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Synthesis and anticancer activity of cyclotriphosphazenes functionalized with 4-methyl-7-hydroxycoumarin†

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As an important branch of heterocyclic compounds, coumarin and its derivatives with diverse potential biological activities have attracted wide attention and have been applied in medical-related fields. In this article, three cyclotriphosphazene derivatives bearing 4-methyl-7-hydroxycoumarin moieties with the numbers of 2, 4, and 6 were synthesized and characterized and their antitumor activities were investigated. All the new compounds were found to display antitumor activity *in vitro* against breast cancer cell lines (MCF-7 and 4T1 cells) with the IC_{50} values in the range of 108.72–188.44 μM and 75.93–154.91 μM, respectively. In contrast, the coumarin monomer displayed the values of 4140 μM and 1640 μM (IC_{50}). Our results suggested that the antitumor activity was significantly enhanced when coumarin was introduced onto the surface of cyclotriphosphazenes, thereby providing potent candidate molecules for pharmaceutical applications.

Introduction

Cyclotriphosphazene (HCCP) with six active chlorine atoms can be easily functionalized to yield a number of derivatives with various functional groups.[1–4] These derivatives have been applied in various fields such as chemistry,[5,6] biology[7,8] and medicine.[9,10] Recent studies indicate that some of the cyclotriphosphazene derivatives display potential anti-inflammatory,[11] anti-tumor[12–16] and anti-Alzheimer activities.[17] Interestingly, these new cyclotriphosphazene systems usually present unique properties from the aspect of monomer molecules.[18] For instance, some Edecrin-containing derivatives display moderate to strong antiproliferative activity (IC_{50} 0.1–8.5 μM) against solid tumors (KB cell line), while the ethacrynic acid (EA) derivatives show low antiproliferative activity (IC_{50} ~ 11 μM).[19] Chalcone–phosphazene compounds are much more effective for fighting PC-3 and LNCaP cancer cell lines than the mono-chalcone compounds.[20–22] Moreover, we found that some imidazole/cyclicamine-containing cyclotriphosphazene derivatives exhibit specific hydrolytic/oxidation activity as metalloenzymes.[23,24]

Coumarin and its derivatives, as some of the classical flavonoids with a benzo-α-pyrone structure, are particularly useful molecules, showing wide biological and pharmaceutical activities,[25,26] which have attracted chemists to explore the natural coumarins or synthetic analogs as drugs. For instance, natural products re-isolated from *calophyllum* cordato-oblongum containing coumarin moieties were found to have anti-HIV-1 activity with IC_{50} of 12.3 μM (Fig. 1a). A natural product warfarin is a clinical anticoagulant drug[27] and has been used to treat or prevent blood clotting in veins or arteries (Fig. 1b). Indeed, numerous molecules based on the coumarin skeleton have been prepared for their antitumor,[28] anti-HIV,[29] anti-Alzheimer,[30,31] anti-bacterial,[32–34] anti-allergic,[35,36] and anti-oxidant properties.[37–39] Of particular interest in cancer

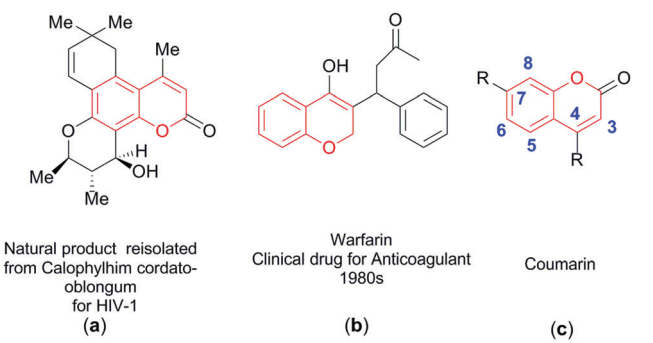

Fig. 1 The structures of coumarin derivatives.

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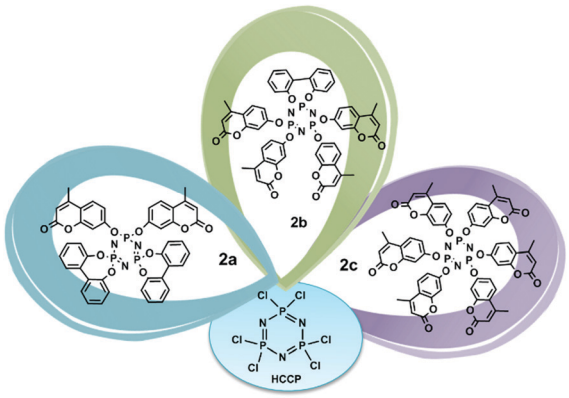


Fig. 2 Structures of cyclotriphosphazene derivatives functionalized with 4-methyl-7-hydroxy coumarin (**2a–2c**).

