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Synthesis of bisquinoline–pyrrole oligoamide as G-quadruplex binding ligand

Chi Wi Ong [a,*], Meng-Chi Liu [a], Kun-Da Lee [a], Keng Wei Chang [a], Ya-Ting Yang [a], Hung-Wei Tung [a], Keith R. Fox [b]

[a] National Sun Yat-Sen University, No. 70, Lienhai Rd., Kaohsi0ung 804, Taiwan
[b] Centre for Biological Sciences, Life Sciences Building, University of Southampton, Southampton SO17 1BJ, United Kingdom

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ABSTRACT

A one-pot procedure using ammonium formate under palladium catalysis for the reductive dechlorination and reduction of nitro group of 4-chloro-8-nitro–quinoline derivatives has be successfully carried out. This has lead to the synthesis of bisquinoline–pyrrole oligoamide **1**, which show significant G-quadruplex selectivity in preference to duplex DNA. The cooperativity between the bisquinoline and pyrrole oligoamide moieties for good binding affinity to G-quadruplex was proven by synthesizing **2** and **3** lacking a quinoline ring and pyrrole amide, respectively, and both show much reduce affinity to G-quadruplex. Altogether, the results demostrate that the appropriate combination of two chromophores to form the hybride can attenuate binding affinity and selectivity towards G-quadruplex, an important criteria for the rational drug design.

1. Introduction

G-quadruplexes secondary structure are found in G-rich regions of DNA through the association of four guanine to form the guanine tetrad, followed by stacking of the guanine tetrad on top of each other.[1] The ability of G-rich sequences in telomeres and numerous gene promoters to form quadruplex structures has been exploited for the development of anticancer agents that promote or stabilize G-quadruplex.[2–6,14,23] The main strategy is the design of large flat aromatic ligands with or without containing cationic side chains that binds to the G-tetrad through π-π stacking and electrostatic interaction,[1b,3e,f,7] such as macrocyclic telomestatin,[8] pentacyclic acridinium ligands,[9] cationic porphyrin,[10] 4,7-diamino-1,10-phenanthroline derivatives[11] and bisquinolinium compounds.[12] However the grooves of quadruplex structures remains an opportunity for ligands binding. More recently, distamycin, a DNA minor groove binding agent has been found to interact with the grooves of quadruplexes.[13] Till today, the design of quadruplex binding ligands has mainly focused individually on π–π stacking at the G-tetrads or hydrogen bond at the groove, while their cooperative interaction has rarely been discussed.[14]

Quinoline oligoamides has been reported to fold into predictable and very stable secondary motifs,[15a,b] and recently shown to be a good candidate as G-quadruplex ligands.[15c] The tetramer of 8-amino-2-quinoline carboxylic acid with a 1.5 turn helically folded architecture has been shown to have significant binding affinity and selectivity for G-quadruplex without any evidence of DNA-duplex binding.[15c] It should be noted that the 4-position of the quinoline ring contain a cationic side chains to confer electrostatic interaction with the G-quadruplex, and possibly improved water solubility. Interestingly, the bisquinoline adopting a planar crescent-like structure was found to be a poor G-quadruplex ligand. Can the π-rich bisquinoline be transform into a good G-quadruplex ligand? Herein, we hope to use cooperative effect by incooperating pyrrole oligoamide to the bisquinoline and study the ability to stabilize G-quadruplex.

In this contribution we demonstrated that the incorperation of pyrrole oligoamide to bisquinoline in **1** favours G-quadruplex stabilization. As shown in Fig. 1, the bisquinoline can adopt a near planar conformation (**1b**), whereby playing the role of π–π stacking with the G-tetrads, and the pyrrole oligoamide further attenuating the G-quadruplex stabilization. We next need to offer prove of cooperativity between the bisquinoline and pyrrole amide moieties for the good binding affinity and selectivity towards G-quadruplex. The role of π–π stacking ligand for bringing the groove binding ligand to close proximity was further tested by replacing one quinoline ring of compound **1** with a phenyl ring in compound **2**. By replacing one of the quinoline ring of compound **1** with a phenyl ring to form compound **2** we have reduced the available π–π stacking interaction. Compound **3** was constructed to contain two quinolines rings tethered to dimethylaminopropane, but without an attached pyrrole amide. Both compound **2** and **3** have a lower binding affinity fo G-quadruplex. Furthermore, our compound **1**–**3** do not possess a functional group at 4-position of

* Corresponding author. Tel.: +886 952311150; fax: +886 7 5253908; e-mail address: cong@mail.nsysu.edu.tw (C.W. Ong).

