BrCH_2CH_2Br$ (8.0 equiv.), dry acetone, K_2CO_3 (2.0 equiv.), M.W., 130 ºC, 30 min, 49%.



Scheme 2 Synthesis of compounds **10a-d** and **13a-d**.

Synthesis of the 3,4-diphenyl coumarins (**5a-d** and **7a-d**) was achieved according to the previous procedures[8] as outlined in Scheme 1. Briefly, commercially available resorcinol reacted with 4-hydroxybenzoic acid to yield the benzophenone (**1**) under Fries reaction conditions. The treatment of **1** with phenyl acetic acid mainly gave the acylated 3,4-diaryl coumarin derivative (**2**) via Perkin reaction route. The acetyl groups in **2** were removed in acidic solution to obtain **3** and further coupled with different amounts of 1,2-dibromoethane to obtain **4** or **6**. The SN2 nucleophilic substitution of **4** or **6** with a variety of basic amine provided the final products **5a-d** containing two amino alkyl chains or **7a-d** (poor solubility) containing one side chain on 7-position, respectively. Microwave radiation (M.W.) could efficiently improve the Perkin reaction and the nucleophilic substitution. Following the same procedures, the target products **13a-d** containing three amino side chains and **10a-d** containing one amino side chain at 4-phenyl were synthesized from the starting materials, 3-methoxyphenol and 4-hydroxyphenylacetic acid, respectively (Scheme 2).

The structures of all the newly compounds were determined by NMR, MS, and elemental analysis. Both analytical and spectral data of compounds are in agreement with the proposed structures. The amino side chain was on the 7-position in **7** was confirmed by the absence of the 7-OH proton signal in d_6-DMSO ^{1}H NMR in comparison to that in **3**.

Compounds **5a-d**, **7a-d**, **10a-d**, and **13a-d** and their precursors **3**, **8**, and **11** were subjected to anti-proliferative tests against the following cancer cell lines, A549 (human lung cancer), K562 (chronic myeloid leukemia), MCF-7 (human breast cancer), Bel-7402 (human hepatocellular carcinoma), and HL-60 (human promyelocytic leukemia) cells. Cisplatin and tamoxifen were used as positive controls. As shown in table 1, three compounds **5b-d** containing two amino alkyl chains (**5b** R = pyrrolidinyl, **5c** R = piperidinyl, **5d** R = NEt_2) exhibited significant anti-proliferative activity against five cancer cells at IC_{50} of near 10 μM, and better than the positive controls. Four compounds **7b**, **10c**, **13c**, and **13d** showed moderate anti-tumor activities and the others left showed weak or no activity. Neither the compounds with morpholinyl alky chain nor the precursors without the amino side chain (**3**, **8**, and **11**) expressed anti-proliferative activity. These observations suggested that: 1) the number of the amino alkyl chain on the 3,4-diphenyl coumarin had notable impact on anti-proliferative activity, and two side chains were more preferable for this activity; 2) the weaker basic amino group on the side chain, for example the morpholinyl, demonstrated a detrimental effect on anti-proliferative activity. It seemed that compounds **5b-d** exhibited a broad-spectrum anti-proliferative activity.

