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# A General Method for the Synthesis of the $N^2$- and $N^6$- Carcinogenic Amine Adducts of 2′-Deoxyguanosine and 2′-Deoxyadenosine[1]

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**Abstract:** A number of simple arylamino compounds (Figure 1) are well-established as pro-carcinogenic agents. Metabolic activation leads to a series of unstable N-hydroxy derivatives that on solvolysis, give nitrenium ions. The latter, which are regarded as the primary mutagenic/carcinogenic agents attack DNA to give a variety of adducts. Principal among these are the C-8 arylamination products of 2′-deoxyguanosine (dG) and the $N^2$- and $N^6$-(2-acetylamino)arylation adducts of dG and 2′-deoxyadenosine (dA), respectively. The latter types of adducts have received little biological attention because synthetic methods for their preparation have been lacking. We now describe a general high-yield method for the synthesis of both of these types of *N*-arylated 2′-deoxynucleosides. The key step is a Buchwald−Hartwig coupling reaction between an appropriately protected derivative of dG or dA (**1** and **7**, respectively) and an *o*-nitroaryl bromide or triflate (**2a**−**e**). Subsequent reduction, acetylation, and deprotection of the $N^2$-adducts (**3b**−**e**) of dG and of the $N^6$-adduct (**8c**) of dA then gives the desired adducts **6b**−**e** (overall yield 70−88%) and **11** (overall yield 43%), respectively.

## Introduction

In chemical carcinogenesis, the first critical step in the process of tumor formation is thought[2,3] to be the covalent binding of a mutagenic substance, frequently an electrophile, to specific sites in genomic DNA. Such substances fall into many different classes, but there are broad groups of substances such as polycyclic hydrocarbons, nitrosamines, and a large number of arylamines that have been identified as pro-carcinogens, all having the common requirement of metabolism before mutagenesis can occur. Currently, we are interested in the carcinogenic amines. A correlation between industrial exposure to certain of these substances and bladder cancer was first reported by Rehn[4] in 1895. At the time he believed that the culprit was aniline, but later work[5] showed that other substances including the dyestuff magenta violet were the true mutagens. Since the initial report a large number of aromatic amines both hydrocarbon and heterocyclic have been identified as carcinogenic agents.[6−8] Among these and for historical reasons, the first three compounds noted in Figure 1, have received considerable attention[9−12] and are regarded as prototypes for this class

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(1) Presented in part at the 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21−25, 1999.
(2) Miller, E. C.; Miller, J. A. *Pharmacol. Rev.* **1966**, *18*, 805.
(3) Miller, J. A. *Cancer Res.* **1970**, *30*, 559−576.
(4) Rehn, L. *Arch. Klin. Chir*. **1895**, *50*, 588−600.
(5) Case, R. A. M.; Hosker, M. E.; McDonald. D. B.; Pearson, J. T. *Br. J. Ind. Med*. **1954**, *11*, 75−104.
(6) Singer, B.; Kusmierek, J. T. *Annu. Rev. Biochem*. **1982**, *52*, 655−693.
(7) Hemminki, K. *Arch. Toxicol*. **1983**, *52*, 249−285.
(8) Schut, H. A.; Snyderwine, E. G. *Carcinogenesis* **1999**, *20*, 353−368.
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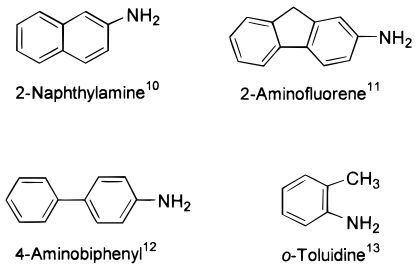
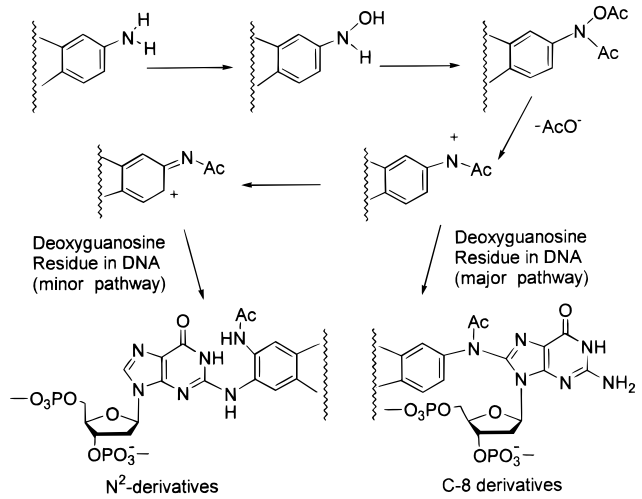



**Figure 1.**

**Scheme 1**




as a whole. More recently *o*-toluidine has been identified[13] as a carcinogen and possibly represents the simplest example of this class of arylamine.

Physiologically, the aromatic amines are metabolized[3,14,15] oxidatively at nitrogen to the corresponding hydroxylamine, principally in the liver by the cytochromes $P_{450}$. In a second step, these products are frequently *O*-sulfonylated or acetylated, again largely by hepatocytes, and the resulting compounds on spontaneous solvolysis generate nitrenium ions. The latter, depending on the structure of the initial amine, may isomerize to carbonium ions. Both of these types of ion damage DNA and the products from dG residues that have been identified are shown in Scheme 1 (only the "*N*-acetyl-*N*-acetoxy" intermediate is illustrated). The dominant type of lesion involves nitrenium ion attack at the C-8 position of a deoxyguanosine residue.[16] Minor adducts arise from carbonium ion attack at the 2- and 6-amino groups of deoxyguanosine (dG) and deoxyadenosine (dA), respectively. In some instances such as in the naphthalene series,[17] the acetyl group may not be present in the final product.

Interestingly the C-8 adducts have been found to be only moderately mutagenic,[18−24] and there is now reason to suspect that the minor N-arylation adducts may be the more important from a biological standpoint. Despite the fact that more than twenty-five years have elapsed since the first report[16] of the finding of an exocyclic amine adduct in the DNA of animals treated with 2-aminofluorene, with the exception of a paper by Shibutani et al.,[25] virtually no biological work on this type of lesion has been reported. This appears largely to be due to the fact that the quantities formed in DNA are small and that total synthesis of these nucleoside adducts has proved difficult.

## Synthetic Background

In keeping with our continuing studies on the mutagenic behavior of damaged bases in DNA, we have for some time been interested in methods that allow the synthesis of these modified 2′-deoxynucleosides, in quantity. The availability of such bases usually allows their incorporation into oligomeric DNA by standard automated protocols. Recently, for the reasons noted above, our synthetic interests have been focused on the carcinogenic amine adducts of the exocyclic amino groups of dG and dA.

Methods for the synthesis of $N^2$-alkyl substituted derivatives of the dG are well-established. Casale and McLaughlin[26] employed an exocyclic adduct of dG, namely, 2′-desmethylwyosine, which they found could be alkylated at the desired nitrogen. This was followed by a degradation sequence that produced the required $N^2$-arylmethyl derivative of dG, but the method is not applicable to haloaryl derivatives directly. In very elegant work, Harris and his associates[27] have shown that 2-fluoropurine derivatives related to dG will react with aliphatic amines to give the expected *N*-alkyl derivatives. In related work Steinbrecher et al.[28] have used 2-trifluoromethylsulfonyl derivatives of purines. These react easily with aliphatic amines and, in contrast to the 2-fluoro derivatives, also with aromatic amines, although much more slowly. By this method the adducts of 1,2-phenylene diamine and 3-acetylamino-4-aminobiphenyl were obtained. Nonetheless in our hands neither the synthesis of the triflate, which is lengthy, nor the amine substitution reaction, proved to be reliable on a larger (10 times) scale. In our own work[29] we were able for the first time to synthesize the $N^2$-(2-acetylaminofluoren-3-yl) derivative of dG starting with a direct arylation of the bis-TBDMS derivative of dG by 3-bromo-2-nitrofluorenone. Although the method gives good overall yields,

