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Synthesis of 1*H*-pyrrolo[3,2-*h*]quinoline-8-amine derivatives that target CTG trinucleotide repeats

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ABSTRACT

We describe a new molecular design, synthesis, and investigation of small molecules that bind to CTG trinucleotide repeats in DNA. 1*H*-Pyrrolo[3,2-*h*]quinoline-8-amine (**PQA**) has a tricyclic aromatic system with unique non-linear hydrogen-bonding surface complementary to thymine. We have synthesized a series of **PQA** derivatives with different alkylamino linkers. These **PQA**s showed binding to pyrimidine bulge DNAs and CNG (N = T and C) repeats depending on the linker structure, while quinoline derivatives lacking the pyrrole ring showed much lower binding affinity. **PQA** is a useful molecular unit for both CTG and CCG repeat binding.

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Myotonic dystrophy type 1 (DM1), the most common form of muscular dystrophy presenting 1 in 8000 people, is one of more than 30 inheritable disorders classified as trinucleotide repeats (TNR) disorders that are caused by aberrant expansion of triplet repeats of specific genes.[1,2] DM1 is caused by the anomalous expansion of CTG trinucleotide repeats in 3′-untranslated region of dystrophia myotonica protein kinase (DMPK) gene. Normal individuals have <37 CTG repeats, while DM1 patients carry between 50 and many thousands of repeats sequence. The expanded CTG is transcribed to CUG repeats, which cause toxic gain of functions.[3–8] Targeting the toxic RNA by oligonucleotides and small molecular ligands has been a promising strategy to alleviate the pathologic features.[8–14] Targeting CTG repeat DNA could be another approach for the diseases, which could affect on transcription step and repeat stability related to repeat expansion and contraction.[15–17] Here, we report a series of new molecules consisting of 1*H*-pyrrolo[3,2-*h*]quinoline-8-amine (**PQA**) skeleton as a CTG repeat binding ligand. Binding assays including thermal melting temperature, surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) measurements showed that the **PQA** derivatives bound to CTG and CCG repeats but not to CAG and CGG repeats.

CTG repeats sequence was suggested to form hairpin structure consisting of a tandem array of non-canonical T–T mismatch base pair flanked by G–C base pairs.[18] We have developed a series of synthetic ligands for mismatched base pairs in DNA.[19–22] The T–T mismatch could be a target in order to develop small ligands for CTG repeats because T–T mismatch specifically forms in the CTG repeats hairpin structure. To our knowledge, there is few known small molecule that selectively and strongly binds to T–T mismatch.[9,23–25] The difficulty can be attributed to the alternating hydrogen-bonding motif of acceptor–donor–acceptor (A–D–A) in thymine, which is known to form weak base pair, because of the repulsive secondary interactions between the positively polarized donor hydrogens and between the negatively polarized atoms.[26–28] For example, association constant (K_A) between thymine and 2,6-diaminopyridine having A–D–A/D–A–D motif was reported to be 100 M^{-1}, which is 100 to 1000-fold lower than that of G–C base pair having A–D–D/D–A–A motif (Fig. 1a). This can be rationally explained by the presence of secondary repulsive force in the hydrogen-bonded pair: 2,6-diaminopyridine–thymine have four repulsive interactions, while G–C has two repulsive and two attractive interactions. The limitation in A–D–A/D–A–D motif underscores the need to develop a new motif for thymine recognition. We here designed 1*H*-pyrrolo[3,2-*h*]quinoline-8-amine (**PQA**) as a thymine recognition unit (Fig. 1b). **PQA** is a tricyclic aromatic heterocycle having a complementary hydrogen-bonding surface to thymine. Non-linear arrangement of hydrogen bond donor and acceptor in **PQA** will reduce the secondary repulsive interaction by the longer distance, and the extended aromatic system will increase the stacking interaction with the neighboring bases. We carried out the molecular modeling simulations using MacroModel in Maestro (Schrödinger). In this simulation, we used DNA duplex containing a T–T mismatch as a host structure in which one of thymine base is flipped out. The simulated complex structure and the **PQA**–thymine pair in the complex are shown in Figure 1c and d, respectively. The distance between hydrogens of pyrrole N–H and thymine N3–H was 2.69 Å (Fig. 1d) and is longer than that in