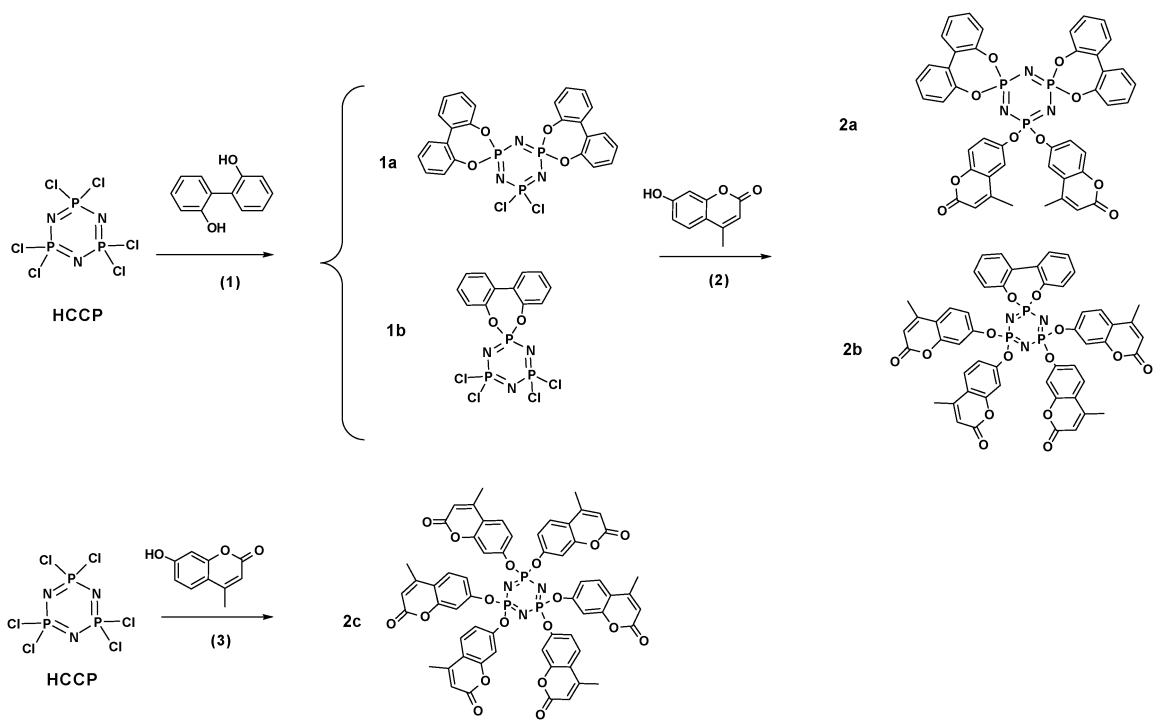
chemotherapy, 7-hydroxycoumarin analogs (Fig. 1c) display cytostatic activity in human cancer cell lines, such as A549 (lung),[40] ACHN (renal),[41] MCF-7 (breast)[42,43] and HL-60 (leukemia).[44] For example, coumarin (4-methyl-7 hydroxycoumarin) has shown anticancer potentials against DMBA-induced skin cancer in mice.[45]

With the above-mentioned encouraging results, we attempted to develop a series of cyclotriphosphazenes and coumarins. We attempted to develop a series of cyclotriphosphazene and coumarin conjugates to construct new bioactive molecules for anticancer applications (Fig. 2). The synthesized conjugates with multiple coumarin moieties were well characterized and their anticancer activities were tested using breast cancer (MCF-7) and murine breast cancer (4T1) cell lines. In this study, three cyclotriphosphazene-based coumarin derivatives (**2a–2c**) were obtained in good yields (85–90%) under mild conditions by two steps (Scheme 1). In order to evaluate the anticancer activities of these new molecules, mono-phosphorylated coumarin (**3a**) was also prepared (Scheme 2).