(11) Grunberger, D.; Weinstein, B. In *Chemical Carcinogens and DNA*; Grover, P. L., Ed.; CRC Press: Boca Raton, FL, 1979; Vol. 2, pp 60−93.
(12) (a) Kriek, E. *Chem.-Biol. Interact.* **1971**, *3*, 19−28. (b) Kriek E. In *Proc. 11th Int. Cancer Congress*; Buccalossi, P., Veronesi, U., Cascenelli, N., Eds.; Excerpta Medica: Amsterdam, 1975; Vol. 2, pp 36−40.
(13) (a) Hecht, S. S.; El-Bayoumy, K.; Rivenson, A.; Fiala, E. *Cancer Lett.* **1982**, *16*, 103−108. (b) Sellers, C.; Markowitz, S. *Regul. Toxicol. Pharmacol*. **1992**, *16*, 301−317.
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(16) Kriek, E. *Cancer Res.* **1972**, *32*, 2042−2048.
(17) Kadlubar, F. F.; Unruch, L. E.; Beland, F. A., Straub, K. M.; Evans, F. E. *Carcinogenesis* **1980**, *1*, 139−150.
(18) Mitchell, N.; Stohrer, G. *J. Mol. Biol.* **1986**, *191*, 177−180.
(19) Michaels, M. L.; Johnson, D. L.; Reid, T. M.; King, C. M.; Romano, L. J. *J. Biol. Chem*. **1987**, *262*, 14648−14654.
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(21) Gupta, P. K.; Johnson, D. L.; Reid, T. M.; Lee, M. S.; Romano, L. J. King, C. M. *Proc. Am. Assoc. Cancer Res.* **1987**, *28*, 104.
(22) Moriya, M.; Takeshita, M.; Johnson, F.; Peden, K.; Will, S.; Grollman, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 1586−1589.
(23) Burnouf, D.; Koehl, P.; Fuchs, R. P. P. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 4147−4151.
(24) Shibutani, S.; Suzuki, N.; Grollman, A. P. *Biochemistry* **1998**, *37*, 12034−12041.
(25) Shibutani, S.; Gentles, R.; Johnson, F.; Grollman, A. P. *Carcinogenesis* **1991**, 813−818.
(26) Casale, R.; McLaughlin, L. W. *J. Am. Chem. Soc.* **1990**, *112*, 5264−5271.
(27) (a) Harris, C. M.; Zhou, L.; Strand, E. A.; Harris, T. M. *J. Am. Chem. Soc.* **1991**, *113*, 4328−4329. (b) De Corte, B. L.; Tsarouhtsis, D.; Kuchimanchi, S.; Cooper, M. D.; Horton, P.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol.* **1996**, *9*, 630−637.
(28) (a) Steinbrecher, T.; Wameling, C.; Oesch, F.; Seidel, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 404−406. (b) Edwards, C.; Boche, G.; Steinbrecher, T.; Scheer, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1887−1893.
(29) Bonala, R. R.; Yu, P.-L.; Johnson, F. *Tetrahedron Lett.* **1999**, *40*, 597−598.

it proved to be compound-specific. No other halo-nitroaryl compound, with the exception of 2,4-dinitrofluorobenzene could be made to react under conditions that retained the deoxyribosyl moiety of the nucleoside.

The situation with regard to the synthesis of the $N^6$-aryl derivatives of dA is even less favorable. Although appropriate halopurine derivatives, including the fluoro analogue, will react directly with aliphatic amines and the postsynthetic introduction of an aralkylamine via a fluoropurine nucleoside has been recorded,[30] no direct substitution by an aromatic amine has been reported. In our hands, no conditions could be found for such substitutions that did not simultaneously depurinate the nucleoside. We also explored several other synthetic approaches to the dG adducts including a Smiles rearrangement of $N^2$-(*o*-nitroaryloxyacetyl) derivatives of dG[31] and the cupric-ion-catalyzed coupling of an aryboronic acid with O-protected derivatives of dG (a variant[32] of the Suzuki reaction). Although these methods led to the desired coupled products, the yields in both approaches were unacceptably low.

We now present a general method which remarkably allows the synthesis of both the $N^2$- and the $N^6$-(*o*-aminoaryl) derivatives of dG and dA, respectively, in excellent overall yield and which is easily reproducible on a large scale.

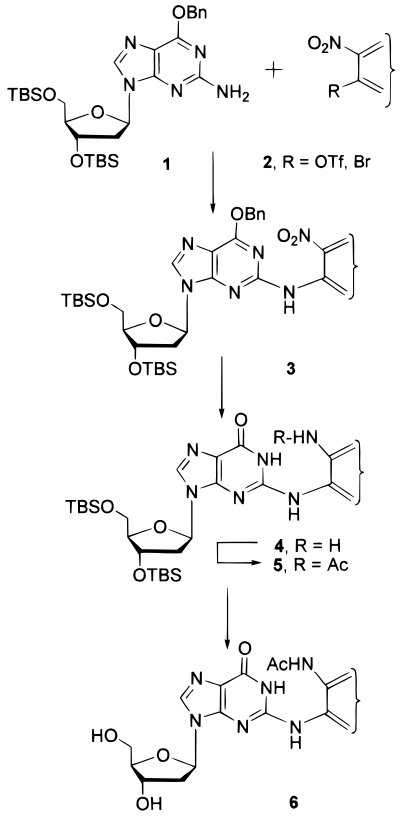
## Results and Discussion

The key step of the successful synthetic strategy involves a Buchwald−Hartwig Pd-catalyzed arylation[33] between protected[34] 2′-deoxyguanosine (**1**) or 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine and *o*-nitroaryl triflates or bromides (**2**) in the presence of catalytic amounts of palladium(II) acetate and racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), simultaneously using stoichiometric quantities of the mild base, cesium carbonate.

In the 2′-deoxyguanosine series (Scheme 2) we observed high yields in all the reactions (>86%) for all of the aromatic donors **2** used in the coupling step. No complications were observed, and the products **3** were easily purified by flash chromatography. The conversion of these protected $N^2$-nitroaryl-2′-deoxyguanosines (**3**) to the desired final products **6** required only conventional chemistry. In each case hydrogenation of the coupled products **3**, over a 10% palladium-on-carbon catalyst at 50 psi, both removed the $O^6$ benzyl group and reduced the nitro group to furnish the arylamino derivatives **4** in high yield (TLC analysis). However, because all of these amines proved to be very sensitive to aerial oxidation, they were immediately acetylated, with acetic anhydride in methylene chloride, to give the stable derivatives **5**. The use of hot acetic anhydride in pyridine led to the formation of diacetylated products.

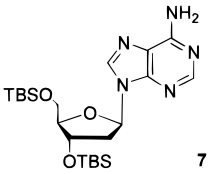
Finally, the *tert*-butyldimethylsilyl (TBS)-protecting groups were then easily removed using a 1 M solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran to yield the desired adducts **6**. The compounds with structure **6** that we have prepared so far, are listed in the Table 1. It should be noted

**Scheme 2**




that the reductive step on the fluorenyl adduct **3e**, derived from the coupling between **1** and 2-nitro-3-bromofluoren-9-one (**2e**), was accompanied also by the deoxygenation of the fluorenone carbonyl group. The product, after acetylation, proved to be identical spectroscopically with the material that we had prepared earlier.[29] However, in this one-step reduction, the yield was low, and we used the previously reported reduction procedures[29] to obtain the 73% yield quoted in Table 1.

Application of this reaction sequence in the 2′-deoxyadenosine series gave equally gratifying results. When the 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**7**)




was treated with an electron-deficient triflate or bromide (**2b**−**e**) essentially under the condition described for the dG series, the coupled products **8b**−**e** (Table 2) were obtained in high yield. However, one difference from the 2′-deoxyguanosine series lies in the stoichiometry. When equivalent amounts of **7** and a triflate or the bromide were used, the reaction was complicated by the formation of some of the $N^6$-disubstituted product. This is illustrated experimentally in the case of the naphthalene derivative **9**

which was formed in 62% yield when 1.4 equiv of the triflate **2c** were employed. Therefore, in the dA series approximately a 40% excess of **7** was used in all of the cases to suppress the formation of the disubstituted products related to **8**, and all quoted yields are based on unrecovered **7**.

Adduct **8c** was selected for conversion to the $N^6$-(2-acetylaminonaphth-1-yl) derivative of dG (Scheme 3). Reduction of

(30) Kim, S. J.; Stone, M. P.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1992**, *114*, 5480−5481.