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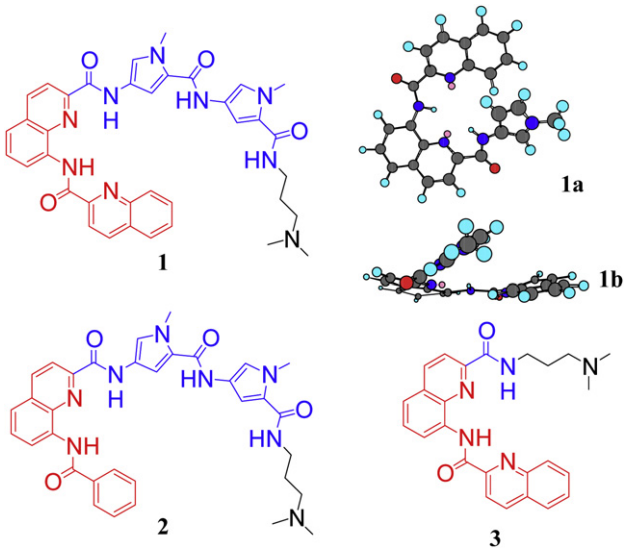


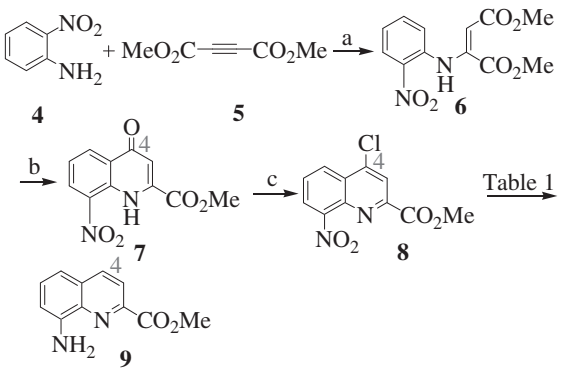
Fig. 1. Compounds **1**–**3** to probe the cooperative between guanine tetrad π–π stacking ligand and DNA minor goove binding ligands. **1a** and **1b**, top and side view of **1** with one pyrrole ring showing the near planarity of the bisquinoline rings with the pyrrole ring sticking outwards.

quinoline that may aid G-quadruplex stabilization. We have found an expedient method for silencing the 4-position of quinoline by converting 4-chloro-8-nitro-quinoline derivative to the 8-amino-quinoline derivatives under hydrogenation condition, a one-pot procedure for the reductive dechlorination with consecutive reduction of nitro group to amine.

2. Results and discussion

Our synthesis began with the reaction of 2-nitroaniline **4** with dimethyl-acetylenedicarboxylate **5** give **6**, followed by cyclization to **7** and aromatization to give 4-choro-8-nitro-quinoline-2-carboxylic ester **8** using reported procedures,[16] but with slight modifications (Scheme 1). We found that the cyclization of compound **6**–**7** was best performed using a 1:2 w/w ratio of compound to polyphosphoric acid at 180 °C for a short reaction time (<1 h), whereby prolong reaction time gave a much lower yield. Our first task was to dehalogenate compound **8** using several reported reductive delogenation conditions as shown in Table 1. The use of sodium amalgam or copper powder in organic acid[17] failed to give the required product. Interestingly, the use of ammonium formate with Pd/C catalysis[18] for the dechlorination of **8** was found to simultaneously reduced the nitro group to the amine in one-pot to give directly the key intermediate **9**. Compound **9** was subsequently reacted with benzoyl chloride and quinoline-2-carbonyl chloride in the presence of DIPEA to give **10** and **11**, respectively, in high yield. The ester of **10** and **11** was hydrolyzed to the acid and then converted to the acid chloride **10a** and **11a**, respectively, for the subsequent preparation of our model **1**–**3**. The coupling of **10a** and **11a** with the previous reported pyrrole oligoamide **12**[19] gave the desired product **1** and **2**, respectively, in moderate yield. Similarly reaction of **11a** with *N*,*N*-dimethylaminopropylamine gave **3** (Scheme 2).

