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# Synthesis and photophysical properties of 8-arylbutadienyl 2'-deoxyguanosines

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#### ABSTRACT

We have developed novel push-pull-type 8-arylbutadienyl 2'-deoxyguanosine derivatives,  ${}^{AB}G$  (1a) and  ${}^{CB}G$  (1b). These nucleosides exhibit strong solvent polarity dependent fluorescence emission at long wavelength (ca. 490–550 nm). These environmentally sensitive fluorescent deoxyguanosines are powerful tools for structural studies of nucleic acids and also in molecular diagnostics.

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Currently, fluorescence nucleosides are widely implemented as reporter molecules for molecular recognition in diverse fields, such as chemistry, biology, biotechnology and medicinal chemistry.<sup>1</sup> Among these nucleosides, fluorescent guanosines are of greatest importance owing to their unique supramolecular properties of forming a variety of self-assembled structures and tetrameric complexes of high biological interests.<sup>2</sup> The design of environmentally sensitive fluorescent guanosines is, therefore, of utmost importance, since they can function not only as fluorescent DNA probes and fluorescence sensors, but also as fluorescent building blocks in supramolecular chemistry.

Recently, we have reported push-pull-type fluorescent guanosines, <sup>Ac</sup>G and <sup>CN</sup>G, which contain a covalently linked electron donor-acceptor system consisting of guanosine as the electron donor and pyrene fluorophore as the acceptor (Fig. 1).<sup>3</sup> Although these guanosine derivatives exhibited interesting solvatofluorochromic properties, the steric bulkiness of the C8-substituents in both <sup>Ac</sup>G and <sup>CN</sup>G causes considerable destabilization of the DNA duplex structure, and thus, they may not be applicable to the general use as fluorescent DNA probes. A great demand accordingly remains for further development of more simple, low-cost solvatochromic fluorescence guanosine analogues, which can be synthesized more easily. Therefore, we have designed simple guanosine derivatives, which contain a phenyl group  $\pi$ -conjugated with a butadiene linker at C8 position of guanosine. In addition to the novel structure of these butadienyl nucleosides, to the best of our knowledge, no report exists regarding the synthesis of a fluorescent nucleoside containing butadiene linker. In constructing such push-pull-type nucleosides, various substituents were introduced into the arylbutadienyl guanosine derivatives and their photophysical properties were examined. We herein report the first synthesis of novel 8-arylbutadienyl 2'-deoxyguanosines, ABG (1a) and <sup>CB</sup>G (1b) and their photophysical properties in solvents of different polarity.

The synthetic route of arylbutadienyl guanosines, <sup>AB</sup>G (1a) and <sup>CB</sup>G (1b) is outlined in Scheme 1. *E*- $\beta$ -bromostyrene derivatives, **4a–b**, which contain an electron-withdrawing substituent in the *para*-position of phenyl ring, were prepared from the corresponding styrene derivatives.<sup>4</sup> These bromostyrene analogues were coupled with 8-vinyl guanosine derivative **3**<sup>5</sup> via Pd(0)-mediated Heck reaction to afford **6a–b**.<sup>6</sup> After deprotection of the DMF acetal group with 28% aq NH<sub>4</sub>OH–methanol, two arylbutadienyl guanosine derivatives **1a–b** containing electron-withdrawing substituents were obtained.<sup>7</sup>

Because of the low reactivity of bromostyrene derivatives with electron-donating substituents, corresponding *E*- $\beta$ -iodostyrene derivatives **5a–b** were used for the Pd-mediated cross-coupling reactions.  $\beta$ -lodostyrene derivatives, **5a** and **5b**, which were prepared from the corresponding cinnamic acids,<sup>8</sup> were coupled with 8-vinylguanosione **3** using Pd(PPh<sub>3</sub>)<sub>4</sub> to afford **7a** and **7b**, respectively. Deprotection of **7a–b** with 28% aq NH<sub>4</sub>OH–methanol afforded arylbutadienyl guanosine derivatives **MBG** (**2a**) and **DABG** (**2b**).

The photophysical properties of newly synthesized guanosine derivatives **1a-b** and **2a-b** were examined. Initially, we measured the fluorescence spectra of arylbutadienyl guanosines containing electron-withdrawing substituents in various solvents of different polarity. As shown in Figure 2, arylbutadienyl derivatives <sup>AB</sup>G (1a) having longer conjugated system than 8-aryl or 8-arylethynyl guanosines emitted strong fluorescence at a longer wavelength. With excitation of <sup>AB</sup>G (1a) in 1,4-dioxane, strong fluorescence emission at 494 nm was observed. Upon excitation of <sup>AB</sup>G (1a) in ethyl acetate and acetonitrile, medium fluorescence emission was observed at 510 and at 547 nm. In contrast, very weak fluorescence emission was observed for ABG (1a) in polar solvents, such as ethanol (558 nm) and methanol (554 nm). Thus, ABG (1a) showed a considerably large solvatofluorochromicity ( $\Delta \lambda$  = 60 nm). A similar solvatofluorochromicity was observed with <sup>CB</sup>G (1b) ( $\Delta\lambda$  = 40 nm) (Table 1). These results indicated that push-pull-type arylbutadienyl guanosines, such as <sup>AB</sup>G (1a) and <sup>CB</sup>G (1b) exhibited a remarkable solvatofluorochromic property, as is evident from the fluorescence colour image shown in Figure 2c.