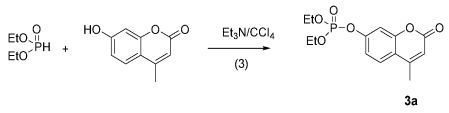
Results and discussion

Although some important findings of the phosphazene and coumarin systems have been reported,[46–50] the underlying molecular events between phosphazene and coumarin are still largely unknown. Therefore, in this paper, coumarin-cyclotriphosphazene conjugate compounds **2a–2c** were prepared; we systematically studied their antitumor activity against two kinds of breast cancer cell lines: MCF-7 (human breast cancer cells) and 4T1 (murine breast cancer) cell lines by CCK-8 assays. As shown in Fig. 3, the % cell viability was first investigated; three active molecules (**2a–2c**) exhibited obvious inhibition on the 4T1 cell growth, with the cell viabilities of 42%, 38%, and 48%, respectively. However, both mono-phosphorylated coumarin (96%) and coumarin monomer (83%) had almost no inhibition effect. This indicated that the new active molecules (**2a–2b**) showed unique bioactivity when coumarin was introduced onto the surface of cyclotriphosphazenes.

In order to further evaluate their *in vitro* anti-tumor activity, the 4T1 and MCF-7 cells were treated with different concentrations of cyclotriphosphazene derivatives (1, 5, 25, 50 and 100 μM); the IC_{50} values were determined and shown in Table 1.



Scheme 1 The schematic diagram of **2a–2c**, *reagents and conditions*: (1) phenol, 2.0 equiv. (**1a**); 1.0 equiv. (**1b**), THF, Cs_2CO_3, r.t., 8 h; (2) coumarin, 2.2 equiv. (**2a**); 4.4 equiv. (**2b**); THF, Cs_2CO_3, 50 °C, overnight.; (3) 6.6 equiv. (**2c**), THF, Cs_2CO_3, 50 °C, overnight.



Scheme 2 Synthesis of the phosphorylated coumarin (DEPH, acetone, Et_3N/CCl_4, 0 °C, 8 h).

For the 4T1 cells and MCF-7 cells, **2a–2c** displayed moderate to strong antiproliferative activity; the IC_{50} values were in the range of 110–145 μM and 75–155 μM, respectively, which were significantly lower than that of free coumarin (4140 μM). All these molecules (**2a–2c**), particularly **2b**, displayed a lower IC50 value on the MCF-7 cells than that on the 4T1 cells. Based on previous studies (ref. 23 and 24), it was speculated that the platform of cyclotriphosphazenes plays an important role in mediating antitumor activities. Moreover, the antiproliferative activities (IC50 μM) of cyclotriphosphazene derivatives (**2a**, **2b** and **2c**) in the MCF-7 and 4T1 cells *versus* the number of terminal coumarin moieties were analyzed and the data are shown in Fig. S1 (ESI†). The above results indicate that there can be cooperativity among these multi-domain systems.

In this paper, three coumarin–phosphazene conjugates were first reported with good yields (85–90%). Due to six active chlorine atoms, cyclotriphosphazenes easily produced multiple substituted products. The parameters related to the preparation process such as the proportion of substrates, reaction temperature and time were first investigated and optimized. It is necessary to obtain the pure product in the first step. The substituted products (**1a** and **1b**) could be isolated in high yields with 1.1 and 2.2 biphenol, respectively. For avoiding multiple substitutions, the reaction of (2) with excess coumarin (1.1 equiv. of per chlorine) was carried out under 50 °C for the reaction time from 8 h to 12 h, resulting in compounds **2a–2c** according to Scheme 1. As the different chemical environments of phosphorus show different chemical shifts,[51] characterization was done using ^{31}P NMR. Compounds **2a** and **2b** with symmetric structures showed two typical coupling signals in the ^{31}P NMR spectrum, while that of the fully substituted compound **2c** showed a single peak. Moreover, the novel compounds were screened for antitumor activity against the

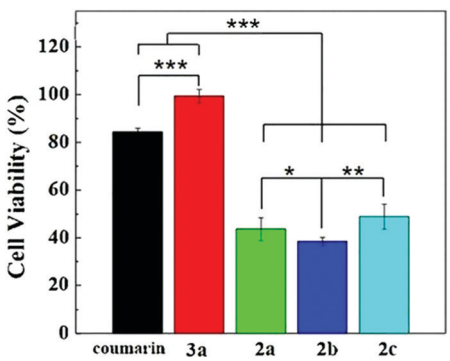


Fig. 3 The relative cell viability (%) of 4T1 cells followed by exposure to all the compounds (200 μM in 1% DMSO solution) for 24 h (*$p < 0.05$, **$p < 0.001$, ***$p < 0.001$).