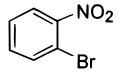
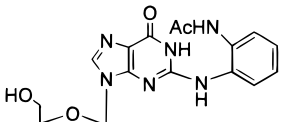
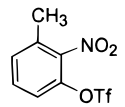
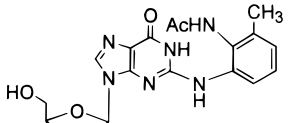
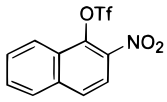
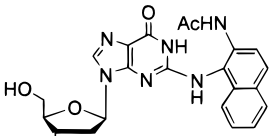
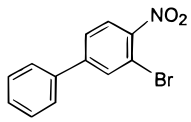
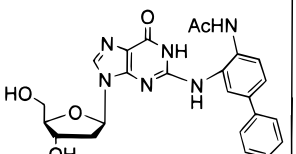
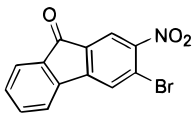
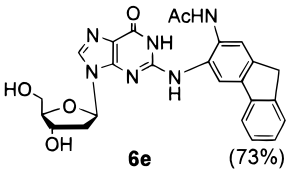
(31) Bonala, R. R.; Nakajima, N.; Ubukata, M.; Johnson, F.; Presented at the 214th National Meeting of the American Chemical Society, Las Vegas, NV, September 7−11, 1997.

(32) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933−2936.

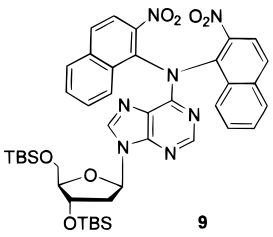
(33) For a recent review of this type of coupling, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (d) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615−2623.

(34) When the bis-TBS derivative of dG (i.e., unprotected at $O^6$) was used in this coupling, virtually none of the expected product was formed.

**Table 1.** Aryl Donors and $N^2$-Arylnucleosides Synthesized

| Aryl donor | $N^2$-aryl nucleosides (yield)[a] |
|---|---|
|  **2a** |  **6a** (87%) |
|  **2b** |  **6b** (84%) |
|  **2c** |  **6c** (70%) |
|  **2d** |  **6d** (85%) |
|  **2e** |  **6e** (73%) |

[a] Overall yields (from **1** to **6**) are referred to isolated, purified products.

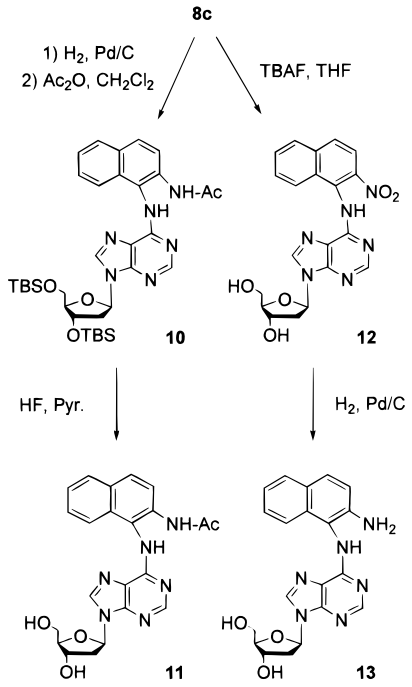



**9**

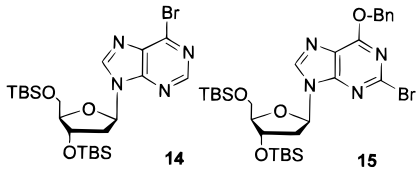
the nitro group with hydrogen over a palladium-on-charcoal catalyst led to the corresponding amine, which was immediately acetylated to give the air-stable intermediate **10**. The latter, on treatment with HF/pyridine, afforded **11**. When **8c** was deprotected by TBAF in tetrahydrofuran and the resulting product **12** then hydrogenated over a palladium catalyst, the free $N^6$-(2-aminonaphth-1-yl)-2′-deoxyadenosine was obtained in excellent overall yield (80%). The $^1$H NMR spectrum of this material showed resonance peaks that were identical to those reported by Kadlubar et al.[17] in 1980, thus finally confirming the structure of this adduct by synthesis.

After this work was complete, Lakshman and his associates[35] in a diametrically opposite strategy, reported that $N^6$-arylated dA derivatives could be obtained by the reaction of **14** with

**Scheme 3**




simple aromatic amines in 52−72% yield. This method also uses a variation of the Buchwald−Hartwig reaction. In a related reaction Harwood et al.[36] have shown that under Buchwald−Hartwig conditions **15** may be coupled to a suitably protected dG derivative at the 2-amino group to give the known coupled dG "dimer" which was then incorporated into DNA by standard methods.




## Conclusions

We have shown that the Buchwald−Hartwig Pd-catalyzed *N*-arylation reaction is broadly applicable in the field of purine nucleosides. The method provides easy access respectively to the previously unavailable $N^2$- and $N^6$-carcinogenic-amine-modified derivatives of 2′-deoxyguanosine and 2′-deoxyadenosine. The application of this method to the arylation of amino groups in other nucleosides should now be possible, and studies along these lines are being pursued. Attempts are also being made to incorporate these aryl derivatives of dG and dA into DNA with the objective of studying their mutagenic potential.

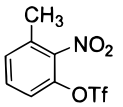
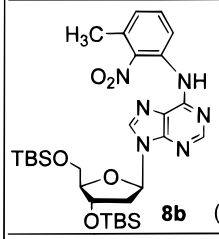
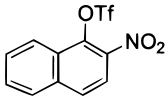
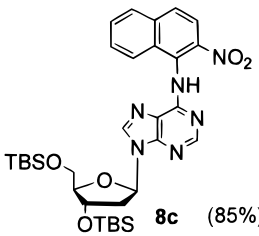
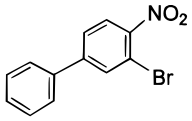
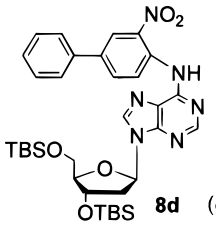
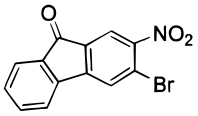
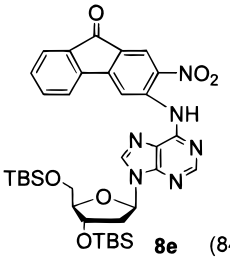
## Experimental Section

**General.** All reagents and solvents were of commercial grade and used as such unless otherwise specified. NMR ($^1$H and $^{13}$C) spectra were recorded on a Bruker AC-250 spectrometer. Samples prepared for NMR analysis were dissolved in $CDCl_3$, $CD_3OD$, DMSO-$d_6$, or $C_5D_5N$. Chemical shifts are reported in ppm relative to TMS in the proton spectra and to the deuterated solvent in the carbon spectra. Mass spectra were recorded on a Micromass Trio 2000 in fast atom bombardment (FAB) mode. High-resolution FAB MS spectra were

(35) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090−6091.

(36) Harwood, E. A.; Sigurdsson, S. Th.; Edfeldt, N. B. F.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 5081−5082.

**Table 2.** Aryl Bromides and Triflates Used and $N^2$-Aryl nucleosides Synthesized

| Aryl donor | $N^6$-aryl nucleosides (yield)[a] |
|---|---|
|  **2b** |  **8b** (88%) |
|  **2c** |  **8c** (85%) |
|  **2d** |  **8d** (85%) |
|  **2e** |  **8e** (84%) |

[a] Yields based on recovered starting material (see Experimental Section).

performed by the Mass Spectrometry Laboratory of the School of Chemical Sciences, University of Illinois at Urbana−Champaign. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, 56−19, 37th Avenue, Woodside, NY. Thin-layer chromatography (TLC) was performed on silica gel sheets (Riedel-deHaën, Sleeze, Germany) containing a fluorescent indicator. Components were visualized by UV light ($\lambda = 254$ nm) or by spraying with a solution of phosphomolybdic acid. Flash column chromatographic separations were carried out on 60 Å (230−400-mesh) silica gel (TSI Chemical Company, Cambridge, MA). All experiments dealing with moisture or air-sensitive compounds were conducted under dry nitrogen. The starting materials and reagents, unless otherwise specified, were the commercially best grade available (Aldrich, Fluka) and were used without further purification. All new products showed a single spot on TLC analysis, after purification.

***N*²-(Nitroaryl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3a−e). General Procedure.** An oven-dried reaction vial was charged with **1** (0.100 g, 0.171 mmol), cesium carbonate (0.078 g, 0.24 mmol, 1.4 equiv), palladium acetate (0.004 g, 0.017 mmol, 0.1 equiv), BINAP (0.016 g, 0.025 mmol, 0.15 equiv), the aryl bromide or triflate (0.22 mmol, 1.3 equiv), and toluene (1 mL). The vial was flushed with argon prior to sealing. The reaction mixture was stirred for 30 min at room temperature, heated at 80 °C for 16 h, and then diluted with ethyl acetate. Centrifugation and concentration in a vacuum of the supernant liquid afforded a residue, which was purified by flash chromatography (silica gel, 10−30% ethyl acetate in hexane) to afford the desired compound.

