Supplementary data

Chemical syntheses

13-diphenylmethylberberine chloride **(BR1):** To a solution of dihydroberberine (2 mmol) and bromodiphenylmethane (6 mmol) in acetonitrile (50 mL) is added sodium iodide (2 mmol) and the resulting mixture is stirred for 12 h at reflux temperature under nitrogen. The mixture is concentrated under vacuum, diluted with water and the unstable iminium salt filtered off and dried. To a solution of the above obtained iminium salt in absolute ethanol, sodium borohydride (10 mmol) is added portionwise and the resulting suspension stirred for 45 min at room temperature. More sodium borohydride (8 mmol) is added and the suspension stirred for an additional hour at room temperature. The solvent is evaporated under vacuum, water is added and the mixture extracted with ethyl acetate. The combined organic phases are dried and evaporated under vacuum. The residue is chromatographed on silica gel eluting with hexane-ethyl acetate (10-20%) to give 13-diphenylmethyltetrahydroberberine as an opaque white solid. To this intermediate dissolved in chloroform is added N-chlorosuccinimide (3.5 mmol) and the resulting solution is stirred overnight at r. t., then washed with water. The organic layer is separated, dried, concentrated under vacuum to give a yellow residue which is purified by column chromatography on silica gel eluting with CH_2Cl_2 -MeOH (1-15%). δ, ppm: 11.00 (s, 1H), 7.70 (s, 1H), 7.50 (s, 1H), 7.10 (s, 1H), 7.90 - 7.30 (m, 11H), 6.70 (s, 1H), 6.50 (s, 1H), 6.00 (s, 2H), 5.50 (m, 2H), 4.30 (s, 3H), 4.00 (s, 3H), 3.30 (m, 2H).

Syntheses of 13-diphenylethyll berberine chlorides and higher homologues (**BR2 - BR6):** The following general procedure is an adaption of a published method(K. Iwasa, M. Kamigauchi, M. Sugiura, H. Nanba, *Planta Med.*, 1997, **63,** 196-198.) To a solution of dihydroberberine (10mmol) in 80% ethanol (30 ml) and acetic acid (6 ml) is added the appropriate diphenylalkyl aldehyde (10 mmol). The mixture is heated to 85 – 95° for 5-7h and the progress of the reaction is monitored by TLC (CH_2Cl_2 : MeOH 9:1). The solvent is removed under vacuum. The residue is acidified with 2N HCl and the mixture stirred for 1-2 h at r.t. The aqueous mixture is filtered and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts are dried and then evaporated to give a residue which is column chromatographed eluting with CH_2Cl_2 - MeOH (1-15%). The 13-diphenylalkyl berberine chloride is obtained in 40-50% yield as yellow brown solid. The diphenylalkyl aldehydes used for the preparations of the berberine derivatives are either commercially available, or derived from the commercially available corresponding alcohols and esters by standard chemical methodologies, or obtained by homologation of the corresponding lower aldehydes with commercially available Wittig-Horner reagents.

13-(2'.2'-diphenyl ethyl) berberine chloride, **BR2.** δ, ppm: 10.3 (s,1H), 7.9 (d, 1H), 7.85 (d, 1H), 7.40 (m, 10H). 7.00 (s, 1H), 6.8 (s, 1H), 6.15 (s, 2H), 5.9 (t, 2H), 4.30 (s, 3H), 4.10 (s, 3H), 3.50 (m, 2H), 3.3 (m, 2H), 2.7 (m, 1H), 2.6 (m,2H), 2.5 (2H), 1.5 (m. 1H).

13-(3',3'-diphenylpropyl) berberine chloride, **BR3**. δ, ppm: 9.85 (s, 1H), 8.15 (d, 1H), 7.20 (m, 10H), 7.10 (s, 1H), 7.10 (s, 1H), 6.20 (s, 2H), 4.8 (t, 2H), 4.10 (s, 3H), 4.10 (s, 3H), 3.30 (m, 2H), 3.10 (d, 2H), 2.50(m, 2H), 1.5 (m, 1H). 13-(4',4'-diphenylbutyl) berberine chloride, **BR4**. δ, ppm: 10.8 (s, 1H), 7.70 (d, 1H), 7.50 (d, 1H). 7.30 (m, 10H), 7.0 (s,1H),

6.90 (s, 1H), 6.10 (s, 3H), 5.30 (d, 2H9, 4.35 (s, 3H), 4.10 (s, 3H), 4.00 (m,4H), 3.3 (m, 2H). 3.15 (s, 1H). 2.35 (m, 2H).