We next investigated the ability of these compounds **1**–**3** to bind to duplex DNA and G-quadruplex. The comparative thermal stabilization (ΔT_m) of calf thymus (CT) duplex by compounds **1**–**3** was performed using UV absorbance–temperature plot under identical conditions of buffer and pH. The results show that **3** displayed slight binding for CT DNA (ΔT_m=0.7 °C) as compared with **1** and **2** (ΔT_m<0.3 °C) (see ESI). Deoxyribosenuclease I footprinting analysis is a useful technique for locating the specific binding site of small molecule on DNA. Footprinting of compounds **1**–**3** with Hex B



Scheme 1. Preparation of quinoline motif. (a) MeOH, rt, 18 h then reflux 6 h, 82%. (b) PPA/**6**=2.26, 180 °C, 45 min, 84%. (c) $POCl_3$, reflux 2 h then rt, 1 h, 95%.

Table 1
Dehalogenation of **8**

Entry	Conditions	Product
1	Na(Hg), rt, 4 h in THF/MeOH=1:1	*
2	Hexanoic acid, Cu power, 160–170 °C, 10 min.	**7**
3	Ammonium formate, 5% Pd/C, in MeOH, reflux 10.5 h	**9**

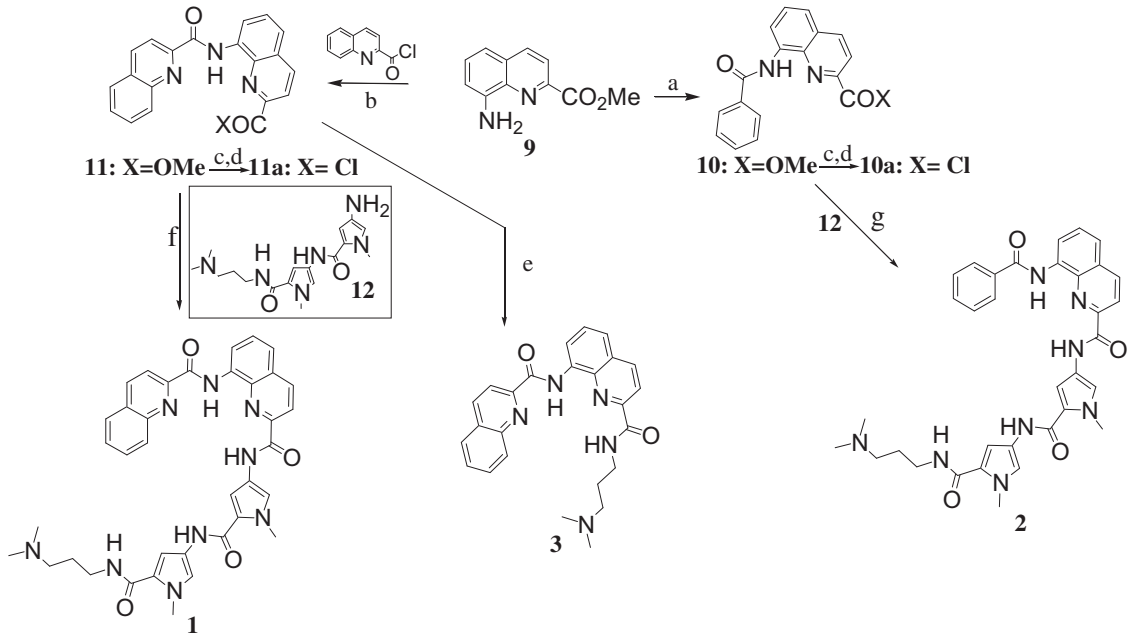
● Complex mixtures.

show no protection mapping with concentration greater than 10 μM. This substatiate the comparative thermal stabilization results, which showed that compounds **1**–**3** have minimal affinity to duplex DNA.