Table 1. Anti-proliferative activity of compounds against the cancer cell lines

Compds	IC_{50} (μM)				
	A549	K562	MCF-7	Bel-7402	HL-60
3	>100 [a]	>100	>100	N. T. [b]	N. T.
8	>100	>100	>100	N. T.	N. T.
11	>100	>100	>100	N. T.	N. T.
5a	>100	>100	>100	>100	>100
5b	6.31 ± 0.42	4.58 ± 1.31	12.35 ± 1.60	8.66 ± 0.61	5.93 ± 0.19
5c	6.64 ± 0.44	2.91 ± 0.09	11.36 ± 1.60	8.19 ± 0.52	5.28 ± 5.23
5d	8.31 ± 0.42	3.79 ± 0.29	7.90 ± 0.82	8.04 ± 0.30	3.98 ± 0.12
7a	94.10 ± 4.06	>100	>100	N. T.	N. T.
7b	54.28 ± 3.17	44.54 ± 3.54	50.00 ± 3.48	N. T.	N. T.
7c	91.25 ± 5.12	81.25 ± 5.12	86.57 ± 4.64	N. T.	N. T.
7d	>100	>100	>100	N. T.	N. T.
10a	>100	>100	>100	N. T.	N. T.
10b	89.84 ± 7.31	93.26 ± 8.38	>100	N. T.	N. T.
10c	23.43 ± 1.42	19.64 ± 1.37	29.64 ± 1.84	N. T.	N. T.
10d	60.78 ± 4.58	88.79 ± 5.38	76.66 ± 5.67	N. T.	N. T.
13a	>100	>100	>100	N. T.	N. T.
13b	86.29 ± 6.39	75.33 ± 6.24	92.81 ± 8.06	N. T.	N. T.
13c	56.27 ± 4.05	39.44 ± 4.62	48.20 ± 5.61	N. T.	N. T.
13d	45.16 ± 3.28	41.88 ± 4.35	68.78 ± 5.16	N. T.	N. T.
Tamoxifen	N. T.	N. T.	13.45 ± 1.92	N. T.	N. T.
Cisplatin	20.40 ± 5.67	12.92 ± 1.36	16.22 ± 3.35	14.12 ± 1.68	13.36 ± 1.47

[a] No activity; [b] Not Test.

The active compounds **5b-d** were also evaluated for possible cytotoxicity in normal cell, for example, osteoblast (Table 2). It could be found that all the tested compounds did not significantly affect the growth of osteoblasts, suggesting that these molecules had selectivity for inducing growth inhibition of tumor cells. The results suggested that compounds **5b-d** might be suitable as potential drug candidate for cancer chemotherapy.

Table 2. Cytotoxicity of compounds **5b-d** towards osteoblast.[a]

Compds	% cell cytotoxicity				
	1 μM	10 μM	20 μM	40 μM	100 μM
5b	-5.1 ± 2.3 [b]	-6.7 ± 1.2**	10.1 ± 1.6*	18.2 ± 0.9**	36.1 ± 0.8***
5c	-8.0 ± 1.9* [c]	-2.6 ± 1.4	7.4 ± 1.1	14.2 ± 1.2*	39.2 ± 0.9***
5d	-3.1 ± 2.2	3.2 ± 1.5*	12.2 ± 0.9**	20.6 ± 0. 7*	42.2 ± 0.2***

[a] Primary cultured osteoblasts (separated from newborn mice skull) were treated with active coumarin compounds at varying concentrations for 48 h and induced cell death was measured with MTT assay; [b] The data presented are means ± SEM and six repilcates were performed. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ with respect to the untreated cells.

In order to seek for the potential anti-tumor target of our coumarin derivatives, UV-Vis, fluorescence, and CD spectroscopies and DNA thermal denaturation experiment were used to ascertain the DNA binding properties of compounds **3**, **10c**, **5a**, **5c**, and **13c** with calf thymus (Ct) DNA.

The DNA binding properties of compounds **3**, **10c**, **5a**, **5c**, and **13c** with Ct-DNA were investigated by UV-Vis spectra in phosphate buffer (10 mM, pH 7.4) containing 50 mM NaCl at 25 ºC. As shown in Figure 1, the absorption intensities of compounds **3**, **10c**, and **5a** enhanced with increased Ct-DNA concentrations in low hyperchromities of 8%, 12% and 13%, respectively, while the intensities of compounds **5c** and **13c** decreased in middle hypochromicities of 23% and 25%,

respectively. These results indicated that the binding capacities of the 3,4-diphenyl coumarin derivatives and Ct-DNA would be enhanced as the increasing amounts of amino side chains (except morpholinyl). The maximum absorption (λ_{max}) of all the tested coumarin derivatives showed rarely bathochromic shift in the presence of increasing concentration of Ct-DNA, except that the λ_{max} of compound **13c** exhibited obviously red shift (9 nm). The observed spectral changes (significant red shift and hypochromism) in compound **13c** implied that **13c** would insert into the base pairs of DNA as a DNA-intercalating agent,[12] while **10c** (middle hypochromism), **5a**, and **5c** (low hyperchromism but little shift) possibly acted in a same binding mode with DNA.[13] There was no interaction between **3** and Ct-DNA.

