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Design of a fused triazolyl 2-quinolinone unnatural nucleoside via tandem CuAAC-Ullmann coupling reaction and study of photophysical property

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Dedicated to Professor Isao Saito (Emeritus Prof. of Nihon University and Kyoto University) on his 77th Birth day.

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ABSTRACT

This report presents the design and synthesis of a novel fused triazolyl 2-quinolinone (**FTQuon**) nucleoside as a new generation of angularly widened unnatural nucleobase surrogate with two possible H-bonding faces-one H-bond acceptor and another donor. The synthesis via a tandem CuAAC-Ullmann coupling, the study of photophysical properties and theoretical calculation in the context of DNA are the main contents of this report. The newly designed nucleoside shows interesting photphysical property with slight blue shifted solvatochromicity. It also shows pH sensitive emission. All the theoretical DNA duplexes containing the **FTQuon** show right–handed B-form helicity as revealed from a molecular dynamics simulation using Schrodinger Macromodel. A theoretical (DFT) study indicates a good stabilizing property of **FTQuon** via pairing with natural pyrimidine bases. It also shows good interaction property with BSA protein signalled via a switch on fluorescence response.

1. Introduction

The Nature's power of delegation for encoding the complex information necessary for life is given to DNA orchestrated only by H-bonded two base pairs.[1a] However, the motivation toward enhancement of functional ability has spurred the research to expand the genetic alphabets via the design of unnatural nucleobases by mimicking the natural H-bonded base pairing.[1] The pioneering work by Professor Alex Rich and later on by Prof. Steven A. Benner have led to expand the genetic alphabet from four to six letters featuring orthogonal H-bonding complementarity.[1] Since then an increasing amount of research works has resulted in the acceleration of progress towards expanding the genetic alphabets via the design and synthesis of unnatural H-bonded base pairs.[2,3]

The creation of non-H-bonded unnatural nucleobase surrogates by Kool et al., has opened a new dimension in the design of hydrophobic DNA base analogues.[4a–c] Since then, much efforts have been put forth to develop non-natural, stable, hydrophobic nucleosides.[4d–j] Many of such hydrophobic base pairs are found to be recognized by polymerase enzymes creating an increased numbers of genetic alphabets. In recent time, the development of size expanded DNA bases as well as widened base pairs has impacted greatly in the field of design of hydrophobic as well as H-bonded nucleosides.[5] Furthermore, the lack of practical fluorescence property of the natural nucleobases and harnessing for the nucleic acid based diagnostics and sensing materials, have greatly drawn interest, in recent time, toward the design of unnatural DNA base pairs with tuned photophysical properties.[6a–c] Toward this end, several unnatural nucleosides have appeared in the literature for the development of functional nucleic acids.[6d–f]

Therefore, the attractive forces like H-bonding, aromatic stacking, hydrophobic or CH-π interactions have well been explored in the context of design of isomorphic or other unnatural DNA bases.[1–5] In general, in the design of isomorphic DNA bases, the structural modification of purine in the five-membered ring is considered mostly. Several studies have reflected that such modifications, especially for 2′-deoxyisoguanosine, are tolerated as long

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as the Watson-Crick face of the nucleoside is not perturbed.[7] As for an example, 8-azaguanine d(**8aza**)**G** is capable of forming three hydrogen bonds with cytosine, similar to natural G-C pair.[8] Studies also show that the replacement of **G** by d(**8aza**)**G** does not alter the thermal stability and the helicity of a DNA duplex.[7d] In this context several other analogues have been reported utilizing glycosylation strategy and their photophysical and biophysical properties in the context of DNA have been evaluated.[7d]

1.1. The design concept

However, till the date, in the design of isomorphic purines, the concept of size expansion or widening the shape in a similar fashion as has been shown by Kool et al., were not considered.[5b,c,9,10] This might provide several advantages of more effective π-stacking or arresting the inherent tautomerisation.[1a,9,10] However, in such a design, one has to sacrifice one H-bond stabilization energy. Even though, replacing one H-bond by hydrophobic benzene would be beneficial as non-H-bonding/hydrophobic/π-π stacking forces (4–15 kcal/mol/base pair) are stronger than H-bonding force (2–3 kcal/mol/base pair). Furthermore, unnatural bases with the above ability and novel chemical functionalities expectedly would expand the functional potential of DNA. As a part of our ongoing research effort toward generation of molecules with tuned photophysical properties via click reaction and the recent development of click chemistry derived triazolyl-/tetrazolyl-nucleosides containing donor/acceptor aromatics (**P**, Fig. 1)[11a] and widened aryl fused hydrophobic triazolyl nucleosides (**Q**, Fig. 1),[11b] we thought that it would be worthwhile to synthesize aryl fused triazolyl-*N*-nucleoside with H-bonding ability and widened shape with strong stacking ability. This design would expectedly produce modulated photophysical response into the unnatural nucleosides (UNNs) and render strong π-stacking interaction inside a DNA duplex if incorporated. With this view we wanted to report the design and synthesis of a fused triazolyl 2-quinolinone (**1**, **FTQuon**, Fig. 1) nucleoside with two H-bonding faces-one H-bond acceptor and another donor via click chemistry and study the photophysical properties. We also wanted to study the property inside a DNA duplex theoretically.