***N*²-(2-Nitrophenyl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3a):** yellow amorphous solid (0.116 g, 96%); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.07 (6H, s, $CH_3Si$), 0.13 (6H, s, $CH_3Si$), 0.91 (9H, s, $(CH_3)_3C$), 0.93 (9H, s, $(CH_3)_3C$), 2.47 (2H, m, H-2′), 3.81 (2H, m, H-5′), 4.02 (1H, m, H-4′), 4.58 (1H, m, H-3′), 5.63 (2H, s, $CH_2$−Ph), 6.44 (1H, t, $J = 6.6$ Hz, H-1′), 7.00 (1H, t, $J = 7.5$ Hz, $-C_6H_4NO_2$), 7.28−7.51 (5H, m, $CH_2-C_6H_5$), 7.52 (1H, t, $J = 7.5$ Hz, $-C_6H_4NO_2$), 8.10 (1H, s, H-8), 8.24 (1H, d, $J = 7.5$ Hz, $-C_6H_4NO_2$), 8.90 (1H, d, $J = 7.5$ Hz, $-C_6H_4NO_2$), 10.47 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.5 (× 2), −4.8 (× 2), 17.9, 18.3, 25.7 (× 3), 25.9 (× 3), 41.6, 62.8, 68.5, 71.9, 84.0, 87.8, 117.5, 120.2, 120.4, 126.0, 128.0, 128.1 (× 2), 128.4 (× 2), 135.2 (× 2), 136.1, 137.4, 139.1, 152.4, 153.9, 160.3; FABMS *m*/*z* 707 $[M + 1]^+$. Anal. Calcd for $C_{35}H_{50}N_6O_6Si_2$: C, 59.46; H, 7.13; N, 11.89. Found: C, 59.40; H, 6.72; N, 11.80.

***N*²-(2-Nitro-3-methylphenyl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3b):** yellow solid (0.115 g, 93%); mp 112 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.07 (6H, s, $CH_3Si$), 0.10 (6H, s, $CH_3Si$), 0.91 (9H, s, $(CH_3)_3C$), 0.93 (9H, s, $(CH_3)_3C$), 2.41 (1H, m, H-2′), 2.43 (3H, s, $CH_3$−Ph), 2.50 (1H, m, H′-2′), 3.78 (2H, m, H-5′), 3.99 (1H, m, H-4′), 4.57 (1H, m, H-3′), 5.57 (2H, s, $CH_2$−Ph), 6.36 (1H, t, $J = 6.6$ Hz, H-1′), 6.93 (1H, t, $J = 7.5$ Hz, $-C_6H_3NO_2$), 7.28−7.51 (5H, m, $CH_2-C_6H_5$), 7.30 (1H, m, $-C_6H_3NO_2$), 8.04 (1H, s, H-8), 8.21 (1H, d, $J = 7.5$ Hz, $-C_6H_3NO_2$), 8.25 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.6 (× 2), −4.9 (× 2), 17.8, 18.3, 19.5, 25.6 (× 3), 25.8 (× 3), 41.3, 62.7, 68.2, 71.8, 83.9, 87.6, 117.1, 120.0, 124.6, 127.9, 128.0 (× 2), 128.2 (× 2), 131.1, 132.4, 133.4, 136.1, 138.8, 141.3, 152.7, 154.4, 160.3; FABMS *m*/*z* 721 $[M + 1]^+$. Anal. Calcd for $C_{36}H_{52}N_6O_6Si_2$: C, 59.97; H, 7.27; N, 11.66. Found: C, 59.61, H, 7.02; N, 11.56.

***N*²-(2-Nitronaphth-1-yl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3c):** yellow solid (0.114 g, 88%); mp 95−97 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.05 (6H, s, $CH_3Si$), 0.09 (6H, s, $CH_3Si$), 0.90 (18H, s, $(CH_3)_3C$), 2.24 (1H, m, H-2′), 2.40 (1H, m, H′-2′), 3.69 (2H, m, H-5′), 3.92 (1H, m, H-4′), 4.46 (1H, m, H-3′), 5.08 (2H, s, $CH_2$−Ph), 6.18 (1H, t, $J = 6.6$ Hz, H-1′), 7.06−7.20 (5H, m, $CH_2-C_6H_5$), 7.48 (1H, t, $J = 8.0$ Hz, $-C_{10}H_6$), 7.64 (1H, t, $J = 8.0$ Hz, $-C_{10}H_6$), 7.75 (1H, d, $J = 9.1$ Hz, $-C_{10}H_6$), 7.90 (1H, d, $J = 8.0$ Hz, $-C_{10}H_6$), 7.99 (1H, s, H-8), 8.09 (1H, d, $J = 9.1$ Hz, $-C_{10}H_6$), 8.12 (1H, d, $J = 8.0$ Hz, $-C_{10}H_6$), 8.74 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.5 (× 2), −4.7 (× 2), 17.9, 18.3, 25.7 (× 3), 25.9 (× 3), 40.9, 62.7, 68.1, 71.8, 84.1, 87.7, 117.3, 120.6, 125.3, 126.5, 127.2, 127.8, 128.1 (× 3), 128.4 (× 2), 129.2, 129.7, 133.1, 135.8, 136.1, 138.9, 140.2, 152.8, 155.8, 160.3; FABMS *m*/*z* 757 $[M + 1]^+$. Anal. Calcd for $C_{39}H_{52}N_6O_6Si_2$: C, 61.88; H, 6.92; N, 11.10. Found: C, 61.45; H, 6.81; N, 10.97.

***N*²-(2-Nitro-5-(phenyl)phenyl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3d):** yellow solid (0.129 g, 96%); mp 76 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.09 (6H, s, $CH_3Si$), 0.10 (6H, s, $CH_3Si$), 0.91 (9H, s, $(CH_3)_3C$), 0.92 (9H, s, $(CH_3)_3C$), 2.41 (1H, m, H-2′), 2.61 (1H, m, H′-2′), 3.80 (2H, m, H-5′), 3.98 (1H, m, H-4′), 4.56 (1H, m, H-3′), 5.53 (2H, s, $CH_2$−Ph), 6.40 (1H, t, $J = 6.6$ Hz, H-1′), 7.10 (1H, d, $J = 9.0$ Hz, $-C_{12}H_8NO_2$), 7.28−7.64 (9H, m, $CH_2-C_6H_5$, $-C_{12}H_8NO_2$), 8.17 (2H, m, $-C_{12}H_8NO_2$), 9.39 (1H, m, $-C_{12}H_8NO_2$), 10.61 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$), $\delta$ −4.7 (× 2), −4.5 (× 2), 18.2, 18.5, 25.8 (× 3), 26.0 (× 3), 41.5, 62.5, 68.8, 71.3, 83.9, 87.7, 117.5, 118.3, 118.7, 126.7, 127.2 (× 2), 128.1, 128.4 (× 2), 128.9, 129.0 (× 2), 129.1 (× 2), 133.7, 135.9, 137.8, 139.1, 139.3, 148.0, 152.0, 154.0, 160.4; FABMS *m*/*z* 783 $[M + 1]^+$. Anal. Calcd for $C_{41}H_{54}N_6O_6Si_2$: C, 62.89; H, 6.95; N, 10.73. Found: C, 62.86; H, 6.85; N, 10.83.

***N*²-(2-Nitro-9-oxo-fluoren-3-yl)-*O*⁶-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (3e):** yellow solid (0.127 g, 92%); mp 88 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.08 (6H, s, $CH_3Si$), 0.09 (6H, s, $CH_3Si$), 0.90 (18H, s, $(CH_3)_3C$), 2.53 (1H, m, H-2′), 2.61 (1H, m, H′-2′), 3.85 (2H, m, H-5′), 4.05 (1H, m, H-4′), 4.63 (1H, m, H-3′), 5.68 (2H, s, $CH_2$−Ph), 6.47 (1H, t, $J = 6.6$ Hz, H-1′), 7.25−7.70 (9H, m, $CH_2-C_6H_5$, $-C_{13}H_6NO_2$), 8.21 (1H, s, H-8), 8.51 (1H, s, $-C_{13}H_6NO_2$), 9.30 (1H, s, $-C_{13}H_6NO_2$), 11.11 (1H, s, N−H); $^{13}$C NMR (62.5

MHz, $CDCl_3$) $\delta$ −5.5 (× 2), −4.7 (× 2), 17.9, 18.3, 25.7 (× 3), 25.9 (× 3), 41.6, 62.5, 68.8, 71.4, 84.0, 87.8, 110.6, 118.1, 121.0, 122.9, 124.1, 125.1, 128.1 (× 2), 128.5 (× 2), 130.8, 133.6, 134.6, 135.6, 136.2, 139.9, 141.7, 143.0, 149.2, 152.2, 152.8, 160.3, 189.7; FABMS *m*/*z* 809 $[M + 1]^+$. Anal. Calcd for $C_{42}H_{52}N_6O_7Si_2$: C, 62.35; H, 6.48; N, 10.39. Found: C, 62.10; H, 6.01; N, 9.90.