The poor binding to duplex DNA of **1**–**3** upto a concentration of over 10 μM encourages us to investigate whether these compounds can behave as a good selective G-quadruplex binding agent. The stabilization to various G-quadruplexes was also investigated by fluorescence melting analysis[20] using human telomeric G-quadruplex (HT), *c-kit* and *c-myc* promoters. The thermal melting temperatures of the various quadruplexes were determined using the fluorescence melting technique developed previously by Darby et al.[21a] for assessing the stability of related quadruplexes[21b–e] in the present or absent of ligands. The stabilization of the quadruplex increases its melting temperature (ΔT_m). At the concentration of 2 μM, distamycin and compound **12** showed no stabilization for all the G-quadruplex in this study (see ESI). As such, a concentration of 2 μM for ligand **1**–**3** was chosen to study their ability to stabilize G-quadruplex. The synthesized ligand **1**–**3** showed good to moderate stabilization of the G-quadruplex and the results are shown in Fig. 2 and Table 2. The T_m enhancement (ΔT_m) for each compound is tabulated in Table 2.

Our results indicate clearly that ligand **1** was the best in stabilizing all the G-quadruplex, with a ΔT_m value of 7 °C for HT, 5.4 °C for *c-kit*, and 4.1 °C for *c-myc*, respectively. Compound **2**, with reduced π–π stacking, while compound **3**, which lacks the bispyrrole oligoamide, in our design strategy were uniformly weaker G-quadruplex binders. To our delight, the bisquinoline pyrrole oligoamide hybrid **1** has a cooperative effect in enhancing binding affinity and selectivity for G-quadruplex.

Recently, there have been growing interest to design small molecules that show some discrimination between G-quadruplexes.[22–25] These results provide some hints for designing ligand to discriminate between G-quadruplexes ligands based on π-rich bisquinoline and pyrrole oligoamide. For the HT sequence, the ΔTm produced by **1** is greater than that for **2** and **3**. This suggests that both π–π stacking and pyrrole oligoamide are required for optimal binding to HT sequence. Compound **1** and **3** has a higher ΔTm than **2** with the *c-kit* sequence, this indicate that π–π stacking is playing a more predominant role for binding to *c-kit* sequence.



Scheme 2. Synthesis of model compounds **1**–**3**. (a) PhCOCl, NEt_3, CH_2Cl_2, rt, 77%. (b) DIEA, CH_2Cl_2, 0 °C ~rt, 30%. (c) KOH, THF:MeOH=2:1, rt, 80%. (d). $SOCl_2$, C_6H_6, reflux-rt (e) *N*1,*N*1-Dimethyl-propane-1,3-diamine, DIEA, 0 °C ~rt, 52%. (f) 4-Amino-*N*-(5-(3-(dimethylamino)propylcarbamoyl)-1-methyl-1*H*-pyrrol-3-yl)-1-methyl-1*H*-pyrrole-2-carboxamide **12**, DIEA, 0 ~rt, 35%. (g). **12**, DIEA, CH_2Cl_2, 0 °C ~rt, 32%.

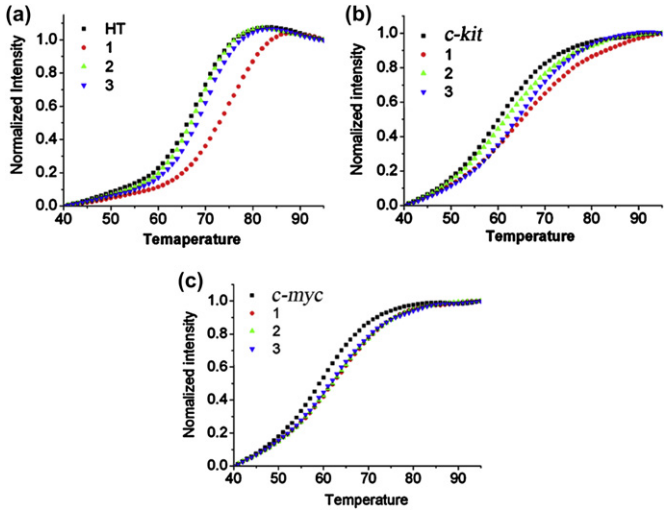


Fig. 2. Melting curve of 1 μM intramolecular G-quadruplex in the present of 2 μM ligands.

On the other hand, the slightly lower stabilization of the *c-myc* sequence by **3** indicate the pyrrole oligoamide might playing a role for *c-myc* sequence. Highly specific recognize to a particular G-quadruplex sequence may thus be achieved at the molecular level.