The logic behind our choice of triazole fused H-bonded nucleobase was: (a) the nucleoside would be the widened version of isomorphic base analogue of 8-azaguanosine with ability to form two H-bonds; (b) the vertically (60°) widened (by 2.4 A) fused benzene expectedly would provide more stacking interaction with possibly widening the groove size; (c) it could form H-bonding pair with d**T**/d**U** or d**C** as well as render good stacking stabilization of DNA if incorporated; (d) the presence of the tautomeric >**CO**–**NH** would possibly offer interesting photophysical property such as pH and/or microenvironment sensitive fluorescence emission and interaction ability with biomolecule.

Recently, we reported the bi-conically expanded fused triazolylphenanthrene nucleoside (**Q**, **FTPhen**, Fig. 1) with no H-bonding faces.[11b] Now, we wanted to report a similar analogue having H-banding faces which could be treated as conically widen version of d(**8aza**)**G** with a concept earlier shown in the design of dy**A** and dy**G** by Kool's group.[5b,c,9a] The design concept is explained in Fig. 1. The expansion is only possible via deletion of one H-bonding face *i.e.* by replacing the amine group of d**G** or d(**8aza**)**G** with a hydrophobic benzene moiety. In doing so, the 2-H-bonding and hydrophobic/stacking interaction from additional phenyl ring would allow the base to pair with natural d**T**/d**U**/d**C** either in a monomeric state or in a DNA if incorporated. This molecular design would lead the vertical dimension of the base 2.4 Å wider than the d**G** or d(**8aza**)G conically.[5b,c,9a] Thus, the base would be an widened version of 8-azaguanosine with two H-bonding faces.[7d,8]

1.2. The synthesis

Before going to synthesize, we drew a retrosynthetic path which suggested that click chemistry between β-azido-deoxyriboside **3** and *N*-benzyl-*N*-(2-iodo-4-methylphenyl)propiolamide **4** followed by an intramolecular C–C coupling are the two key steps to achieve our target nucleoside **FTQuon** (**1**). Thus, the β-azido-deoxyriboside in bis-toluoyl protected form **5** was synthesized following our

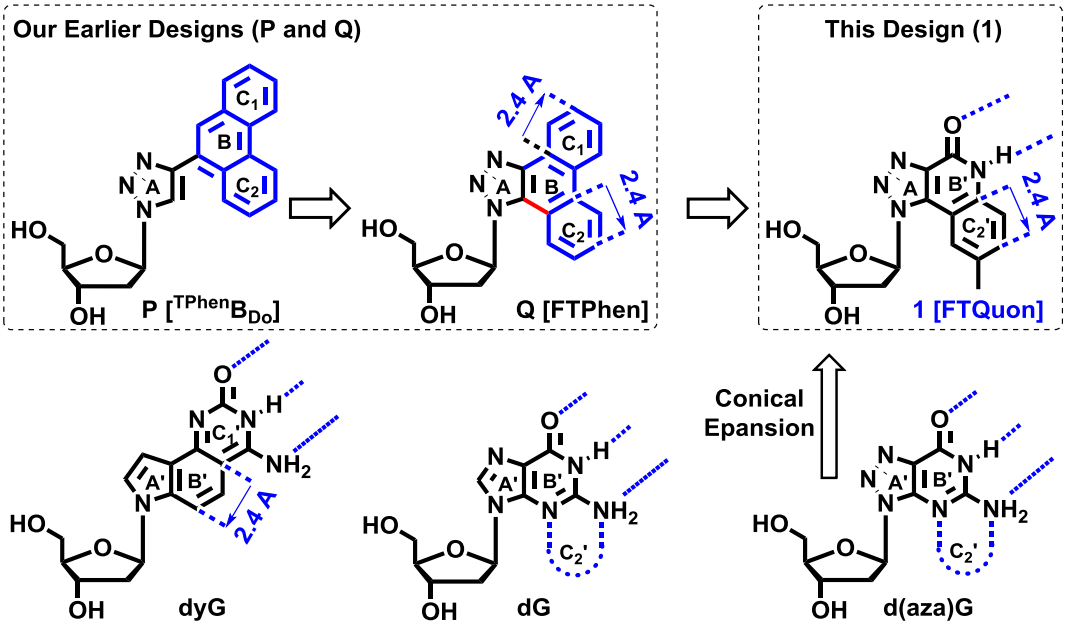

Fig. 1. The design concept. Chemical structures of our earlier reported bases (**P** and **Q**), present design (**1**), Kool's dy**G**, natural d**G** and d(**aza**)**G**.