***N*²-(2-Acetylaminoaryl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5a−e). General Procedure.** To a solution of **3a**−**e** (0.1 mmol) in ethyl acetate/ethanol (1:1, 10 mL) was added a 10% palladium-on-carbon catalyst. The flask was evacuated (50 Torr) and flushed with hydrogen three times. The reaction mixture was hydrogenated for 16 h at 50 psi with stirring. It was then filtered through a pad of Celite and concentrated under reduced pressure. The residue was dried for 6 h in a vacuum oven, the crude product was redissolved in methylene chloride (10 mL), and acetic anhydride (10 equiv) was added. Stirring was continued at room temperature for 16 h. Concentration under vacuum and purification by flash chromatography (silica gel, 0−20% methanol in ethyl acetate) afforded the desired compound.

***N*²-(2-Acetylaminophenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5a):** white solid (0.060 g, 96%); mp 148−150 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.03 (6H, s, $CH_3Si$), 0.04 (6H, s, $CH_3$-Si), 0.81 (9H, s, $(CH_3)_3C$), 0.82 (9H, s, $(CH_3)_3C$), 1.96 (3H, s, $CH_3$-CO), 2.21 (1H, m, H-2′), 2.35 (1H, m, H′-2′), 3.68 (2H, m, H-5′), 3.89 (1H, m, H-4′), 4.43 (1H, m, H-3′), 6.22 (1H, t, $J$ = 6.3 Hz, H-1′), 7.02 (1H, t, $J$ = 7.5 Hz, $-C_6H_4$), 7.18 (2H, m, $-C_6H_4$), 7.99 (1H, s, H-8), 8.21 (1H, d, $J$ = 8.0 Hz, $-C_6H_4$), 9.41 (1H, s, N−H), 10.72 (1H, s, H-8), 11.33 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.9 (× 2), −4.6 (× 2), 17.9, 18.4, 22.8, 25.7 (× 3), 25.9 (× 3), 42.5, 62.5, 72.3, 84.4, 87.8, 117.6, 121.6, 123.7, 127.4, 127.9, 129.7, 135.5, 136.7, 149.7, 150.7, 158.4, 171.4; FABMS *m*/*z* 629 $[M + 1]^+$.

***N*²-(2-Acetylamino-3-methylphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5b):** white solid (0.061 g, 95%); mp 154−156 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.07 (6H, s, $CH_3Si$), 0.11 (6H, s, $CH_3Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.93 (9H, s, $(CH_3)_3C$), 2.11 (3H, s, $CH_3CO$), 2.33 (3H, s, $CH_3-Ph$), 2.34 (1H, m, H-2′), 2.44 (1H, m, H′-2′), 3.81 (2H, m, H-5′), 4.01 (1H, m, H-4′), 4.50 (1H, m, H-3′), 6.33 (1H, t, $J$ = 6.3 Hz, H-1′), 7.02 (1H, t, $J$ = 7.5 Hz, $-C_6H_3$), 7.20 (1H, dd, $J$ = 8.0, 7.5 Hz, $-C_6H_3$), 7.95 (1H, s, H-8), 8.17 (1H, d, $J$ = 8.0 Hz, $-C_6H_3$), 9.57 (1H, s, N−H), 10.77 (1H, s, N−H), 11.36 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.4 (× 2), −4.7 (× 2), 17.9, 18.3, 22.8, 25.7 (× 3), 25.9 (× 3), 42.6, 62.8, 72.1, 84.5, 88.0, 117.4, 119.0, 125.0, 126.7, 127.2, 135.9, 136.2, 137.4, 149.7, 150.8, 158.4, 171.1; FABMS *m*/*z* 643 $[M + 1]^+$.

***N*²-(2-Acetylaminonaphth-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5c):** yellow amorphous solid (0.060 g, 88%); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ −0.07 (6H, s, $CH_3Si$), −0.06 (6H, s, $CH_3Si$), 0.78 (9H, s, $(CH_3)_3C$), 0.80 (9H, s, $(CH_3)_3C$), 1.90 (1H, m, H-2′), 2.07 (1H, m, H′-2′), 2.13 (3H, s, $CH_3CO$), 3.40 (2H, m, H-5′), 3.74 (1H, m, H-4′), 4.11 (1H, m, H-3′), 5.79 (1H, t, $J$ = 6.3 Hz, H-1′), 7.39 (3H, m, $-C_{10}H_6$), 7.78 (2H, m, $-C_{10}H_6$), 7.80 (1H, s, H-8), 7.95 (1H, m, $-C_{10}H_6$), 8.19 (1H, m, $-C_{10}H_6$), 8.92 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.6 (× 2), −4.8 (× 2), 17.8, 18.1, 24.5, 25.6 (× 6), 40.3, 62.8, 72.0, 84.5, 87.8, 117.7, 122.6 (× 2), 123.4, 124.9, 126.1, 127.5, 127.9, 130.8, 131.4, 133.1, 136.1, 150.3, 151.7, 159.3, 169.2; FABMS *m*/*z* 679 $[M + 1]^+$.

***N*²-(2-Acetylamino-5-(phenyl)phenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5d):** white solid (0.067 g, 96%); mp 161−163 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.04 (6H, s, $CH_3Si$), 0.11 (6H, s, $CH_3Si$), 0.85 (9H, s, $(CH_3)_3C$), 0.94 (9H, s, $(CH_3)_3C$), 2.10 (3H, s, $CH_3CO$), 2.41 (2H, m, H-2′), 3.79 (2H, m, H-5′), 3.92 (1H, m, H-4′), 4.52 (1H, m, H-3′), 6.30 (1H, t, $J$ = 6.3 Hz, H-1′), 7.39 (5H, m, $-C_{12}H_8$), 7.63 (2H, m, $-C_{12}H_8$), 8.21 (1H, s, H-8), 8.60 (1H, m, $-C_{12}H_8$), 9.61 (1H, s, N−H), 10.77 (1H, s, N−H), 11.50 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.9 (× 2), −4.6 (× 2), 17.9, 18.4, 23.1, 25.7 (× 3), 26.0 (× 3), 42.2, 61.9, 70.0, 84.0, 87.4, 117.6, 120.7, 122.4, 127.0 (× 2), 127.3, 128.7 (× 3), 129.8, 135.4, 137.0, 140.3, 140.9, 149.8, 150.6, 158.4, 171.4; FABMS *m*/*z* 705 $[M + 1]^+$.

***N*²-(2-Acetylaminofluoren-3-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (5e):**[29] yellow amorphous solid (0.031 g, 43%); $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ −0.05 (6H, s, $CH_3Si$), −0.10 (6H, s, $CH_3Si$), 0.74 (9H, s, $(CH_3)_3C$), 0.75 (9H, s, $(CH_3)_3C$), 2.11 (3H, s, $CH_3CO$), 2.25 (1H, m, H-2′), 2.90 (1H, m, H′-2′), 3.45 (2H, m, H-5′), 3.73 (1H, m, H-4′), 3.87 (2H, s, $C_{13}H_8$), 4.29 (1H, m, H-3′), 6.11 (1H, t, $J$ = 6.6 Hz, H-1′), 7.30 (2H, m, $C_{13}H_8$), 7.56 (1H, d, $C_{13}H_8$), 7.62 (1H, s, $C_{13}H_8$), 7.76 (1H, d, $C_{13}H_8$), 7.97 (1H, s, H-8), 8.11 (1H, s, N−H), 8.36 (1H, s, $C_{13}H_8$), 9.66 (1H, s, N−H), 11.27 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$), $\delta$ −5.5 (× 2), −5.4 (× 2), 17.9, 18.4, 23.3, 25.7 (× 3), 26.0 (× 3), 36.72, 41.9, 62.8, 71.7, 84.7, 88.1, 114.5, 118.3, 119.6, 124.7, 125.0, 126.6, 126.9, 128.7, 132.9, 136.8, 139.3, 140.5, 141.8, 144.1, 150.6, 151.1, 158.8, 170.7; FABMS *m*/*z* 717 $[M + 1]^+$.