Table 2
Thermal stability of quadruplex DNA and ligands

DΔTm at 2 μM conc./°C					
Sequences	Compounds				
	1	**2**	**3**	**12**[a]	Distamycin[a]
HT	7.0	1.3	1.8	0	0
c-kit	5.4	1.3	4.5	0	0
c-myc	4.1	3.5	2.6	0	0

The experiments were performed in 10 mM Li_2PO_4 pH 7.4 containing 100 mM KCl (HT and *c-kit*) or 0.1 mM KCl (*c-myc*). Each reactions contained 1 μM oligonucleotide and 2 μM ligand; heated at 0.5 °C min^{-1}.

[a] At 5 μM, ΔTm=<1.0.

Finally, we carried out a competition binding assay for G-quadruplex versus duplex DNA. As shown in Table 3 (entry 2), CT DNA has a minimal effect on the melting temperature of HT quadruplex. Next, competitive binding for compound **1** to HT quadruplex in the presence of varying amounts of CT-duplex DNA was carried out. As shown in Table 3 (entry 7) the ΔTm of the HT quadruplex was largely unchanged in the presence of a 20-fold excess of calf thymus DNA. This result indirectly shows that compound **1** bind preferentially to quadruplex DNA.

Table 3
Competitive binding assay of quadruplex versus duplex

Entry	Ratio of HT:CT: 1[a]	ΔTm (°C)
1	1:0:0	0
2	1:20:0	0.9
3	1:0:2	6.7
4	1:1:2	6.3
5	1:5:2	6.3
6	1:10:2	5.5
7	1:20:2	5.4

[a] Concentration in μM.

3. Conclusion

In summary, we have synthesized three new bisquinoline derivatives and study their interaction with duplex and quadruplex DNA. The results ascertain the importance of tethering pyrrole polyamide groove binding ligand to bisquinoline π–π stacking ligand in enhancing quadruplex stabilization, and more importantly with the discrimination against duplex DNA. This can be a useful strategy of choice for the future design of new anticancer agents.

4. Experimental section

4.1. General

All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware. CH_2Cl_2 was distilled over calcium hydride. DMSO, MeOH and EtOH were purchased from Merck and used as

received. Nuclear magnetic resonance spectra were recorded on a Varian Gemini-200 MHz and Varian Unity-INOVA-500 MHz spectrometer. ($CDCl_3$, MeOD-d_3 or DMSO-d_6). Chemical shifts are reported in parts per million relative to residual $CHCl_3$ (δ=7.26, ^{1}H; 77.0, ^{13}C). Mass spectra were obtained on JEOL JMS-HX110, ESI on Bruker APE (II) FT-MS or Bruker Autoflex MALDI-TOFMS. *N*,*N*-Dimethyl-propane-1,3-diamine is commercially available. Synthesis of **12** was referred to in Ref. 19.

4.2. Fluorescence melting studies

The ligands were dissolved in DMSO, which was kept below 1% final concentration in the capillary. Fluorescence melting experiments were conducted in a Roche LightCycler as previously described[21] in a total reaction volume of 20 μl. Intramolecular oligonucleotides (final concentration 1 μM) were prepared in 10 mM lithium phosphate pH 7.5, which was supplemented with various concentrations of potassium chloride or sodium chloride. The LightCycler has one excitation source (488 nm) and the changes in fluorescence were measured at 520 nm. As previously described, hysteresis effects with the intramolecular quadruplexes were suppressed by performing the melting experiments at a slow rate of heating and cooling (0.5 °C min^{-1}) by increasing the temperature in 1 °C steps, leaving the samples to equilibrate for 2 min at each temperature before recording the fluorescence. In a typical intramolecular sequences experiment, the oligonucleotides were first denatured by heating to 95 °C for 5 min. They were then annealed by cooling to 30 °C at 0.5 °C.min^{-1} and melted by heating to 95 °C at the same rate. Under these conditions, no hysteresis was observed. Melting temperatures (T_m values) were determined from the first derivatives of the melting profiles using the Roche LightCycler software. The sequence code used in this study were HT: F-A(GGGTTA)3GGGT-Q, *c-kit*: F-AGGGAGGGCGCTGGGAG GAGGG-Q and *c-myc*: F-TGGGGAGGGTGGGGAGG-Q. Where F is dR-FAM at 5′-end and Q is dR-Met Red at 3′-end.

