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Facile syntheses of disubstituted bis(vinylquinolinium)benzene derivatives as G-quadruplex DNA binders

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ABSTRACT

A series of disubstituted bis(vinylquinolinium)benzene derivatives were designed, which were prepared through a facile three-component one-pot reaction in good yield. FRET results showed that 1,3-disubstituted benzene derivatives had much stronger stabilization effect on G-quadruplex DNA than that of 1,4-disubstituted benzene derivatives. The introduction of substituted amine side chain at quinolinium obviously increased the binding affinity of compounds to G-quadruplex DNA. It was also found that 1,3-disubstituted benzene derivatives and 1,4-disubstituted benzene derivatives had different effects on the conformation of G-quadruplex DNA by CD spectroscopy analysis. The differences for the interactions of these two classes of compounds with G-quadruplex were further studied and elaborated through molecular modeling experiments.

1. Introduction

Guanine-rich sequences can self-associate into planar guanine quartets (G-quartets) that stack on each other to form unusual structures called G-quadruplexes.[1] Studies revealed the prevalence of G-quadruplex-forming sequences in promoter regions,[2] such as *c-myc*,[3] *c-kit*,[2d,4] and *k-ras*,[5] as well as in the telomeric chromosomal terminals.[6] The formation or stabilization of G-quadruplexes in these regions may play important role in the regulation of gene expression and the maintenance of telomere length. For example, formation of quadruplex structures at the promoter regions can regulate gene expression at the transcriptional level.[7] Formation of a quadruplex at the telomeric end can stop the function of the telomerase enzyme.[8] Small molecules that can selectively induce G-quadruplex formation or stabilization are therefore promising lead compounds for cancer treatment.[7,9]

Up to now, several classes of G-quadruplex ligands have been developed. Most of them share a common planar aromatic core, interacting with the terminal G-tetrad via π–π stacking. One notable class of potent G-quadruplex ligands is bisquinolinium derivatives, such as **360A** (Fig. 1) with a amide linkage between quinolinium moiety and pyridine ring, and the positive charge on quinolinium might be interacted with phosphate groups of the DNA backbone.[10] Czerwinska et al. have reported that 1,4-bis-(vinylquinolinium) benzene (Fig. 1) with a vinyl linkage between quinolinium moiety and benzene ring as a G-quadruplex binder, can be controlled to recognize parallel and anti-parallel G-quadruplex DNA by switching light.[11] In the year of 2010, our group has also reported a series of bisaryldiketene derivatives **M1**–**M4** with a vinyl linkage (Fig. 1) as effective *c-myc* G-quadruplex DNA binders with high selectivity for G-quadruplex over duplex DNA.[12] In addition, Müller et al. have reported a series of pyridostatin analogues as telomeric G-quadruplex DNA ligands and demonstrated that introduction of amine side chain would increase the stabilizing ability and selectivity of compounds to G-quadruplex.[13]

Based on the ligands mentioned above, we known that the introduction of amine side chain would increase the affinities of ligands for G-quadruplex DNA and improve their selectivity for G-quadruplex because the amine side chain may dock onto the groove of G-quadruplex DNA and interact with the G-quadruplex DNA by forming intermolecular hydrogen bond or electrostatic interaction. On the other hand, the quinolium scaffold would also interact with G-quartet plane by π–π stacking or with the phosphate backbone via electrostatic interaction. Considering that those bisquinolinium derivatives mentioned above were all bisquinolinium derivatives with a central aromatic core and the bisaryldiketene derivatives reported by our group were ones with a central alicyclic ketone. So

Abbreviations: CD, circular dichroism; FRET, fluorescence resonance energy transfer; PPA, polyphosphoric acid; S_NAr, nucleophilic aromatic substitution reaction.

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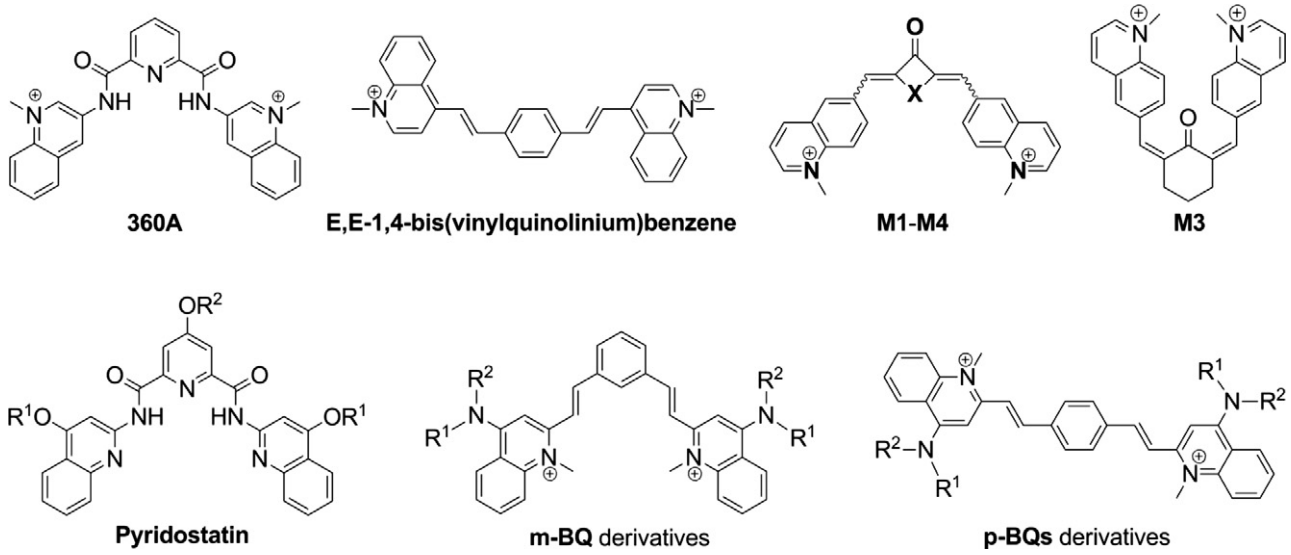