***N*²-(2-Acetylaminoaryl)-2′-deoxyguanosine (6a−e). General Procedure.** A solution of **5a**−**e** (0.1 mmol) in tetrahydrofuran (3 mL) was stirred with a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.22 mL, 0.22 mmol) at room temperature. After 1 h, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (silica gel, 10−20% methanol in methylene chloride) to afford the desired compound.

***N*²-(2-Acetylaminophenyl)-2′-deoxyguanosine (6a):** white solid (0.037 g, 94%); mp 190−193 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.84 (3H, s, $CH_3CO$), 2.24 (1H, m, H-2′), 2.55 (1H, m, H-2′), 3.47 (2H, m, H-5′), 3.79 (1H, m, H-4′), 4.29 (1H, m, H-3′), 4.85 (1H, br s, 5′-OH), 5.27 (1H, s, 4′-OH), 6.12 (1H, t, $J$ = 6.8 Hz, H-1′), 7.09 (1H, t, $J$ = 7.5 Hz, $-C_6H_4$), 7.27 (2H, m, $-C_6H_4$), 8.00 (3H, s, $-C_6H_4$, H-8, N−H), 9.60 (1H, s, N−H), 11.26 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 23.3, 40.4, 61.7, 70.7, 82.9, 87.7, 118.3, 123.1, 123.7, 125.7, 126.1, 129.4, 132.5, 136.5, 149.5, 149.8, 156.6, 169.2; FAB HRMS: exact mass calculated for $C_{18}H_{21}N_6O_5$ $(M + 1)^+$, 401.1573; found, 401.1584.

***N*²-(2-Acetylamino-3-methylphenyl)-2′-deoxyguanosine (6b):** white solid (0.039 g, 95%); mp 195−198 °C; $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 2.25 (3H, s, $CH_3CO$), 2.29 (3H, s, $CH_3-Ph$), 2.42 (1H, m, H-2′), 2.74 (1H, m, H′-2′), 3.65 (2H, m, H-5′), 3.99 (1H, m, H-4′), 4.45 (1H, m, H-3′), 6.30 (1H, t, $J$ = 6.8 Hz, H-1′), 7.13 (1H, d, $J$ = 7.5 Hz, $-C_6H_3$), 7.30 (1H, dd, $J$ = 8.1, 7.5 Hz, $-C_6H_3$),7.93 (1H, d, $J$ = 8.1 Hz, $-C_6H_3$) 8.07 (1H, s, H-8); $^{13}$C NMR (62.5 MHz, $CD_3OD$) $\delta$ 18.4, 22.8, 41.2, 63.2, 72.5, 85.5, 89.2, 119.2, 122.5, 127.5, 128.6, 129.0, 136.0, 137.5, 138.7, 151.6, 159.2, 173.2; FAB HRMS: exact mass calculated for $C_{19}H_{23}N_6O_5$ $(M + 1)^+$, 415.1730; found, 415.1719.

***N*²-(2-Acetylaminonaphth-1-yl)-2′-deoxyguanosine (6c):** white solid (0.040 g, 90%); mp 200−203 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.86 (1H, m, H-2′), 2.08 (3H, s, $CH_3CO$), 2.27 (1H, m, H′-2′), 3.11 (2H, m, H-5′), 3.59 (1H, m, H-3′) 3.88 (1H, m, H-4′), 4.58 (1H, s, 5′-OH), 5.00 (1H, s, 4′-OH), 5.75 (1H, t, $J$ = 6.8 Hz, H-1′), 7.48 (2H, m, $C_{10}H_6$), 7.85−7.94 (5H, m, $C_{10}H_6$ and H-8), 8.60 (1H, s, N−H), 9.77 (1H, s, N−H), 11.25 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 23.6, 40.5, 61.5, 70.7, 82.8, 87.6, 118.0, 123.2, 123.3, 124.1, 125.2, 126.4, 126.9, 128.0, 130.8, 131.2, 132.6, 136.3, 150.1, 151.9, 168.9. FABMS *m*/*z* 451 $[M + 1]^+$; FAB HRMS: exact mass calculated for $C_{22}H_{23}N_6O_5$ $(M + 1)^+$, 451.1730; found, 451.1738.

***N*²-(2-Acetylamino-5-(phenyl)phenyl)-2′-deoxyguanosine (6d):** white solid (0.044 g, 92%); mp 245 °C dec; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 2.12 (3H, s, $CH_3CO$), 2.27 (1H, m, H-2′), 2.60 (1H, m, H′-2′), 3.47 (2H, m, H-5′), 3.87 (1H, m, H-4′), 4.29 (1H, m, H-3′), 4.88 (1H, t, $J$ = 5.1 Hz, 5′-OH), 5.30 (1H, d, $J$ = 3.4 Hz, 4′-OH), 6.27 (1H, t, $J$ = 7.2 Hz, H-1′), 7.32−7.54 (5H, m, $-C_{12}H_8$), 7.69 (2H, m, $-C_{12}H_8$), 8.09 (2H, s, N−H and H-8) 8.51 (1H, s, $-C_{12}H_8$), 9.67 (1H, s, N−H), 11.32 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 23.4, 40.5, 61.7, 70.8, 82.7, 87.9, 118.2, 120.6, 121.5, 126.5 (× 3), 126.8, 127.4, 128.1, 129.2 (× 2), 133.2, 136.1, 137.7, 139.6, 149.7, 156.7, 169.4; FAB HRMS: exact mass calculated for $C_{24}H_{25}N_6O_5$ $(M + 1)^+$, 477.1886; found, 476.1871.

***N*²-(2-Acetylaminofluoren-3-yl)-2′-deoxyguanosine (6e):** yellow amorphous solid (0.045 g, 92%); $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 2.11 (3H, s, $CH_3$), 2.26 (1H, m, H-2′), 2.60 (1H, m, H′-2′), 3.42 (2H, m, H-5′), 3.79 (1H, m, H-4′), 3.89 (2H, s, $-C_{13}H_8$), 4.25 (1H, m, H-3′), 4.84 (1H, t, $J$ = 5.4 Hz, 5′-OH), 5.27 (1H, d, $J$ = 3.6 Hz, 4′-OH), 6.18 (1H, t, $J$ = 6.6 Hz, H-1′), 7.34 (2H, m, $-C_{13}H_8$), 7.57 (2H, m, $-C_{13}H_8$), 7.81 (1H, m, $-C_{13}H_8$), 8.04 (1H, s, H-8) 8.08 (1H, s, N−H), 8.58 (1H, s, $-C_{13}H_8$), 9.63 (1H, s, N−H), 11.28 (1H, br s, N−H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 23.3, 36.0, 61.6, 70.7, 83.1, 87.8, 114.2, 118.2, 119.7, 122.5, 125.0, 126.6, 126.9, 128.4, 131.5, 136.0, 138.3, 138.7,

140.8, 143.4, 149.6, 150.0, 156.7, 169.2; FAB HRMS: exact mass calculated for $C_{25}H_{25}N_6O_5$ (M + 1)$^+$, 489.1886; found, 489.1894.

***N*$^6$-(Nitroaryl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (8b−e).** An oven-dried reaction vial was charged with **7** (0.497 g, 1.00 mmol), cesium carbonate (0.456 g, 1.40 mmol, 1.4 equiv), palladium acetate (0.022 g, 0.10 mmol, 0.1 equiv), BINAP (0.093 g, 0.15 mmol, 0.15 equiv), the aryl bromide or triflate (0.70 mmol, 0.70 equiv), and toluene (6 mL). The vial was flushed with argon prior to sealing. The reaction mixture was stirred for 30 min at room temperature and then it was heated at 80 °C for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL). Centrifugation and concentration of the supernant liquid in a vacuum afforded a residue, which was purified by flash chromatography (silica gel, 10−30% ethyl acetate in hexane) to give adducts **8b**−**e** as a yellow glassy solid. The reported yields are based on recovered starting material.