Table 1 The IC_{50} values of 4T1 and MCF-7 cells after exposure to coumarin and coumarin–phosphazene compounds

	Compound ($IC_{50(\mu M)}$*)			
Cell line	Coumarin	**2a**	**2b**	**2c**
4T1	4140 ± 70	120 ± 10	110 ± 5	145 ± 5
MCF-7	1640 ± 30	155 ± 5	75 ± 5	110 ± 5

4T1 and MCF-7 cell lines (Fig. 3). It was obvious that coumarin–phosphazene conjugates (**2a–2c**) exhibited better activity than mono-phosphorylated coumarin (**3a**). As shown in Table 1, compounds **2a–2c** exhibit potent antitumor effects on these two kinds of cancer cell lines with the IC_{50} values in the range of 108.72–188.44 μM for the MCF-7 cells and 75.93–154.91 μM for the 4T1 cells, while the coumarin moiety showed the values of 1640 μM and 4140 μM. All the results demonstrated that the coumarin moieties attached onto each cyclotriphosphazene platform displayed enhanced anticancer activity.

Experimental

General

All chemical reagents and solvents were obtained commercially and used as received without further purification unless otherwise stated. Ultrapure water was purified from Millipore. Silica gel P60 (Qingdao, mesh number 200–300) was used for column chromatography. HCCP, Cs_2CO_3 and tetrahydrofuran were analytical grade products and their solutions in ultrapure water were used in the selectivity study. The murine breast cancer (4T1) cell lines and human breast (MCF-7) cancer cell lines were retrieved from the Institute of Biochemistry and Cell Biology, the Chinese Academy of Sciences (Shanghai, China). Minimum essential medium (MEM) and fetal bovine serum (FBS) were purchased from Hangzhou Jinuo Biomedical Technology (Hangzhou, China) and Shanghai ExCell Biology, Inc. (Shanghai, China), respectively. Cell Counting Kit-8 (CCK-8) was purchased from Sigma-Aldrich. The water used in all experiments was distilled water. ^1H NMR, ^31P NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument and chemical shifts were given in ppm using the peak of residual proton signals of $CDCl_3$ as the internal standard. Coupling constants (*J*) were given in Hertz (Hz). The terms m, q, t, d and s refer to multiplet, quartet, triplet, doublet and singlet, respectively. Mass spectra were measured using a Finnigan LCQDECA spectrometer and Agilent 1100 LC/MSD with the ESI mode.

General procedure for the preparation of 1a, 2a–2c and 3a

Synthesis of $[N_3P_3Cl_2(O_2C_{12}H_8)_2]$ (1a). To a solution of 2,2′-$HOC_6H_4C_6H_4OH$ (1.18 g, 6.33 mmol) in acetone (15 mL) cooled to 0 °C, solid $[N_3P_3Cl_6]$ (1.00 g, 2.88 mmol) and Cs_2CO_3 (4.69 g, 14.38 mmol) were added and the mixture was stirred at room temperature for 2 h. The volatiles were evaporated *in vacuo* and the residue was extracted with CH_2Cl_2 (5 × 25 mL). Compound **1a** (1.21 g) was obtained in 91.1% yield as a white

solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.58 (m, 16H, Ar–H). ^{31}P NMR: ($CDCl_3$, 162 MHz) δ 19.44 [d, 2P, P($O_2C_{12}H_8$)], 29.22 (dd, 1P, PCl_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.80, 129.85, 128.59, 126.48, 121.83.

Synthesis of [$N_3P_3Cl_4(O_2C_{12}H_8)$] (1b). A mixture of [$N_3P_3Cl_6$] (1.00 g, 2.88 mmol), 2,2′-$HOC_6H_4C_6H_4OH$ (0.59 g, 3.16 mmol), and Cs_2CO_3 (2.06 g, 6.33 mmol) in acetone (20 mL) was stirred at room temperature for 15 min. The volatiles were evaporated *in vacuo* and the residue was extracted with CH_2Cl_2 (3 × 15 mL). Evaporation of the solvent *in vacuo* was followed by recrystallization from CH_2Cl_2/petroleum ether to gain the desired compound **1b** (0.6 g) in 90.9% yield as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.59 (m, 8H, Ar–H). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 12.87 (dd, 1P, P($O_2C_{12}H_8$)), 24.78 (d, 2P, PCl_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.76, 129.84, 128.59, 126.48, 121.83.