13-(5′,5′-diphenylpentyl) berberine chloride, **BR5**. δ, ppm: 10.7 (s, 1H), 7.80 (d, 1H), 7.80 (d, 1H). 7.3 (m, 10H), 7.1 (s,1H9, 6.85 (s, 1H), 6.1 (s, 2H), 5.25 (m, 2H), 4.25 (s, 3H), 4..10 (s, 3H), 3.91 (s, 1H), 3.25 (d, 2H), 3.15 (!H), 2.15 (m, 4H), 1.45 (m, 2H).

13- (6′,6-diphenylhexyl) berberine chloride, **BR6.** δ, ppm: 10.7 (s, 1H), 7.80 (d, 1H), 7.80 (d, 1H), 7.30 (m, 10H), 7.1 (s, 1H), 6.90 (s, 1H), 6.10 (s, 2H), 5.30 (m, 2H), 4.35 (s, 3H), 4.10 (s, 3H), 390 (m, 1H), 3.25 (d, 2H), 3.15 (m, 2H), 2.10 (m, 4H), 1.6 (m, 1H), 1.4 (m, 2H).

Table S1 Optical thermal melting data and binding constants from optical melting data at saturating concentrations of BR and BR analogs with CT DNA[a].

System	T_m (°C)	ΔT_m(°C)	$K_{Tm}\times10^{-5}$(M^{-1})	$K_{uv}\times10^{-5}$(M^{-1})
DNA	65.0	-	-	-
DNA+BR	78.0	13.0	0.77	1.77
DNA+BR1	71.0	6.0	0.75	0.50
DNA+BR2	72.0	7.0	0.95	0.63
DNA+BR3	81.0	16.0	4.59	7.33
DNA+BR4	84.0	19.0	7.14	11.86
DNA+BR5	82.0	17.0	6.09	8.86
DNA+BR6	81.6	16.6	5.94	7.92

[a]Melting stabilization of DNA duplex in the presence of saturating amounts of the alkaloids in CP buffer of 10 mM [Na+], pH 7.0. The data are averages of four determinations. K_{Tm} is the binding constant at the melting temperature, and K_{uv} is the drug-binding constant at 20°C.

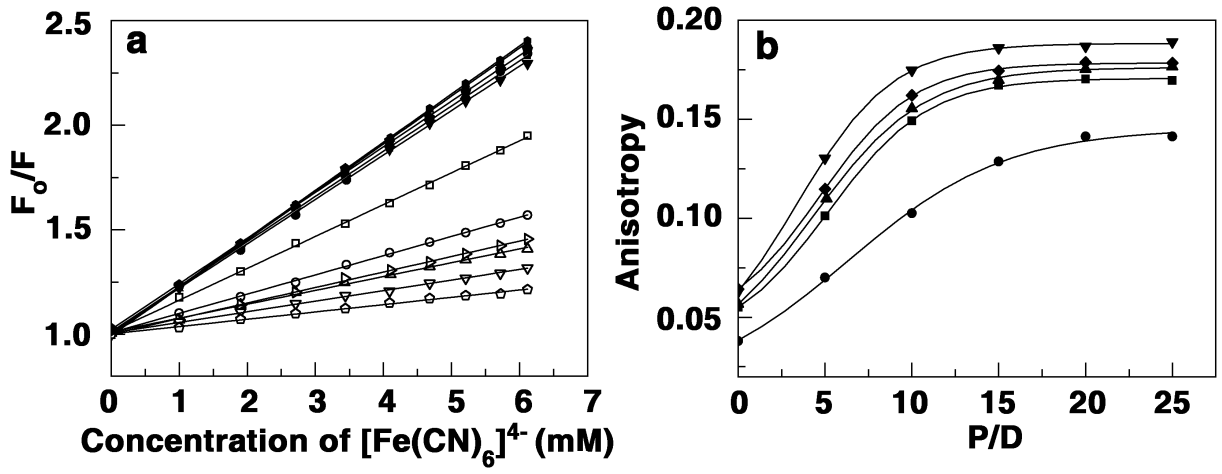

Fig. S1 (a) Stern−Volmer plots for quenching of fluorescence intensity by increasing concentration of $[Fe(CN)_6]^{4-}$ in the absence of DNA of BR (●), BR1(■) ,BR3(►), BR4(⬣), BR5(▼), BR6(▲) and in the presence of DNA BR (O), BR1 (□), BR3 (▷), BR4(⌓), BR5 (▽), BR6 (△) in 10 mM CP buffer, pH 7.0, at 20°C.