***N*$^6$-(2-Nitro-3-methylphenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (8b):** yellow solid (0.405 g, 88%, based on 28% recovered s.m.); mp 118−121 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.07 (6H, s, $CH_3Si$), 0.09 (6H, s, $CH_3Si$), 0.90 (18H, s, $(CH_3)_3C$), 2.40 (4H, m, H-2′ and $CH_3Ph$), 2.66 (1H, m, H′-2′), 3.77 (1H, dd, $J$ = 11.1, 3.4 Hz, H-5′), 3.86 (1H, dd, $J$ = 11.1, 4.3 Hz, H′-5′), 4.00 (1H, m, H-4′), 4.60 (1H, m, H-3′), 6.45 (1H, t, $J$ = 6.4 Hz, H-1′), 7.03 (1H, d, $J$ = 7.5 Hz, $-C_6H_3NO_2$), 7.41 (1H, dd, $J$ = 8.3, 7.5 Hz, $-C_6H_3NO_2$), 8.20 (1H, s, H-2), 8.37 (1H, d, $J$ = 8.3 Hz, $-C_6H_3NO_2$), 8.49 (1H, s, H-8), 8.88 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.8 (× 2), −4.7 (× 2), 18.0, 18.4, 19.5, 25.8 (× 3), 26.0 (× 3), 41.2, 62.8, 72.0, 84.4, 88.0, 121.8 (× 2), 126.5, 131.6, 132.0, 133.0, 140.1, 142.5, 150.0, 151.5, 152.2; FAB HRMS: exact mass calculated for $C_{29}H_{47}N_6O_5Si_2$ (M + 1)$^+$, 615.3146; found, 615.3135.

***N*$^6$-(2-Nitronaphth-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (8c):** yellow solid (0.387 g, 85%, based on 30% recovered s.m.); mp 76−80 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.10 (12H, s, $CH_3Si$), 0.91 (18H, s, $(CH_3)_3C$), 2.45 (1H, m, H-2′), 2.68 (1H, m, H′-2′), 3.77 (1H, dd, $J$ = 11.2, 3.3 Hz, H-5′), 3.88 (1H, dd, $J$ = 11.2, 4.2 Hz, H′-5′), 4.03 (1H, m, H-4′), 4.63 (1H, m, H-3′), 6.47 (1H, t, $J$ = 6.4 Hz, H-1′), 7.51 (1H, t, $J$ = 8.0 Hz, $-C_{10}H_6NO_2$), 7.65 (1H, d, $J$ = 8.0 Hz, $-C_{10}H_6NO_2$), 7.84 (1H, d, $J$ = 9.1 Hz, $-C_{10}H_6NO_2$), 7.91 (1H, d, $J$ = 8.0 Hz, $-C_{10}H_6NO_2$), 8.06 (2H, m, $-C_{10}H_6NO_2$), 8.25 (1H, s, H-2), 8.27 (1H, s, H-8), 9.11 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.5 (× 2), −4.8 (× 2), 18.0, 18.4, 25.7 (× 3), 25.9 (× 3), 41.2, 62.7, 71.8, 84.5, 87.9, 120.6, 121.4, 126.6, 127.1, 127.4, 128.3, 129.4, 129.9, 130.7, 135.9, 140.2, 141.7, 150.0, 152.8; FABMS *m*/*z* 651 [M + 1]$^+$; Anal. Calcd for $C_{32}H_{46}N_6O_5Si_2$: C, 59.05; H, 7.12; N, 12.91. Found: C, 58.74; H, 6.96; N, 12.61.

***N*$^6$-(2-Nitro-5-(phenyl)phenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (8d):** yellow amorphous solid (0.414 g, 85%, based on 28% recovered s.m.); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.07 (6H, s, $CH_3Si$), 0.10 (6H, s, $CH_3Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.91 (9H, s, $(CH_3)_3C$), 2.45 (1H, m, H-2′), 2.70 (1H, m, H′-2′), 3.77 (1H, dd, $J$ = 11.1, 3.4 Hz, H-5), 3.86 (1H, dd, $J$ = 11.1, 4.3 Hz, H′-5′), 4.03 (1H, m, H-4′), 4.64 (1H, m, H-3′), 6.47 (1H, t, $J$ = 6.4 Hz, H-1′), 7.25−7.49 (4H, m, $-C_{12}H_8NO_2$), 7.68 (2H, m, $-C_{12}H_8NO_2$), 8.26 (2H, m, H-2 and $-C_{12}H_8NO_2$), 8.59 (1H, s, H-8), 9.59 (1H, s, $-C_{12}H_8NO_2$), 11.17 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.8 (× 2), −4.7 (× 2), 18.0, 18.4, 25.8 (× 3), 26.0 (× 3), 41.1, 62.8, 72.0, 84.5, 88.0, 120.0, 120.1, 122.5, 126.6 (× 2), 127.5 (× 2), 129.0 (× 2), 134.7, 136.8, 138.9, 140.6, 148.3, 149.9, 151.2, 152.1; FAB HRMS: exact mass calculated for $C_{34}H_{47}N_6O_5Si_2$ (M + 1)$^+$, 677.3303; found, 677.3209.

***N*$^6$-(2-Nitro-9-oxofluoren-3-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (8e):** yellow solid (0.412 g, 84%, based on 30% recovered s.m.); mp 212−215 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.08 (6H, s, $CH_3Si$), 0.12 (6H, s, $CH_3Si$), 0.90 (9H, s, $(CH_3)_3C$), 0.92 (9H, s, $(CH_3)_3C$), 2.47 (1H, m, H-2′), 2.71 (1H, m, H′-2′), 3.77 (1H, dd, $J$ = 11.1, 3.4 Hz, H-5′), 3.87 (1H, dd, $J$ = 11.1, 4.3 Hz, H′-5′), 4.03 (1H, m, H-4′), 4.64 (1H, m, H-3′), 6.45 (1H, t, $J$ = 6.4 Hz, H-1′), 7.30 (1H, t, $J$ = 7.3 Hz, $-C_{13}H_6NO_2$), 7.49 (1H, t, $J$ = 7.3 Hz, $-C_{13}H_6NO_2$), 7.59 (2H, m, $-C_{13}H_6NO_2$), 8.22 (1H, s, H-2), 8.34 (1H, s, H-8), 8.60 (1H, s, $-C_{13}H_6NO_2$), 9.51 (1H, s, $-C_{13}H_6NO_2$), 11.60 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.8 (× 2), −4.6 (× 2), 18.0, 18.4, 25.8 (× 3), 26.0 (× 3), 41.1, 62.8, 72.0, 84.6, 88.1, 112.3, 120.0, 122.7, 122.9, 124.2, 126.2, 131.0, 134.5, 134.8 (× 2), 136.0, 141.3, 141.8, 142.4, 149.6, 150.2, 151.8, 189.9; FAB HRMS: exact mass calculated for $C_{35}H_{47}N_6O_6Si_2$ (M + 1)$^+$, 703.3096; found, 703.3105.

***N*,$^6$*N*$^6$-Bis-(2-nitronaphth-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (9):** An oven-dried reaction vial was charged with **7** (0.497 g, 1.00 mmol), cesium carbonate (0.456 g, 1.40 mmol, 1.4 equiv), palladium acetate (0.022 g, 0.10 mmol, 0.1 equiv), BINAP (0.093 g, 0.15 mmol, 0.15 equiv), 2-nitro-1-naphthyl triflate (1.4 mmol, 1.40 equiv) and toluene (6 mL). The vial was flushed with argon prior to sealing. The reaction mixture was stirred for 30 min at room temperature, then it was heated at 80 °C for 16 h. The reaction mixture was quenched with ethyl acetate (10 mL). Centrifugation and concentration in a vacuum of the supernant liquid afforded a residue, which was purified by flash chromatography (silica gel, 10−30% ethyl acetate in hexane) to give bis-adduct **9** as a yellow oil, 0.510 g, 62%; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.01−0.11 (12H, $CH_3Si$), 0.84−0.91 (18H, s, $(CH_3)_3C$), 2.50 (2H, m, H-2′), 3.70 (2H, m, H-5′), 4.01 (1H, m, H-4′), 4.59 (1H, m, H-3′), 6.38 (1H, m, H-1′), 7.35−8.18 (14H, m, $-C_{20}H_{12}NO_2$, H-2 and H-8), $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −4.8 (× 2), −4.7 (× 2), 18.0, 18.4, 25.8 (× 3), 25.9 (× 3), 40.8, 53.5, 62.8, 72.1, 84.1, 88.1, 120.3, 121.1, 121.2, 125.4, 126.3, 126.7, 127.7, 128.3, 128.5, 128.7, 128.9, 129.8, 130.0, 130.3, 135.7, 136.1, 137.5, 137.6, 143.9, 144.1, 144.3, 144.4, 146.3 (× 2), 146.9; FAB HRMS: exact mass calculated for $C_{42}H_{52}N_7O_7Si_2$ (M + 1)$^+$, 822.3467; found, 822.3454.