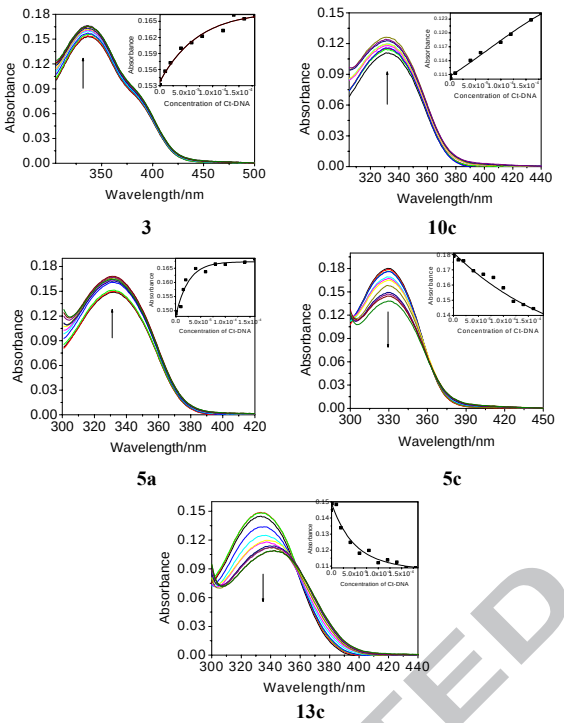


Fig. 1 UV-Vis spectral changes of compounds **3**, **10c**, **5a**, **5c**, and **13c** at the concentration of 1.0×10^{-5} M upon addition of Ct-DNA (0 μM-180 μM) in phosphate buffer (10 mM, pH 7.4) containing 50 mM NaCl and 4% DMSO at 25 °C. Inset: the fitting plots for **3**, **10c**, **5a**, **5c**, and **13c** with Ct-DNA obtained at the maximum absorption.

The fluorescence properties were performed to investigate the interactions between compounds **3**, **10c**, **5a**, **5c**, and **13c** and Ct-DNA in phosphate buffer (10 mM, pH 7.4) containing 50 mM NaCl at 25 °C. As shown in Figure 2, compounds **10c**, **5c**, and **13c** which had amino side chain on 4-phenyl showed similar binding properties with Ct-DNA around 455 nm in the fluorescence spectra. Upon addition of DNA, fluorescence intensities increased markedly, possibly due to the coplanar modulation of the conformation of 3- and 4-phenyl groups induced by Ct-DNA.[14] The maximum emission bands of **10c** and **5c** didn't shift, while the band of **13c** was blue shifted ~ 17 nm. These observations implied that **10c**, **5c**, and **13c** entered Ct-DNA-stacking region with lower polarity than the buffer solution,[15] and intercalated into the bases of the Ct-DNA.[14a] The fluorescence intensities of **3** and **5a** with morpholinyl alky chain increased slightly with increased Ct-DNA concentrations, which was consistent with their low hyperchromities on UV. These results demonstrated that there were nearly no interactions between the compound **3** or **5a** and Ct-DNA. The observed fluorescence intensities were quantified by plotting F/F_0 as a function of Ct-DNA concentrations, where F_0 and F are the fluorescence intensity without and with Ct-DNA, respectively. Stern-Volmer analysis gave deep insight into the binding efficiency of fluorescence enhancement of the coumarins with increasing concentrations of Ct-DNA[14a]. The calculated binding efficiency were 5.41×10^{2} M^{-1}, 3.12×10^{3} M^{-1}, 2.68×10^{2} M^{-1}, 4.21×10^{3} M^{-1} and 3.16×10^{4} M^{-1} of compounds **3**, **10c**, **5a**, **5c**, and **13c** (Fig. 3, inset), respectively.[16] The Stern-Volmer plots indicate that the fluorescence of compound **13c** possessing three amino side chains is highly sensitive to the Ct-DNA concentrations.