(b) A plot of the variation of anisotropy values versus P/D ratio for the complexation of BR (●), BR3 (■), BR4 (▼), BR5 (◆) and BR6 (▲) with CT DNA.

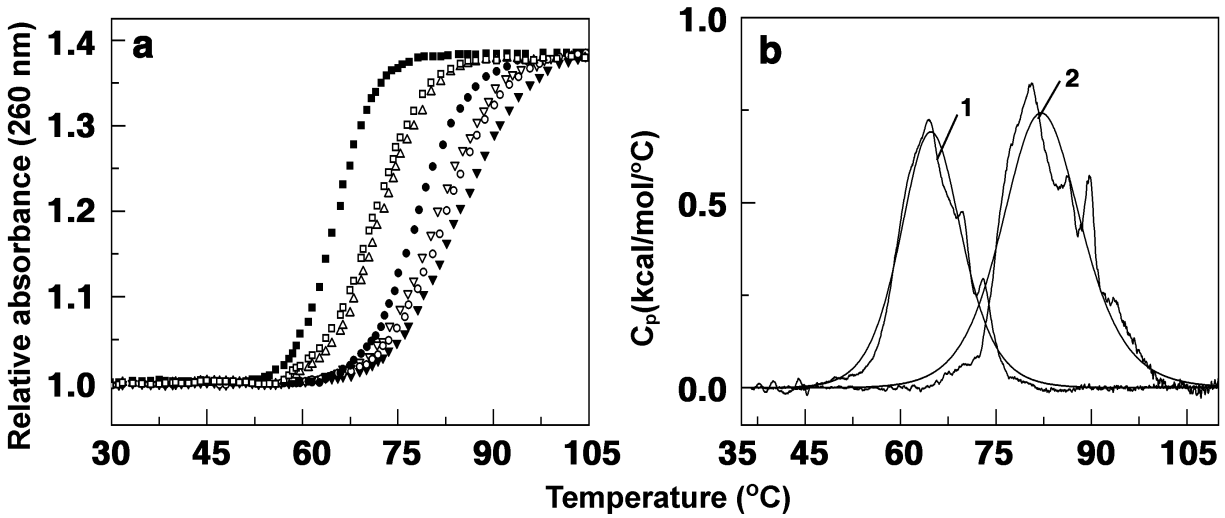

Fig. S2 (a) Thermal melting profiles (absorbance change at 260 nm versus temperature) of DNA (■) and its complexes with BR (●), BR1 (□), BR2 (△), BR3 (▽), BR4 (▼) and BR5 (○).

(b) DSC thermogram of (curve 1) CT DNA and (curve 2) its complex with BR4.

