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Synthesis and evaluation of 10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone derivatives as selective telomeric G-quadruplex DNA ligands

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ABSTRACT

A class of 9(10*H*)-acridone derivatives with terminal ammonium substituents at C2 (and C7) position(s) on the acridone ring were successfully synthesized. The relative affinities of the acridone compounds to G-quadruplex DNA have been investigated and the results showed that these compounds had a binding specificity for G-quadruplex over duplex sequences. The acridones with two terminal ammonium substituents had much more effects on the human telomeric G-quadruplex DNA than the corresponding acridone derivatives with one terminal ammonium substituent, and more positive charges introduced to the side chains can improve the formation and stabilization of the G-quadruplex.

1. Introduction

Cancer is a class of diseases, which may affect people's health greatly at all ages. The result of cancer is from unlimited growth of a given cell.[1,2] Human telomerase is a specialized ribonucleoprotein, which participates in the maintenance of telomere length.[3–7] The consequence of telomere length maintenance renders tumor cells with a capacity to divide and to be immortal. As the telomerase is active in 85–90% of cancer cells and inactive in normal cells, telomerase can be used as an important target for cancer chemotherapy.[8–10]

Human telomeres are characterized by repeats of guanine-rich sequence d[(TTAGGG)*n*] at the end of eukaryotic chromosomes. In normal somatic cells, the telomeres are gradually shortened during cell division. Once telomeres reach a critical minimum length, cells exit the cell cycle to senescence and apoptosis.[11] In tumor cells, telomere erosion can be compensated by telomerase, which requires a linear, non-folded telomere DNA primer in order for telomere extension to take place. The single-stranded G-rich sequence may fold into G-quadruplex under physiological conditions,[12] which could be stabilized by a number of molecular ligands. The stabilized G-quadruplex may inhibit the activity of telomerase in vitro. Therefore, growing attention has been paid on developing molecular ligands, which can stabilize quadruplex structures.[13–19] Acridine and acridone derivatives, which have planar tricyclic chromophore frameworks, may form π–π interactions with guanine tetrads of quadruplex DNA. A group of substituted acridine and acridone derivatives have been developed as good G-quadruplex stabilizers and antitumor agents.[20–30]

We have been focused on searching and developing acridine and acridone derivatives with potent antitumor activity for several years.[31–35] Here, we report on the synthesis and characterization of several 10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone derivatives with terminal amino substituents at C2 (and C7) position(s) on the acridone ring. The structure of these compounds comprises acridone scaffold, which can form π–π interactions with guanine tetrads, and one or two side chains with ammonium at the termini of the chains, which may form electrostatic interaction with the negative grooves of quadruplex DNA. Consequently, the acridone derivatives designed may be as potent G-quadruplex stabilizers. The binding affinities of these acridone derivatives with human telomeric G-quadruplex DNA and duplex DNA were studied.