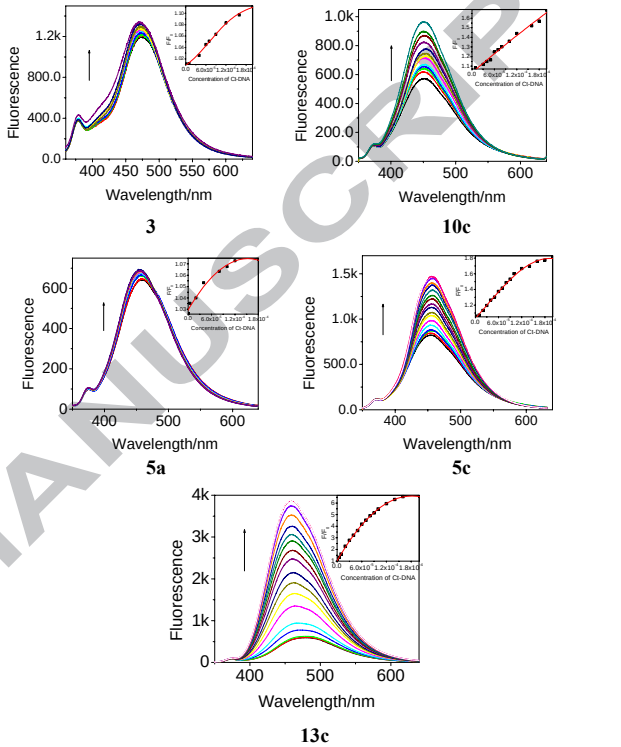


Fig. 2 Fluorescence spectral changes of **3** (λ_{ex}= 336 nm), **10c** (λ_{ex}= 331 nm), **5a** (λ_{ex}= 332 nm), **5c** (λ_{ex}= 331 nm), and **13c** (λ_{ex}= 329 nm) at the concentration of 5.0×10^{-6} M upon addition of Ct-DNA (0 μM- 90 μM) in phosphate buffer (10 mM, pH 7.4) containing 50 mM NaCl and 4% DMSO at 25 °C. Both excitation and emission slit widths were 10.0 nm. Inset: Stern-Volmer plots for the observed fluorescence enhancement upon addition of Ct-DNA to the coumarin derivatives.

CD is a useful technique to investigate the conformational changes in DNA morphology during small molecules-DNA interactions. As shown in Figure 3, the CD spectrum of free Ct-DNA showed a negative band at 247 nm due to the polynucleotide helicity, and a positive band at 277 nm due to the base staking, which indicated that the Ct-DNA existed in the right-band B form.[17] Upon addition of compound **13c**, the intensity of the positive band at 277 nm increased obviously, while the intensity of the negative band at 247 nm decreased (without significant wavelength change). This observation implied that **13c** could intercalate DNA and induce a B to A conformational change on Ct-DNA.[18] For compounds **10c**, **5a**, and **5c**, the positive intensity changes found at 277 nm suggested that these compounds could insert into the bases of the Ct-DNA with the order of the intensity change of **5c** (middle intercalation) **> 10c ≈ 5a** (poor intercalation), which was in agreement with the UV-Vis analysis. The little intensity change of **3** with Ct-DNA further demonstrated that there was no interaction between them. Additional, weak positive induced circular dichroisms (ICD) signals were observed in the region of the characteristic

absorption of these triphenylethylene-coumarin hybrid derivatives (350-500 nm), which indicated that **10c**, **5a**, **5c**, and **13c** intercalated DNA with a vertical orientation in the intercalation pocket.[19]

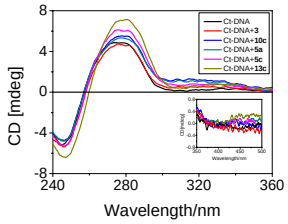


Fig. 3 CD spectra of Ct-DNA (5.0×10^{-5} M) in the absence and presence of **3**, **10c**, **5a**, **5c**, and **13c** (2.0×10^{-5} M) in phosphate buffer (10 mM, pH 7.4) containing 50 mM NaCl and 4% DMSO at 25 °C.