4.3. Synthesis and characterization data for ligands 1–3

*4.3.1. N-(5-(5-(3-(Dimethylamino)propylcarbamoyl)-1-methyl-1H-pyrrol-3-ylcarbamoyl)-1-methyl-1H-pyrrol-3-yl)-8-(quinoline-2-carboxamido)quinoline-2-carboxamide (**1**).* To a solution of quinaldic acid (0.1 g, 0.58 mmol) in benzene (10 mL) was added 1 ml of thionyl chloride and refluxed for 2 h. After further reacting in room temperature for 1 h, the solvent and excess thionyl chloride were removed by rotary evaporator and dried by vacuum. The residue was dissolved in 10 mL CH_2Cl_2 and slowly added to the solution of 8-amino-quinoline-2-carboxylic acid 6 (0.52 g, 2.6 mmol) in 20 ml CH_2Cl_2, which is mixed with DIEA (0.5 ml, 2.9 mmol) under 0 °C. After reacting overnight at room temperature, the solvent was evaporated and the residue was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, and purified by column chromatography using CH_2Cl_2. The desired product **11** as a yellow solid was obtained (0.15 g, 90%) and used directly.

Compound **11** (0.2 g, 0.56 mmol) was dissolved in THF:MeOH=2:1 (15 mL) and added KOH (0.2 g, 3.57 mmol). After reacting at room temperature for 3 h, THF was removed from reaction mixture by rotary evaporator and adjusted ph to 3–4 by 2 M aqueous HCl, and on further cooling in an ice bath gave light yellow precipitate of 8-[(quinoline-2-carbonyl)-amino]-quinoline-2-carboxylic acid. The precipitate was collected, washed with additional cold water, and dried to give 0.15 g light yellow powder product in 80% yield. The 0.1 g (0.29 mmol) of light yellow powder was dissolved in 10 mL benzene with 1 mL of thionyl chloride and refluxed for 1 h. After cooling to room temperature, benzene and excess thionyl chloride were removed by rotary evaporator and further dried by vacuum to give the 8-[(quinoline-2-carbonyl)-amino]-quinoline-2-carbonyl chloride. The residue was dissolved in 10 mL CH_2Cl_2 and slowly added to the solution of amino polypyrrole amide **12** in 20 ml CH_2Cl_2, which is mixed with DIEA (0.5 ml, 2.9 mmol) under 0 °C. After reacting overnight at room temperature, the solvent was evaporated and the residue was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, and purified by column chromatography using CH_2Cl_2:MeOH=2:1 as elution. The desired product **1** as a yellow solid was obtained (0.07 g, 35%). Mp 213–214 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.32 (s, 1H), 10.05 (s, 1H), 10.04 (s, 1H), 9.01 (d, 1H, *J*=7.5 Hz), 8.49 (d, 1H, *J*=8.5 Hz), 8.43 (d, 1H, *J*=8.5 Hz), 8.41～8.39 (m, 2H), 8.18 (d, 1H, *J*=8.0 Hz), 7.91 (d, 1H, *J*=8.0 Hz), 7.71～7.64 (m, 4H), 7.58 (t, 1H, *J*=7.5 Hz), 7.38 (d, 1H, *J*=15 Hz), 7.18 (d, 1H, *J*=1.5 Hz), 6.95 (d, 1H, *J*=1.5 Hz), 6.39 (d, 1H, *J*=1.5 Hz), 4.03 (s, 3H), 3.96 (s, 3H), 3.48 (q, 2H, *J*=6.0 Hz), 2.47 (t, 2H, *J*=6.0 Hz), 2.28 (s, 6H), 1.75 (t, 2H, *J*=6.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$); 162.26, 161.67, 161.57, 158.79, 150.18, 147.95, 146.31, 138.35, 138.05, 137.45, 134.23, 130.22, 130.19, 129.63, 129.42, 129.18, 128.49, 128.00, 123.94, 123.61, 122.13, 121.04, 120.97, 119.96, 119.44, 119.09, 118.46, 117.83, 104.39, 102.84, 58.88, 45.38, 39.28, 36.84, 36.69, 25.80. HRMS (ESI): calcd for $C_{37}H_{38}N_9O_4$, 672.3051, found, 672.3047.