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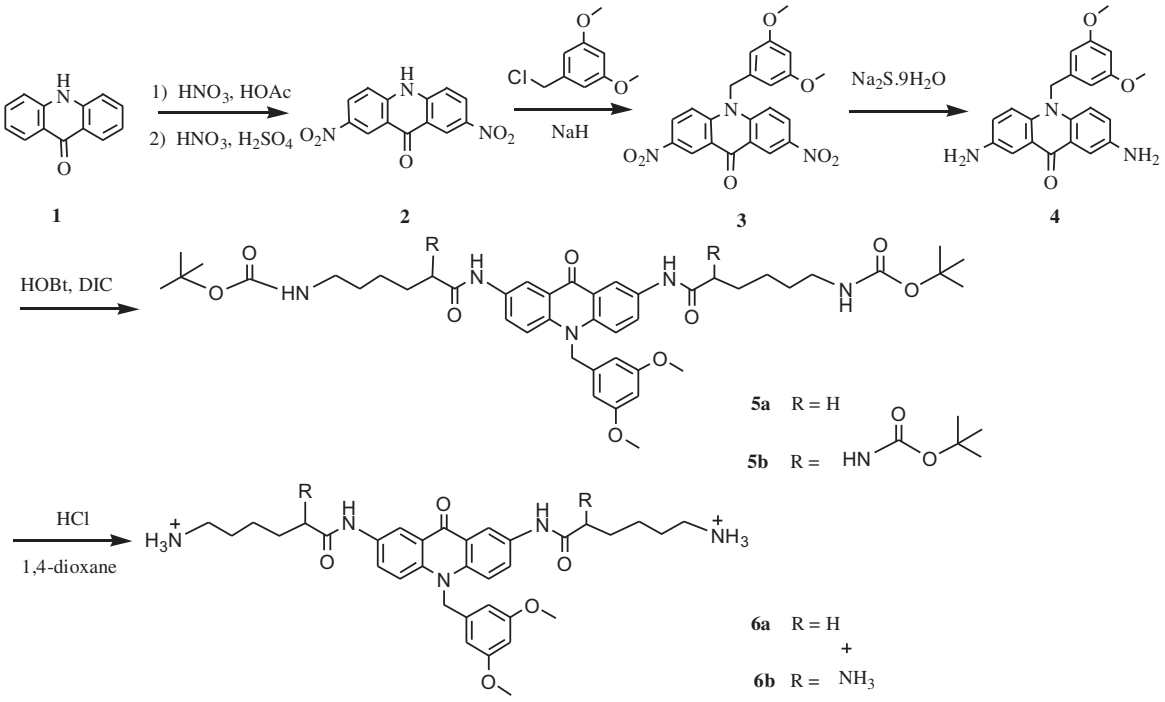
2. Results and discussion

2.1. Chemistry

Scheme 1 summarizes the synthesis of the 2,7-diamino pentyl-carbamoyl-10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone derivatives



Scheme 1. Synthesis of acridone derivatives **6a** and **6b**.

6a and **6b**. The 2,7-diamino-10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone **4** was used as the key compound for the preparation of the final compounds, which was synthesized from the commercially available material acridone **1** in four steps. Initially, we attempted to isolate compounds **2** and **3**, however, the separation is tedious and we did not obtain pure **2** and **3**. Then we tried to react the crude product **3** with Na_2S aqueous solution in ethanol upon refluxing for about 12 h. After the reaction was completed, water was added with rapid stirring at room temperature. The almost pure compound **4** was obtained after filtration. This synthetic method is suitable for larger scale preparation of this agent. It is noteworthy that if water was added in ice water bath, side products will be coprecipitated with **4**. Initial acylation of **4** with appropriate Boc-amino acid in dry tetrahydrofuran in the presence of anhydrous 1-hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropylcarbodiimide (DIC) provided the intermediate **5**. The removal of the *tert*-butoxycarbonyl (BOC) group was readily accomplished by treating with HCl in 1,4-dioxane to give **6a** and **6b** in good yields. It was noted that if 3 M HCl in ethyl acetate was used to remove the BOC group,[32] the amide bond was partially hydrolyzed. The new compounds synthesized were judged pure by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectral data.

Fig. 1 illustrated the structure of 2-amino pentyl-carbamoyl-10-(3,5-dimethoxy)-benzyl-9(10*H*)-acridone derivatives **7a** and **7b**, which were synthesized via the method reported in our previous paper.[32]