It is well known that the temperature at which a half of a DNA sample melts is known as the melting temperature (T_m). A change of T_m may be observed if a molecule binds with DNA.[20] Thus the thermal behavior of DNA in the presence of the triphenylethylene-coumarin hybrid derivatives provides useful information on the conformational changes and the strength of the DNA-compound complexes. The melting curves of Ct-DNA in the absence and presence of **3**, **10c**, **5a**, **5c**, and **13c** are illustrated in Figure 4 and Table 3, respectively. The T_m value for the free Ct-DNA was 67.5 °C. Upon addition of **10c**, **5c**, and **13c**, obvious changes in the DNA melting temperature were observed. The T_m values increased to 70.7, 71.8 and 77.6 °C, respectively, and the levels of the increased melting temperature (ΔT_m) induced by DNA-compound interactions were 3.2, 4.3 and 8.8 °C, respectively. Compounds **3** and **5a** possessed lower DNA melting temperature than other compounds, and the ΔT_m values were 1.1 and 2.0 °C, respectively. These results illuminated that compounds **10c**, **5c**, and **13c** with various amounts of amino side chain (except morpholinyl) on 4-phenyl exhibited middle affinities with Ct-DNA, consistent with the results from the fluorescence data.

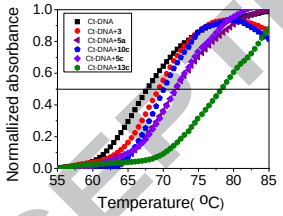


Fig. 4 DNA melting curves for Ct-DNA (5.0×10^{-5} M) in the absence and presence of **3**, **10c**, **5a**, **5c**, and **13c** with concentration of 5.0×10^{-6} M in phosphate buffer (1 mM, pH 7.4) containing 5 mM NaCl and 4% DMSO at 25°C.

Table 3. Average T_m and ΔT_m for Ct-DNA in the absence and presence of **3**, **10c**, **5a**, **5c**, and **13c**

Compds	T_m (°C)	ΔT_m (°C)
Ct-DNA	67.5	0
3	68.6	1.1
10c	70.7	3.2
5a	69.5	2.0
5c	71.8	4.3
13c	77.6	8.8

Considering all the above results, we could conclude that the novel riphenylethylene-coumarin hybrid derivatives with various amounts of amino side chains (except morpholinyl) possessed the intercalative mode of binding properties with DNA, such as **10c**, **5c**, and **13c**. As the amount of amino side chains (except morpholinyl) increases, the intercalative binding is more efficient, possibly due to the extra noncovalent force between the chains and DNA grooves.[21] Among them, compound **13c** containing three amino side chains possessed potential application as novel DNA staining agent. In addition, **5c** (R = piperidinyl) endowed with good anti-tumor activities showed significant binding force with DNA. In contrast, **3** (without amino side chain) and **5a** (R = morpholinyl) showed no or very low interactions with DNA and no anti-tumor activities. These observations allowed us to postulate that DNA might be one of the potential targets for such triphenylethylene-coumarin hybrids as anti-tumor drug candidates.

In summary, a series of novel triphenylethylene-coumarin hybrid derivatives (triphenylethylene-coumarin hybrids) possessing different amounts of amino side chains were designed and synthesized based on the triphenylethylene template. Compounds **5b-d** containing two amino (except morpholinyl) side chains showed a broad-spectrum and excellent anti-tumor activity and low cytotoxicity in osteoblast, which suggested that they might be suitable as potential drug candidate for cancer chemotherapy. The SARs suggested that the amount of the amino alkyl chain on the 3,4-diphenyl coumarin had profound effects on their anti-proliferative activities and DNA binding properties. The similar trends implied that DNA might be one of the potential targets for such 3,4-diphenyl coumarins as anti-cancer drugs.

Acknowledgments

This work was supported by the 973 Program (2010CB534913) and the National Natural Science Foundation of China (NSFC) (20902016).

Supplementary data

Experimental procedures and characterization data for compounds **5a-d**, **7a-d**, **10a-d**, and **13a-d** are available. Supplementary data associated with this article can be found, in the online version, at doi:

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Graphical Abstract

Design, synthesis, and anti-tumor activities of novel triphenylethylene-coumarin hybrids, and their interactions with Ct-DNA

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