Synthesis of [$N_3P_3(OC_{10}H_7O_2)_2(O_2C_{12}H_8)_2$] (2a). A mixture of 4-methyl-7-hydroxycoumarin (0.67 g, 3.83 mmol) and Cs_2CO_3 (2.27 g, 6.97 mmol) in tetrahydrofuran (30 mL) was slowly added to a flask under nitrogen at 0 °C for 30 min; then, **1a** (1.00 g, 1.74 mmol in 20 mL THF) was added dropwise and the mixture was refluxed for 24 h. The volatiles were evaporated *in vacuo* and the residue was purified by chromatography using a silica gel column and petroleum ether/ethyl acetate (4 : 1) as the eluent. Compound **2a** (1.26 g) was obtained in 85.0% yield as a white solid. MP: 303 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 8.7 Hz, 2H, Ar–H), 7.55 (d, J = 7.5 Hz, 4H, Ar–H), 7.45 (t, J = 7.0 Hz, 6H, Ar–H), 7.36 (t, J = 7.8 Hz, 6H, Ar–H), 7.20 (d, J = 8.0 Hz, 4H, Ar–H), 6.31 (s, 2H, Ar–H), 2.47 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.37, 154.43, 152.98, 147.95, 129.78, 128.64, 126.27, 125.63, 121.72, 117.53, 114.44, 109.97, 18.68. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 9.24 (t, 1P, P($OC_{10}H_7O_2$)), 24.82 (d, 2P, P($O_2C_{12}H_8$)). MALDI-TOF MS (ESI) m/z calcd for $[C_{44}H_{30}N_3O_{10}P_3 + Na]^+$: 876.104, found: 876.104.

Synthesis of [$N_3P_3(OC_{10}H_7O_2)_4(O_2C_{12}H_8)$] (2b). A mixture of 4-methyl-7-hydroxycoumarin (1.68 g, 9.55 mmol) and Cs_2CO_3 (5.65 g, 17.36 mmol) in tetrahydrofuran (30 mL) was slowly added to a flask under nitrogen at 0 °C for 30 min; then, **1b** (1.00 g, 2.17 mmol in 20 mL THF) was added dropwise and the mixture was refluxed for 24 h. The volatiles were evaporated *in vacuo* and the residue was purified by chromatography using a silica gel column and petroleum ether/ethyl acetate (3 : 1) as the eluent. Compound **2b** (1.96 g) was obtained in 89.3% yield as a white solid. MP: 310 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, J = 6.4 Hz, 8H, Ar–H), 7.53 (d, J = 7.2 Hz, 2H, Ar–H), 7.42–7.32 (m, 12H, Ar–H), 6.90 (d, J = 7.5 Hz, 2H, Ar–H), 2.53 (s, 12H, CH_3). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 9.36 (d, 2P, P($OC_{10}H_7O_2$)), 25.14 (m, 1P, P($O_2C_{12}H_8$)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.80, 150.60, 147.80, 138.66, 129.77, 128.53, 126.29, 125.61, 125.17, 121.58, 120.81, 26.63. MALDI-TOF MS (ESI) m/z calcd for $[C_{43}H_{32}N_3O_{11}P_3 + Na]^+$: 882.115, found 882.151.

Synthesis of [N_3P_3 ($OC_{10}H_7O_2)_6$] (2c). A mixture of 4-methyl-7 hydroxycoumarin (3.34 g, 18.99 mmol) and Cs_2CO_3 (11.25 g, 34.52 mmol) in tetrahydrofuran (30 mL) was slowly added to a flask under nitrogen atmosphere at 0 °C for 30 min. Then, $N_3P_3Cl_6$ (1.00 g, 2.88 mmol in 20 mL THF) was added dropwise and the mixture was refluxed for 24 h. The volatiles were evaporated *in vacuo* and the residue was washed with water followed by brine and finally dried over anhydrous Na_2SO_4. The solvent was purified and extracted with CH_2Cl_2 (4 × 25 mL) under reduced pressure to gain the crude product and then recrystallized using petroleum ether and ethyl acetate as the solvent. Compound **2c** (3.06 g) was obtained in 90.1% yield as a white solid. MP: 323 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, J = 8.7 Hz, 6H, Ar–H), 7.10 (d, J = 9.8 Hz, 6H, Ar–H), 6.95 (s, 6H, Ar–H), 6.21 (s, 6H, Ar–H), 2.43 (s, 18H, CH_3). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 7.51. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.92; 154.01; 151.05; 117.62; 117.04; 114.45; 109.00; 18.61. MALDI-TOF MS: m/z calcd for $[C_{60}H_{42}N_3O_{18}P_3 + Na]^+$: 1208.157, found 1208.157.