2.2. Mass spectrometry

Electrospray ionization mass spectrometry (ESI-MS) is a highly sensitive method for the investigation of the stoichiometry and extent of drug–DNA interaction, which has many advantages over other methods.[36,37] Therefore, the binding of compounds to human G-quadruplex DNA was firstly analyzed by ESI-MS. Typical mass spectra obtained with the G-quadruplex DNA are presented in Fig. 2. In NH_4OAc buffer, the ESI-MS spectrum of the DNA at a concentration of 25 μM revealed two main ions, which can be assigned to $[G]^{5-}$ and $[G]^{4-}$ confirming the formation of the quadruplex.[38] Because $[G]^{5-}$ was the base peak and the abundance of $[G]^{4-}$ was small (42% of the base peak), the binding affinities were studied by evaluating the abundance ratio of $[complex]^{5-}$ to the $[G]^{5-}$. When compound **6a** was added to the G-quadruplex DNA solution in a 1:1 molar ratio, a mixture of drug–DNA complexes was identified and the quadruplex remained the base peak (Fig. 2B). The mixture of 1:1 and 2:1 **6a**/DNA complex ions had relative abundances of 45% and 22%. As the concentration of **6a** was increased, the peaks of complexes increased. The relative abundances of 1:1 and 2:1 **6a**/DNA complex ions were about 78% and 59% (Fig. 2D). For **7a**, the concentrations of **7a** and G-quadruplex DNA were set in a 1:1 molar ratio, the 1:1 complex ion was only 20%, and almost no 2:1 **7a**/DNA complex occurred (Fig. 2C). These results indicated that the two terminal ammonium chains of acridone are important for their interaction with the G-quadruplex DNA.

The chemical structure of **6b** is almost same as that of **6a** except that two hydrogens in the side chains were replaced by two ammoniums; however, the binding affinity of **6b** to the quadruplex is much stronger than that of **6a** as seen from Fig. 3. ESI-MS spectra of

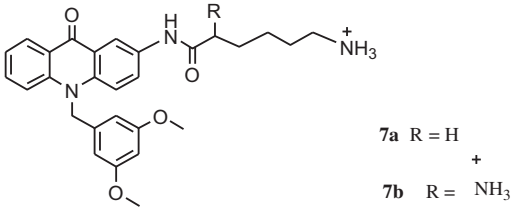


Fig. 1. Structures of **7a** and **7b**.

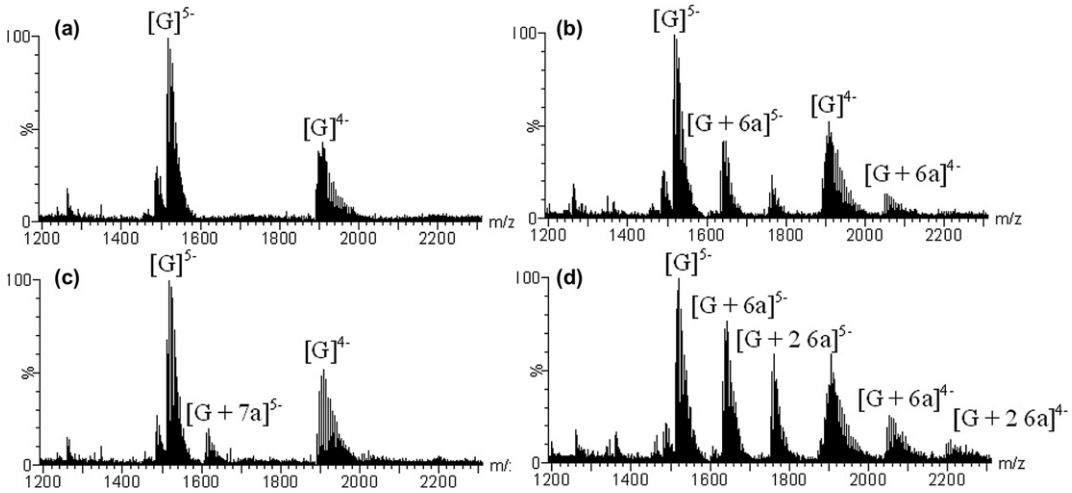


Fig. 2. ESI-MS spectra of G-quadruplex DNA (A) and compounds **6a** and **7a** with G-quadruplex DNA in a 1:1 (B, C) or 2:1 (D) molar ratio in NH_4OAc buffer.