Fig. 1. Structures of the previously reported bisquinolinium G-quadruplex ligands (**360A**, *E*,*E*-1,4-bis-(vinylquinolinium)benzene, **M1**−**M4**, and *pyridostatin* derivatives) and designed target compounds (**m-BQ** and **p-BQ** derivatives).

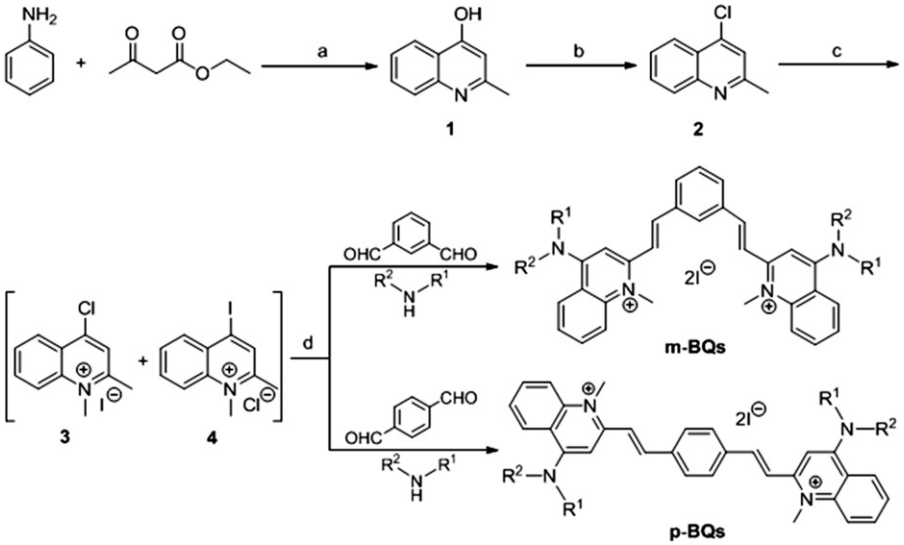
we plan to modify the bisaryldiketene derivatives **M1**−**M4** by changing the central part with an aromatic benzene core. To the best of our knowledge, bisquinolinium derivatives with amine side chain at C-4 position of the quinolinium ring have not been synthesized and characterized as G-quadruplex binders so far. Herein, we designed a series of disubstituted bis(vinylquinolinium)benzene derivatives, which were prepared through a facile three-component one-pot reaction. As shown in Scheme 1, we successfully prepared the target compounds by combining a nucleophilic aromatic substitution reaction (S_NAr reaction) with a Knoevenagel reaction together in one-pot. By using this method, we introduced two quinolinium cores and two amine side chains to the target molecules through one-step reaction. In order to explore the effect of molecular shape on stabilization and conformation of G-quadruplex DNA, we prepared not only a series of 1,3-disubstituted benzene bisquinolinium derivatives (**m-BQ** derivatives) but also a series of 1,4-disubstituted benzene bisquinolinium derivatives (**p-BQ** derivatives). And their interactions with G-quadruplex DNA were investigated by using FRET-melting, FID assay, CD spectroscopy, and molecular modeling study.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, in order to prepare **m-BQ** and **p-BQ** derivatives, we must firstly obtain the intermediate **3**. 2-Methyl-4-hydroxylquinoline (**1**) was prepared by condensation reaction of starting material aniline with ethyl acetoacetate catalyzed by polyphosphoric acid (PPA) at 130 °C in 77% yield. Then compound **1** was treated with phosphorylchloride at 120 °C for 2 h to give 4-chloro-2-methylquinoline (**2**) in 65% yield. Finally, 4-chloro-2-methylquinoline was methylated using methyl iodide to give a mixture of 1,2-dimethyl-4-chloroquinolinium iodide (**3**) and 1,2-dimethyl-4-iodoquinolinium chloride (**4**) with a total yield of 90%. It was found that the ratio of two compounds was 2:1 according to ^{1}H NMR and MS analysis. Considering that this mixture has no effect on next step reaction, the mixture was used directly without further purification.

For the synthesis of target compounds, a model reaction was chosen to optimize reaction condition using 1,3-benzenedicarboxyaldehyde, intermediates **3** and **4**, and pyrrolidine as starting



Scheme 1. Synthetic routes for bisquinolinium derivatives (**m-BQ** and **p-BQ** derivatives): (a) PPA, 130 °C; (b) $POCl_3$, 120 °C; (c) CH_3I, sulfolane, 80 °C; (d) solvents, reflux.