Synthesis of diethyl (4-methyl-2-oxo-2*H*-chromen-7-yl)phosphate (3a). A solution of 4-methyl-7-hydroxycoumarin (1.28 g, 7.24 mmol) and triethylamine (5 mL) in anhydrous acetone (50 mL) was stirred at 0 °C. Then, DEPH (1.00 g, 7.24 mmol) was dissolved in tetrachloromethane (5 mL) and added dropwise for 30 min; subsequently, the mixture was kept for reaction at room temperature for 8 hours. The solution was evaporated to gain the jacinth crude product; this was then dissolved in ethyl acetate and washed several times with NaCl and purified by column chromatography using a silica gel column and petroleum ether : ethyl acetate (5 : 1). Compound **3a** (1.37 g) was obtained in 60.5% yield as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, 1H, J = 8.0 Hz, Ar–H), 7.22 (d, 2H, J = 8.0 Hz, Ar–H), 6.26 (s, 1H, Ar–H), 4.30–4.22 (m, 4H, CH_2), 2.43 (s, 3H, CH_3), 1.40–1.37 (t, 6H, J = 12.0 Hz, CH_3). ^{31}P NMR ($CDCl_3$, 162 MHz) δ −6.86. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.46, 153.27, 151.85, 125.78, 117.10, 116.42, 114.47, 108.61, 65.01, 18.66, 16.07. LCMS-IT-TOF (ESI) m/z calcd for $[C_{14}H_{17}O_6P + H]^+$ 313.084, found 313.074.

Cell culture and cytotoxicity assay

4T1 cells (murine breast cancer cell lines) and MCF-7 cells (human breast cancer cell lines) were grown in RPMI 1640 medium with 10% FBS and 1% penicillin–streptomycin at 37 °C in a 5% CO_2 incubator.

CCK-8 assay

The cytotoxicity evaluation of coumarin–phosphazene was performed using a standard CCK-8 assay according to the protocols described in the literature.[52,53] Briefly, the 4T1 cells or MCF-7 cells were seeded into a 96-well plate at a density of 1 × 10^4 cells per well in 0.1 mL of RPMI 1640 medium overnight. Then, the cells were cultured using a fresh medium containing different concentrations (1, 5, 25, 50 and 100 μM, respectively) of the coumarin–phosphazene compounds for 24 h. Subsequently, the medium in each well was replaced with 0.1 mL of serum-free medium containing 10% CCK-8 solution and the cells were incubated for another 3 h. All plates were read at 450 nm using a Thermo Scientific Multiskan MK3 ELISA reader (Thermo Scientific, Waltham, MA). All the experiments were performed in triplicate and the data were expressed as mean ± SD.

Statistical analysis

The experimental data were evaluated from one-way analysis of variance (ANOVA) statistical method. The value of 0.05 was selected as the statistical significance level and the data were indicated with (*) for $p < 0.05$, (**) for $p < 0.01$, and (***) for $p < 0.001$.

Conclusions

In summary, three novel coumarin–phosphazene derivatives (**2a–2c**) were designed and synthesized and their anticancer activities were evaluated *in vitro* by CCK-8 assays. The results showed that these active molecules have moderate antitumor activities against the MCF-7 and 4T1 cell lines when coumarin was introduced onto the cyclotriphosphazene backbone. The results obviously suggested that **2a–2c** with various coumarin moieties attached onto cyclotriphosphazenes enhanced anticancer activity, which showed that cyclotriphosphazenes play an important role in mediating antitumor activities. The results prompted us to construct new active molecules based on cyclotriphosphazenes for different biomedical applications.

Conflicts of interest

There are no conflicts to declare.

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