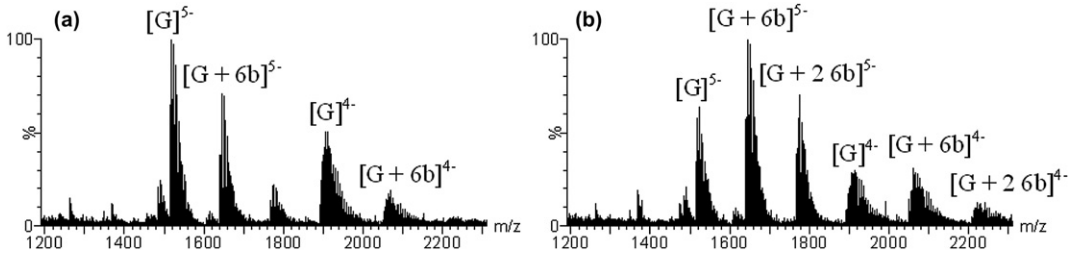


Fig.3. ESI-MS spectra of compound **6b** with G-quadruplex DNA in a 1:1 (A) or 2:1 (B) molar ratio in NH_4OAc buffer.

equimolar solutions of **6b**/quadruplex exhibited 1:1 (70%) and 2:1 (21%) complexes. The intensities of the complexes are much higher than that of **6a**. Moreover, as the concentration of **6b** increased, the signal of the quadruplex decreases dramatically and the 1:1 complex became the base peak. In the case of **7b**, it can also bind with quadruplex (Supplementary data, Fig. 1s), but the intensity is less stronger than that of **6b**, which is consistent with the results of **6a** and **7a**.

To evaluate the relative binding affinity for **6a** and **6b** with G-quadruplex DNA in a 2:1 ratio, BA_i value was calculated according to the following equation.[39]

$$BA_i = \frac{\sum I_r(G + Comp) + \sum I_r(G + 2\ Comp)}{\sum I_r(G) + \sum I_r(G + Comp) + \sum I_r(G + 2\ Comp)}$$

where $\sum I_r(G)$, $\sum I_r(G+Comp)$, $\sum I_r(G+2\ Comp)$ are the total intensities of G-quadruplex, 1:1 and 1:2 complex ions, respectively. The BA_i values of **6a** and **6b** are 0.52 and 0.70, respectively. By considering the binding affinity of **6a** and **6b** with the quadruplex DNA, we can assume that more positive charges favored the formation and stabilization of the quadruplex.

In order to investigate whether compounds **6a** and **6b** can selectively recognize G-quadruplex DNA, a competitive binding study was performed. The G-quadruplex DNA and the duplex DNA were mixed together to obtain the same concentration. The ESI-MS spectrum (Fig. 4) indicated that both **6a** and **6b** bound with G-quadruplex DNA, almost with no complex ions for the duplex DNA, and **6b** showed a higher binding affinity, which is consistent with the above result. All the data indicated that the compounds synthesized were selective binders for human telomeric quadruplex DNA.

2.3. CD spectroscopy

CD spectra have been used extensively to give useful information about DNA structures. The G-quadruplex structure formed by (TTAGGG)4 in 100 mM NH_4Ac solution was further verified by CD spectroscopy. Fig. 5 showed CD spectra of G-quadruplex DNA in the absence and presence of the acridone derivatives. The spectra had a negative peak near 235 nm, a small positive peak at about 250 nm and a positive peak near 295 nm associated with a 274 nm positive shoulder in NH_4Ac buffer, which indicated that the coexistence of antiparallel, parallel G-quadruplex structure and other hybrid forms.[40] Upon addition of compound **6a** to G-quadruplex DNA in buffer containing NH_4^+, there are almost no CD changes at 295 nm, which indicated that the interaction of **6a** did not perturb the antiparallel structure. However, binding of **6a** induced a strong enhancement in the CD intensity at about 265 nm, which suggested that the parallel structure increased.[40] When the same amount of **6b** was added, a similar spectral pattern was also observed. The characteristic peak of complex **6b**/G-quadruplex at about 265 nm was higher than that of **6a**, which demonstrated that **6b** was more efficient than **6a** in converting hybrid G-quadruplex into parallel structure. The results from CD spectra are consistent with those from ESI-MS.