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Figure 1. Structure of 8-arylbutadienyl guanosine derivatives.



Scheme 1. Reagents and conditions: (a) 4 or 5, Pd(PPh<sub>3</sub>)<sub>4</sub>, CH<sub>3</sub>COONa, DMF, 100 °C, 8 h; (b) aq NH<sub>4</sub>OH, MeOH, 50 °C, 5 h.

 Table 1

 Photophysical properties of fluorescent guanosine derivatives

Compound	Solvent	$\lambda_{\max}^{abs}$ (nm)	$\epsilon (M^{-1} cm^{-1})$	$\lambda_{\max}^{\mathrm{fl}}$ (nm)	$\phi^{c}$	Brightness <sup>d</sup> ( $\varepsilon \times \phi$ )
<sup>AB</sup> G (1a)	1,4-Dioxane	399	25,500	494	0.59	15,200
	CH <sub>3</sub> CN	392	21,000	547	0.57	12,000
	MeOH	388	38,300	554	0.015	589
<sup>св</sup> G (1b)	1,4-Dioxane	395	18,600	486	0.75	14,000
	CH <sub>3</sub> CN	387	18,900	526	0.47	9040
	MeOH	381	24,900	522	0.32	8070
<sup>MB</sup> G (2a)	1,4-Dioxane	354	21,400	429	0.71	15,200
	CH <sub>3</sub> CN	352	21,300	441	0.68	14,500
	MeOH	342	23,200	438	0.56	13,200
DABG (2b)	1,4-Dioxane	352	14,200	429	0.70	9980
	CH <sub>3</sub> CN	349	13,800	443	0.75	10,400
	MeOH	343	14,700	438	0.58	8590

 $^a\,$  Absorption spectra were measured at 25 °C using 1 cm path length cell (10  $\mu M$  ). See Figures S1–S4.

<sup>b</sup> Fluorescence spectra were measured at 25 °C using 1 cm path length cell (10 μM). See Figures 2 and 3 and S1–S2.

<sup>c</sup> The fluorescence quantum yields ( $\phi$ ) were calculated by using 9,10-diphenylanthracene as a reference according to Ref. 9.

<sup>d</sup> Brightness factors were calculated by  $\varepsilon \times \phi$ .

The photophysical properties of arylbutadienyl derivatives with electron-donating substituents were also investigated. As shown in Figure 3, fluorescence quantum yields of  $^{MB}G$  (2a) and  $^{DAB}G$  (2b) are larger than those of  $^{AB}G$  (1a) and  $^{CB}G$  (1b). However, the redshift of fluorescence emission when solvent polarities were increased was not large as that observed in the electron withdrawing

arylbutadienyl substituted group. These results clearly indicate that only push-pull-type arylbutadienyl derivatives exhibit highly solvatofluorochromic properties as we expected.

We also examined the photoisomerization of these butadienyl guanosines in each solvent. Although 8-phenylbutadienyl guanosine having no substituent in the phenyl ring was gradually



Figure 2. Fluorescence spectra of (a) ABG (1a, 10 µM) and (b) CBG (1b, 10 µM) in various solvents, (c) fluorescence colours of ABG (1a) in different solvents. The sample solutions were illuminated with a 365 nm transiluminator.



Figure 3. Fluorescence spectra of (a) <sup>MB</sup>G (2a, 10 µM) and (b) <sup>DAB</sup>G (2b, 10 µM) in various solvents.

photoisomerized to a mixture of E- and Z-isomers, no appreciable photoisomerization was observed in UV irradiation followed by HPLC analyses in the case of electron withdrawing group- or electron donating group-substituted arylbutadienyl guanosines (Fig. S5-S9).

In summary, we have synthesized novel push-pull-type 8-arylbutadienyl guanosines for the first time. These newly synthesized guanosine derivatives <sup>AB</sup>G (1a) and <sup>CB</sup>G (1b) possessing large brightness factors ( $\varepsilon \times \Phi$ ) exhibited a strong fluorescence dependency on the solvent polarity at longer wavelengths without photoisomerization. Such environmentally sensitive strong fluorescent guanosines can be used as powerful tools for structural studies of nucleic acids and in molecular diagnostics.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.053.

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5.8, 13.0 Hz, 1H), 2.62 (ddd, *J* = 6.4, 9.0, 13.0 Hz, 1H), 3.64–3.75 (complex, 2H),

3.85 (m, 1H), 4.43 (m, 1H), 5.19 (m, 1H), 5.30 (d, *J* = 4.0 Hz, 1H), 6.31 (dd, *J* = 5.8, 9.0 Hz, 1H), 6.53 (br, 2H), 6.93 (d, *J* = 15.0 Hz, 1H), 7.24–7.39 (complex, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 10.70 (br, 1H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz)  $\delta$  24.6, 61.5, 70.5, 74.5, 82.6, 87.4, 109.5, 117.0, 119.0, 122.2, 124.5, 127.0 (2C), 132.3, 132.6 (2C), 141.5, 143.8, 151.7, 153.4, 156.3; HRMS (ESI) *m*/*z* 443.1439 calcd for C<sub>21</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>, found 443.1444.

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