*4.3.2. 8-Benzamido-N-(5-(5-(3-(dimethylamino)propylcarbamoyl)-1-methyl-1H-pyrrol-3-ylcarbamoyl)-1-methyl-1H-pyrrol-3-yl)-quinoline-2-carboxamide (**2**).* To a solution of benzoyl chloride (1 mL, 3.1 mmol) was slowly added into the solution of 8-amino-quinoline-2-carboxylic acid 6 (0.52 g, 2.6 mmol) in 20 ml CH_2Cl_2, which is mixed with triethylamine (0.43 ml, 3.1 mmol) under 0 °C. After reacting 6 h at room temperature, the solvent was evaporated and the residue was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, and purified by column chromatography using CH_2Cl_2. The desired product **2** as a brown solid was obtained (0.60 g, 75%). Mp 232–235 °C. ^{1}H NMR (500 MHz, DMSO-d_6); δ: 11.23 (s, 1H), 11.03 (s, 1H), 10.04 (s, 1H), 8.90 (d, 1H, *J*=7.5 Hz), 8.64 (d, 1H, *J*=8.5 Hz), 8.28 (d, 1H, *J*=8.5 Hz), 8.15～8.17 (m, 2H), 7.82 (d, 1H, *J*=8.5 Hz), 7.76 (t, 1H, *J*=8.0 Hz), δ 7.4～7.70 (m, 3H), 7.36 (d, 1H, *J*=1.5 Hz), 7.24 (d, 1H, *J*=2.0 Hz), 7.23 (d, 1H, *J*=1.5 Hz), 6.87 (d, 1H, *J*=1.5 Hz), 3.93 (s, 3H), 3.83 (s, 3H), 3.21 (q, 2H), 2.31 (t, 2H, *J*=7.0, Hz), 2.19 (s, 6H), 1.61～1.67 (m, 2H), ^{13}C NMR (125 MHz, DMSO-d_6) δ: 165.90, 161.66, 161.29, 158.51, 149.12, 138.47, 137.15, 135.10, 134.73, 132.17, 128.94, 128.68, 128.17, 123.69, 123.13, 122.42, 122.09, 121.59, 119.69, 118.90, 118.36, 117.98, 105.08, 104.14, 57.01, 45.02, 37.09, 36.31, 36.04, 27.01. HRMS (ESI): calcd for $C_{34}H_{36}N_8O_4$, 621.2938, found, 621.2935.

*4.3.3. N-(3-(Dimethylamino)propyl)-8-(quinoline-2-carboxamido)-quinoline-2-carboxamide (**3**).* Synthesis of compound **3** was started from **8** and similarly prepared as **1** with the use of *N*,*N*-dimethyl-1,3-propanediamine. Yield: 0.13 g, 52%. Light yellow solid. Mp 144–145 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.41 (s, 1H), 9.05 (d, 1H, *J*=7.5 Hz), 8.72 (br, 1H), 8.49 (d, 1H, *J*=8.5 Hz), 8.44 (d, 2H, *J*=4.0 Hz), 8.43 (d, 1H, *J*=4.0 Hz), 8.38 (d, 1H, *J*=8.5 Hz), 8.22 (d, 1H, *J*=8.0 Hz), 7.97 (d, 1H, *J*=8.5 Hz), 7.87 (t, 1H, *J*=7.5 Hz), 7.73～7.69 (m, 2H), 7.65 (d, 1H, *J*=8.0 Hz), 3.82 (q, 2H, *J*=7.0 Hz), 2.44 (t, 2H, *J*=7.0 Hz), 2.11 (s, 6H), 1.75 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.40, 162.45, 150.16, 148.30, 146.46, 138.01, 138.00, 137.53, 134.45, 130.36, 129.63, 129.58, 129.36, 128.97, 128.31, 128.07, 122.02, 119.68, 118.98, 117.50, 57.32, 45.28, 38.46, 29.68, 27.87. HRMS (ESI): calcd for $C_{25}H_{26}N_5O_2$, 428.2089, found, 428.2086.

Acknowledgements

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Supplementary data

UV melting temperature and DNase I footprinting experiments of **1**–**3** and distamycin are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.05.001.

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