2.4. In vitro cell growth inhibition assay

The 3-(4,5-dimethylthiazol-2-yl)-2,5-di-phenyltetrazolium bromide (MTT) cell proliferation assay was used to evaluate the antiproliferative activity of the synthesized compounds. As shown in Table 1, all the compounds exhibited moderate to good cytotoxicity against CCRF-CEM leukemia cells. Compound **6b** demonstrated more cytotoxicity than compound **6a**, however, there was no difference in the cytotoxicity between **7a** and **7b**. Compounds **7a** and **7b** displayed better antiproliferative activity than compounds **6a** and **6b**. The good cytotoxicity of **7a** and **7b** with disubstitution of acridone derivatives than the corresponding trisubstituted acridone derivatives **6a** and **6b** may be due to the relative small steric

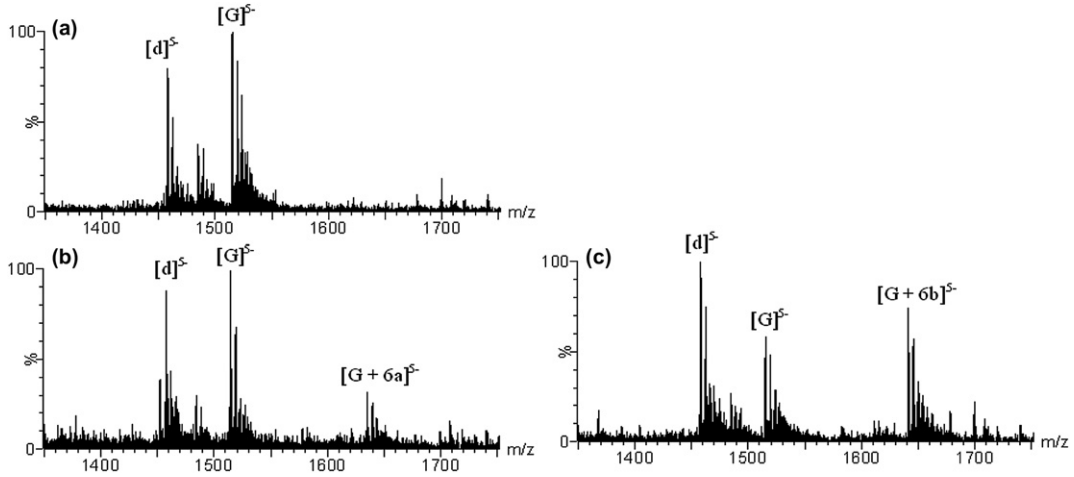


Fig. 4. ESI-MS spectra of the mixture of 5 μM G-quadruplex DNA and 5 μM duplex DNA (A) and compounds **6a** and **6b** with the mixture DNA in a 1:1 molar ratio in NH_4OAc buffer.