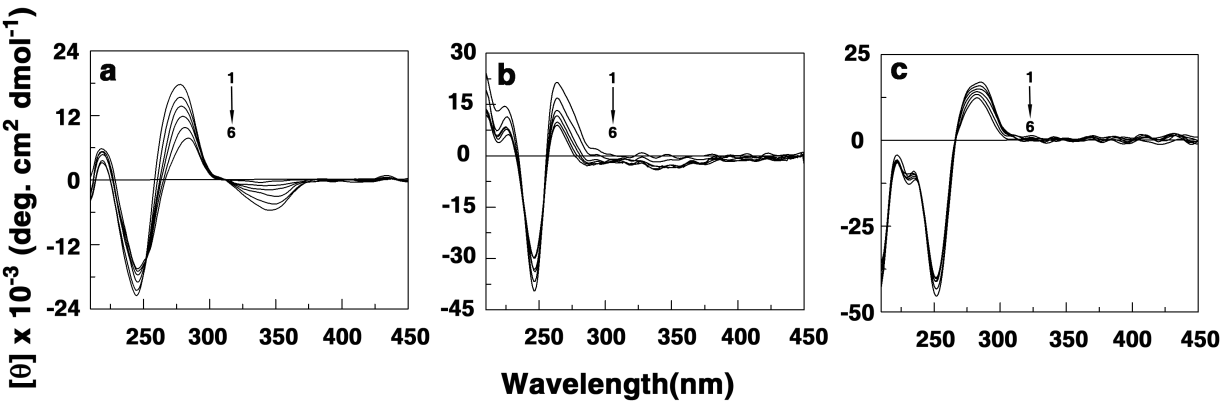

Fig. S3 Representative CD spectral changes resulting from the interaction of BR3 with DNA in CP buffer, pH 7.0 at 20 °C. (a) curves 1−6 denote CT DNA (30 μM) treated with 0, 3.0, 6.0, 12.0, 18.0, and 24.0 μM BR3; (b) curves 1−6 denote poly(dA-dT). poly(dA-dT) (30 μM) treated with 0, 3.0, 6.0, 12.0, 18.0, and 24.0 μM BR3.(c) curves 1−6 denote poly(dG-dC). poly(dG-dC) (30 μM) treated with 0, 3.0, 6.0, 12.0, 18.0, and 24.0 μM BR3.

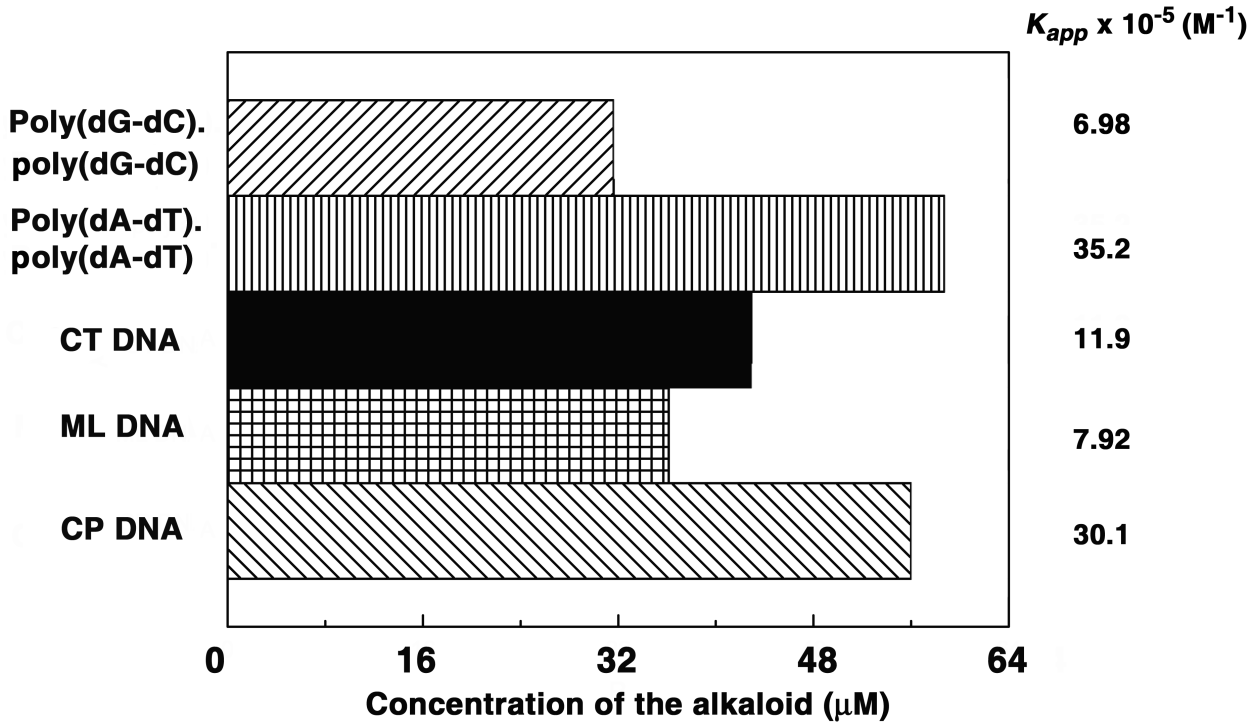

Fig. S4 Results of competition dialysis assay of BC3 (highest binding 13-phenylalkyl berberine analogue) binding to various polynucleotides at 20 °C in 10 mM CP buffer, pH 7.0. The concentration of analogue bound each polynucleotide sample is depicted as a bar graph.