***N*$^2$-(2-Acetylaminonaphth-1-yl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (10):** To a solution of **8c** (0.085 g, 0.131 mmol) in ethyl acetate/ethanol (1:1, 10 mL) was added a 10% palladium on activated-carbon catalyst (0.010 g). The flask was evacuated (50 Torr) and flushed with hydrogen three times. The reaction mixture was hydrogenated for 16 h at 50 psi with stirring. The reaction mixture then was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dried for 6 h in a vacuum oven. The crude product was redissolved in methylene chloride (2 mL) and acetic anhydride (0.040 mL, 0.432 mmol) was added. After stirring at room temperature for 6 h, the reaction was quenched with methanol. Concentration under vacuum and purification by flash chromatography (silica gel, 30−80% ethyl acetate in hexane) afforded the desired compound as a white amorphous solid (0.061 g, 71%); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.09 (6H, s, $CH_3Si$), 0.12 (6H, s, $CH_3Si$), 0.92 (18H, s, $(CH_3)_3C$), 2.00 (3H, s, $CH_3CO$), 2.44 (1H, m, H-2′), 2.63 (1H, m, H′-2′), 3.76 (1H, dd, $J$ = 11.1, 3.4 Hz, H-5′), 3.84 (1H, dd, $J$ = 11.1, 4.5 Hz, H′-5′), 4.03 (1H, m, H-4′), 4.62 (1H, m, H-3′), 6.43 (1H, t, $J$ = 6.4 Hz, H-1′), 7.41 (2H, m, $-C_{10}H_6$), 7.81 (3H, m, $-C_{10}H_6$), 8.03 (1H, d, $J$ = 8.7 Hz, $-C_{10}H_6$), 8.12 (1H, s, H-2), 8.34 (1H, s, H-8), 8.85 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ −5.5 (× 2), −4.8 (× 2), 18.0, 18.4, 24.2, 25.7 (× 3), 25.9 (× 3), 41.0, 62.8, 72.0, 84.5, 88.0, 120.5, 122.2, 123.2 (× 2), 125.4, 126.8, 127.9, 128.3, 130.2, 131.7, 132.3, 139.7, 149.4, 152.5, 153.5, 168.9; FABMS *m*/*z* 663 [M + 1]$^+$; FAB HRMS: exact mass calculated for $C_{34}H_{51}N_6O_4Si_2$ (M + 1)$^+$, 663.3510; found, 663.3487.

***N*$^2$-(2-Acetylaminonaphth-1-yl)-2′-deoxyadenosine (11).** To a solution of **10** (0.039 g, 0.059 mmol) in pyridine (0.250 mL) at 0 °C in a polypropylene vial was added HF/pyridine (70%, 0.030 mL). The flask was held at room temperature for 3 h and then concentrated under a stream of argon. The residue was washed with ethyl acetate and then purified by flash chromatography (silica gel, 5−20% methanol in methylene chloride) to afford the desired compound as a white amorphous solid (0.017 g, 72%); $^1$H NMR (250 MHz, $C_5D_5N$) $\delta$ 2.14 (3H, s, $CH_3CO$), 2.73 (1H, m, H-2′), 2.18 (1H, m, H′-2′), 4.12 (1H, dd, $J$ = 12.0, 3.0 Hz, H-5′), 3.84 (1H, dd, $J$ = 12.0, 3.1 Hz, H′-5′), 4.61 (1H, m, H-4′), 5.18 (1H, m, H-3′), 6.92 (1H, t, $J$ = 6.4 Hz, H-1′), 7.39 (2H, m, $-C_{10}H_6$), 7.88 (2H, m, $-C_{10}H_6$), 8.19 (1H, m, $-C_{10}H_6$), 8.39 (1H, s, H-2), 8.53 (1H, t, $J$ = 9.0 Hz, $-C_{10}H_6$), 8.71 (1H, s, H-8), 10.80 (1H, s, N−H); $^{13}$C NMR (62.5 MHz, $C_5D_5N$) $\delta$ 24.0, 41.4, 63.2, 72.3, 86.1, 89.9, 121.9, 123.5 (under the solvent peak), 124.7, 125.5, 125.9, 126.7, 127.5, 128.5, 132.3, 132.4, 134.4, 140.6, 149.9 (under the solvent peak), 152.8, 155.6, 169.7; FABMS *m*/*z* 435 [M + 1]$^+$; FAB HRMS: exact mass calculated for $C_{22}H_{23}N_6O_4$ (M + 1)$^+$, 435.1781; found, 435.1777.

***N*$^2$-(2-Nitronaphth-1-yl)-2′-deoxyadenosine (12).** A solution of **8c** (0.080 g, 0.123 mmol) in tetrahydrofuran (1.0 mL) was stirred with a

1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.3 mL, 0.3 mmol) at room temperature. After 1 h, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (silica gel, 0−6% methanol in methylene chloride) to afford **12** as yellow amorphous solid (0.050 g, 88%); $^1$H NMR (250 MHz, $CD_3OD$) $\delta$ 2.45 (1H, m, H-2′), 2.85 (1H, m, H′-2′), 3.77 (1H, dd, $J$ = 11.2, 3.5 Hz, H-5′), 3.87 (1H, dd, $J$ = 11.2, 3.0 Hz, H′-5′), 4.10 (1H, m, H-4′), 4.62 (1H, m, H-3′), 6.49 (1H, t, $J$ = 6.4 Hz, H-1′), 7.61 (1H, t, $J$ = 8.0 Hz, $-C_{10}H_6NO_2$), 7.67 (1H, d, $J$ = 8.0 Hz, $-C_{10}H_6NO_2$), 8.04 (3H, m, $-C_{10}H_6NO_2$), 8.12 (1H, s, H-2), 8.22 (1H, d, $J$ = 8.2 Hz, $-C_{10}H_6NO_2$), 8.44 (1H, s, H-8); $^{13}$C NMR (62.5 MHz, $CD_3OD$) $\delta$ 41.5, 63.5, 72.9, 87.1, 89.8, 121.8, 122.1, 126.3, 129.0, 129.1, 129.5, 130.3, 131.9, 137.2 (× 2), 142.5, 144.7, 150.7, 152.8, 155.0; FABMS *m*/*z* 423 $[M + 1]^+$; FAB HRMS: exact mass calculated for $C_{20}H_{19}N_6O_5$ $(M + 1)^+$, 423.1417; found, 423.1396.

***N*$^2$-(2-Aminonaphth-1-yl)-3′,5′-bis-*O*-2′-deoxyadenosine (13).** To a solution of **12** (0.050 g, 0.120 mmol) in ethanol (5 mL) was added a 10% palladium on activated-carbon catalyst (0.010 g). The flask was evacuated (50 Torr) and flushed with hydrogen three times. The reaction mixture was hydrogenated for 16 h at 45 psi with stirring. The reaction mixture then was filtered through a pad of Celite and concentrated under reduced pressure to give **13** as a glassy solid (0.042 g, 91%); $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 2.30 (1H, m, H-2′), 2.77 (1H, m, H′-2′), 3.55 (1H, dd, $J$ = 11.9, 4.1 Hz, H-5′), 3.66 (1H, dd, $J$ = 11.9, 2.2 Hz, H′-5′), 3.91 (1H, m, H-4′), 4.45 (1H, m, H-3′), 5.23 (2H, bs, $-NH_2$), 6.41 (1H, t, $J$ = 7.0 Hz, H-1′), 7.12 (2H, m, $-C_{10}H_6$), 7.25 (1H, d, $J$ = 7.0 Hz, $-C_{10}H_6$), 7.44 (1H, $J$ = 8.4 Hz, $-C_{10}H_6$), 7.64 (1H, $J$ = 8.8 Hz, $-C_{10}H_6$), 7.71 (1H, d, $J$ = 7.0 Hz, $-C_{10}H_6$), 8.06 (1H, s, H-8 or H-2), 8.45 (1H, s, H-2 or H-8), 9.24 (1H, s, NH); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 40.0 (under the solvent peak), 61.9, 71.0, 84.1, 88.0, 113.5, 118.7, 120.1, 121.0, 126.0, 127.5 (× 3), 132.7, 139.8, 143.2, 150.0, 152.1, 154.8; FABMS *m*/*z* 393 $[M + 1]^+$; FAB HRMS: exact mass calculated for $C_{20}H_{21}N_6O_3$ $(M + 1)^+$, 393.1675; found, 393.1684.

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**Supporting Information Available:** $^1$H NMR spectra of **3a**−**e**, **5a**−**e**, **6a**−**e**, **8b**−**e**, **9**, **10**, **11**, **12** and **13** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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