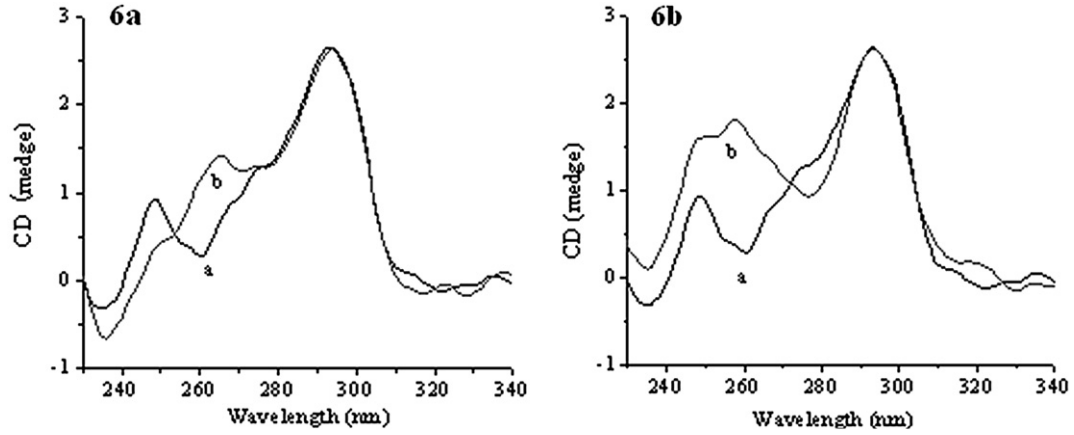


Fig. 5. CD spectra of 10 μM G-quadruplex DNA with compounds **6a** and **6b** in NH_4Ac buffer: (a) 0 μM compound; (b) 40 μM compound.

Table 1
Antiproliferative activity against CCRF-CEM cells of acridone compounds

Comp.	**6a**	**6b**	**7a**[32]	**7b**[32]
IC_{50}(μM)	55	8	0.75	0.75

effects on the acridone group, which may interact with double DNA and the DNA corresponding enzymes.[32]

3. Conclusion

We have prepared a series of 10-(3,5-dimethoxy)benzyl-9(10*H*)-acridone derivatives, which can effectively and selectively bind with telomeric G-quadruplex DNA. Our results demonstrated that the binding affinity for G-quadruplex DNA can be modulated by introducing more side chains with terminal ammonium substituents or introducing more positive charges to the side chains. Further investigations of the biological activities are in progress.

4. Experimental procedures

4.1. Synthesis and characterization

Melting points (mp) were recorded on an SGW X-4 melting point apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR in Me_2SO-d_6 solution with tetramethylsilane as the internal standard, respectively. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet signal; m, multiplet; br s, broad singlet. HRMS were recorded on a QSTAR XL spectrometer and Waters Q-Tof Premier spectrometer.

4.1.1. 2,7-Diamino-10-(3,5-dimethoxybenzyl)-9,10-dihydroacridone ***4*** Acridone (0.59 g, 3 mM) in 3 mL 36% acetic acid was stirred vigorously and then glacial acetic acid (6 mL) and nitric acid (65%, 3 mL) were added. The reaction mixture was stirred for about 3–4 h at about 50 °C. Water was slowly added with rapid stirring under ice-water bath. A yellow precipitate was formed, which was filtered and dried. The precipitate was dissolved in sulfuric acid (6 mL) by stirring. A solution of nitric acid fuming (160 μl) in sulfuric acid (2 mL) was added dropwise with rapid stirring under ice-water bath. Stirring was maintained for a further 0.5 h, and then poured on to crushed ice. The yellow precipitates **2** (impurity) were collected, washed, and dried, which were then suspended in dry DMF (30 mL), and NaH (144 mg, 3.6 mmol) was added. The mixture was stirred vigorously under nitrogen for 1 h at room temperature. 3,5-Dimethoxyl benzyl chloride (837 mg, 4.5 mmol) and KI (100 mg, 0.6 mmol) were added. The mixture was stirred overnight at room temperature. Water was slowly added with rapid stirring under ice-water bath. Yellow solids **3** (impurity) were obtained after filtration, which were added in ethanol (10 mL) containing sodium sulfide nonahydrate (30%, 20 mL) in water. The mixture was heated at reflux under nitrogen for 12 h. After cooling to room

temperature, water was added with rapid stirring. The resulting yellow solids were filtered off, washed with water, and further purified by recrystallization from ethanol. The yellow solids **4** (230 mg) were obtained. The overall yield of the four-step synthesis was about 20%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.65 (s, 6H, OCH_3), 5.12 (br s, 4H, NH_2), 5.56 (s, 2H, CH_2), 6.22 (s, 2H), 6.39 (s, 1H, Ar*H*), 7.06 (m, 2H, Ar*H*), 7.33 (m, 2H, Ar*H*), 7.46 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9 (*C*H$_2$), 55.3 (O*C*H$_3$), 98.3 (*C*H), 104.3 (*C*H), 107.3 (*C*H), 116.7 (*C*H), 122.0 (*C*), 123.4 (*C*H), 134.2 (*C*), 140.1 (*C*), 142.9 (*C*), 161.1 (*C*), 175.7 (*C*O).