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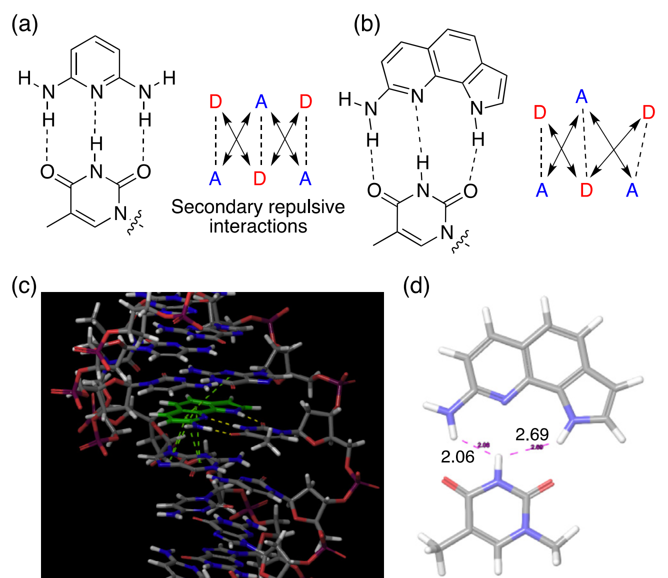
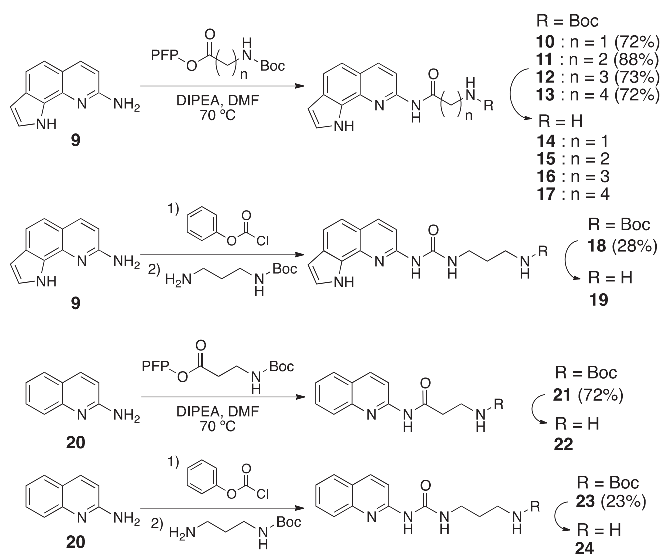


Figure 1. Molecular design of a new ligand targeting thymine. (a) Hydrogen bonding between 2,6-diaminopyridine and thymine. Hydrogen bond donor and acceptor are represented as D and A, respectively. Secondary repulsive interactions are represented by black arrows. (b) Structure of **PQA** and possible hydrogen bonding motif with thymine. (c) Simulated structure of the complex between **PQA** (green) and DNA duplex containing T–T mismatch. The simulated structure shows that **PQA** interacts with thymine and neighboring guanines. The hydrogen-bondings and stacking interaction are represented by yellow and green dashed line, respectively. (d) Energy-minimized structure of **PQA**–thymine. The distances (Å) between two positively polarized donor hydrogens are shown.

2,6-diaminopyridine–thymine pair (2.34 Å, Fig. 1a). Tricyclic system of **PQA** was well stacked with neighboring G–C base pair in this binding pocket (Fig. 1c).