4.1.2. General preparation of compound ***6*** To a solution of Boc-amino acid (1.2 mmol) in dry THF (10 mL) were added HOBt (162 mg, 1.2 mmol), DIC (152 mg, 1.2 mmol), and 2,7-diamino-10-(3,5-dimethoxybenzyl)-9,10-dihydro-acridone **4** (187 mg, 0.5 mmol). The reaction suspension was stirred under nitrogen overnight at room temperature. The volatile parts were removed under reduced pressure and compound **5** was obtained by column chromatography. Compound **5** was suspended and stirred in hydrochloride 1,4-dioxane solution (15 mL), The suspension was stirred at room temperature until TLC indicated completion of reaction. Yellow solids were obtained after filtration.

*4.1.2.1. 2,7-Bis-(6-ammonium-pentyl-carbamoyl)-10-(3,5-dimethoxybenzyl)-9,10-dihydro-acridinone bis-hydrochlorate (**6a**).* Yield 169 mg, 56%; yellow solids; mp 263–265 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.37 (m, 4H, CH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$), 1.57–1.66 (m, 8H, CH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$), 2.36 (m, 4H, COC*H*$_2$), 2.79 (m, 4H, C*H*$_2$NH$_3$), 3.66 (s, 6H, OC*H*$_3$), 5.69 (s, 2H, ArC*H*$_2$), 6.25 (m, 2H, Ar*H*), 6.41 (m, 1H, Ar*H*), 7.61 (m, 2H, Ar*H*), 7.84 (br s, 6H, CH$_2$N*H*$_3$), 7.94 (m, 2H, Ar*H*), 8.66 (m, 2H, Ar*H*), 10.21 (s, 2H, N*H*CO); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.1 (CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 26.0 (COCH$_2$*C*H$_2$), 27.3 (COCH$_2$CH$_2$CH$_2$*C*H$_2$), 36.5 (CO*C*H$_2$), 39.1 (*C*H$_2$NH$_3$), 49.3 (Ar*C*H$_2$), 55.6 (O*C*H$_3$), 98.8 (*C*H), 104.6 (*C*H), 115.8 (*C*H), 117.1 (*C*H), 121.7 (*C*), 127.0 (*C*H), 133.9 (*C*), 138.4 (*C*), 139.5 (*C*), 161.4 (*C*), 171.5 (*C*O),176.6 (*C*O); HRMS calcd for $C_{34}H_{44}N_5O_5$ [M−HCl$_2$]$^+$ 602.3342, found 602.3342.

*4.1.2.2. 2,7-Bis-(2,6-diammonium-2-pentyl-carbamoyl)-10-(3,5-dimethoxybenzyl)-9,10-dihydro-acridinone tetra-hydrochlorate (**6b**).* Yield 161 mg, 51%; yellow solids; mp 92–94 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.47 (m, 4H, CHCH$_2$C*H*$_2$CH$_2$CH$_2$), 1.63 (m, 4H, CHC*H*$_2$CH$_2$CH$_2$CH$_2$), 1.91 (m, 4H, CHCH$_2$CH$_2$C*H*$_2$CH$_2$), 2.78 (m, 4H, CHCH$_2$CH$_2$CH$_2$C*H*$_2$), 3.66 (s, 6H, OC*H*$_3$), 4.11 (m, 2H, C*H*CH$_2$), 5.74 (s, 2H, ArC*H*$_2$), 6.27 (m, 2H, Ar*H*), 6.42 (m, 1H, Ar*H*), 7.69 (m, 2H, Ar*H*), 8.01–8.04 (m, 8H, Ar*H* and CH$_2$N*H*$_3$), 8.52 (br s, 6H, CHN*H*$_3$), 8.74 (m, 2H, Ar*H*), 11.3 (s, 2H, N*H*CO); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.4 (CHCH$_2$*C*H$_2$), 26.5 (CH*C*H$_2$), 30.6 (CHCH$_2$CH$_2$*C*H$_2$), 38.4 (CHCH$_2$CH$_2$CH$_2$*C*H$_2$), 49.5 (Ar*C*H$_2$), 52.8 (*C*HCH$_2$), 55.4 (O*C*H$_3$), 98.5 (*C*H), 104.4 (*C*H), 116.2 (*C*H), 117.2 (*C*H), 121.5 (*C*), 126.9 (*C*H), 132.7 (*C*), 138.7 (*C*), 139.1 (*C*), 161.4 (*C*), 167.6 (*C*O), 176.2 (*C*O) HRMS calcd for $C_{34}H_{46}N_7O_5$ [M−HCl$_2$]$^+$ 632.3560, found 632.3556.

4.2. Biophysical evaluation

4.2.1. Materials Single-stranded oligonucleotides (TTAGGG)2, (CCCTAA)2 and (TTAGGG)4 were purchased from Invitrogen (Guangdong, China). First, the oligonucleotides were denatured by heating to 90 °C for 10 min in a buffer consisting of NH_4AC (pH 7.0). The samples were then allowed to cool slowly to room temperature (over 4 h) to allow time for complete formation of the G-quadruplex.[38] The concentration of quadruplex was determined spectroscopically. The stock solutions of the G-quadruplexes and duplex DNA containing single DNA are 200 μM. The synthesized compounds were dissolved in a mixture of methanol/water (50:50, v/v) at a concentration of 200 μM and further dilutions were made freshly in the appropriate aqueous buffer.

4.2.2. Mass spectra The mass spectra were acquired using a Waters Q-Tof Premier mass spectrometer equipped with an electrospray ionization (ESI) source. The instrument was operated in the negative-ion mode. Each compound and DNA solution were diluted with 20:80 (v/v) methanol/100 mm ammonium acetate. The binding assays were performed at 25 μM DNA and 25 or 50 μM compounds. The competitive experiments were carried out at about 5 μM G-quadruplex, 5 μM duplex DNA mixture, and 10 μM compounds for **6a** and **6b** (20 μM compounds for **7a** and **7b**). Methanol was added to obtain a good spray.[38] The direct infusion flow rate was 10 μL/min. The electrospray source conditions were spray voltage of 2.4 kV and capillary temperature of 120 °C.

4.2.3. Circular dichroism spectra The CD spectra of DNA oligonucleotides were carried out at room temperature by using a J-815 spectropolarimeter (JASCO) with a 0.1 cm path-length quartz cell. The CD spectrum was scanned three times and obtained by taking the average of them. The scan for buffer was subtracted from the average scan each time.

4.3. Bioassay

4.3.1. Cell culture CCRF-CEM leukemia cells were cultured in RPIM 1640 medium (Cibco), containing 10% fetal bovine serum (FBS) (Hyclone Laboratories Inc.), 100 units/mL penicillin, and 100 μg/mL streptomycin in a 5% CO_2-humidified atmosphere at 37 °C.

4.3.2. Cell growth inhibition The cells were suspended at a concentration of 2×10^5 cells/mL and seeded in 96-well microtiter plates. Various concentrations of compound dissolved in DMSO were added to each well in quintuplet followed by incubation for 48 h. After treatment, the cells were incubated with 10 μL of MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide from Sigma) solution (5 mg/mL) for 4 h. The formazan precipitate was dissolved in 100 μL DMSO and the absorbance at 490 nm was measured by a Benchmark microplate reader (Molecular Devices Corporation). IC_{50} values are the concentration at which cell growth was inhibited by 50%.

Acknowledgements

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Supplementary data

HRMS spectra of compounds **6a** and **6b**. The mass spectra of compounds **7b** with G-quadruplex DNA. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.016.

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