We adopted Leimgruber–Batcho indole synthesis for construction of a key 1*H*-pyrrolo[3,2-*h*]quinoline structure (Scheme 1).[29] Starting from commercially available 7-methylquinoline **1**, corresponding N-oxide **2** was obtained by oxidation of **1** with 3-chloroperbenzoic acid. Chlorination of **2** with phosphoryl chloride provided chloroquinoline **3**. **3** was nitrated with nitric acid at 8 position to give **4**. Buchwald–Hartwig cross coupling of **4** with methylcarbamate followed by hydrolysis of the carbamate with lithium hydroxide gave aminoquinoline **6**. **6** was reacted with *N*,*N*-dimethylformamide dimethyl acetal to give a precursor of Leimgruber–Batcho indole synthesis **7**. The cyclization of **7** followed by deprotection with hydrogen chloride to give **9** (**PQA**). In order to enhance interaction of the **PQA** ligands with anionic DNA and solubility in water, cationic alkylamino linker was attached on amino group of **PQA** at position 8 (Scheme 2). **PQA** derivatives **14**–**17** have an alkylamino liker via amide linkage with different number of intervening methylenes, while an alkylamino linker was introduced via carbamide linkage in **19**. In order to investigate the effect of pyrrole ring in **PQA**, control compounds **22** and **24** having a quinoline instead of **PQA** were synthesized.



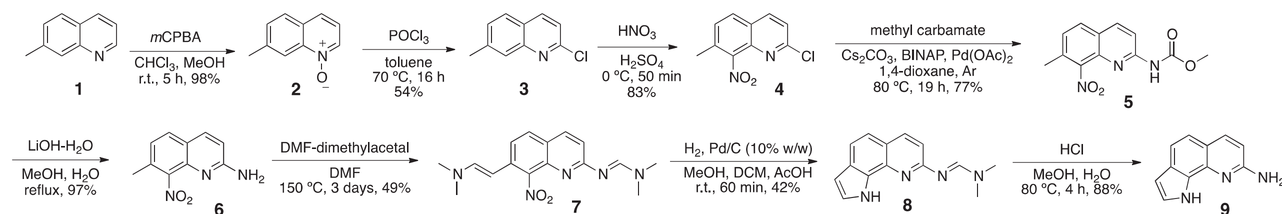
Scheme 2. Synthesis of **PQA** derivatives with alkylamino linker.

Binding ability of synthetic ligands to thymine bulge was investigated by measuring a melting temperature (T_m) of DNA duplex containing a thymine bulge (5′-d(A GGT CTC GTT G)-3′/3′-d(T CCA G_G CAA C)-5′). The effects of ligands were calculated by the difference of the T_m (ΔT_m) in the absence and presence of each ligand (Table 1). The increase of T_m was observed for all **PQA** derivatives **14**–**19** and indicated the stabilization of DNA duplex by the binding of the ligands. Especially, ligand **15** and **19** provided the highest ΔT_m of +4.7 °C and +5.2 °C among the tested ligands (Table 1). The simulation studies indicated that the linker in the ligand **14** is too short to interact with the neighboring bases and phosphate groups. On the other hand, terminal amino group in ligands **15**–**17** can reach to the neighboring bases and phosphate groups, indicating the linkers could contribute to the stabilization of the ligand binding. The high ΔT_m for ligand **15** may be explained

Table 1
ΔT_m (°C) values for DNA duplex containing a T-bulge in the presence of ligands[a]

DNA	Ligand	$T_{m(-)}$[b]	$T_{m(+)}$[c]	ΔT_m
dT bulge	**14**	$30.3_{(0.6)}$	$33.2_{(0.7)}$	$2.9_{(0.7)}$
	15	$30.3_{(0.6)}$	$35.0_{(0.9)}$	$4.7_{(0.9)}$
	16	$30.3_{(0.6)}$	$33.9_{(0.5)}$	$3.6_{(0.5)}$
	17	$30.3_{(0.6)}$	$32.9_{(0.9)}$	$2.6_{(0.9)}$
	19	$30.3_{(0.6)}$	$35.5_{(0.3)}$	$5.2_{(0.3)}$
	22	$30.3_{(0.6)}$	$30.6_{(0.8)}$	$0.3_{(0.8)}$
	24	$30.3_{(0.6)}$	$31.6_{(0.7)}$	$1.3_{(0.7)}$

[a] T_m values of duplexes (5′-d(A GGT CTC GTT G)-3′/3′-d(T CCA G_G CAA C)-5′) (5.0 μM) in buffer (pH 7.0) containing 100 mM NaCl. All measurements were taken three times, and standard deviations are shown in parentheses.
[b] T_m values of duplex.
[c] T_m values in the presence of ligand (50 μM).



Scheme 1. Synthesis of **PQA**.

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