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Synthesis and Utility of 2-Halo-O^6-(benzotriazol-1-yl)-Functionalized Purine Nucleosides

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An efficient synthesis of 2-halo-O^6-(benzotriazol-1-yl)-substituted purine nucleosides has been accomplished via (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)-mediated coupling and subsequent halogenation via diazotization of the 2-amino group of various protected guanosines and directly from guanosine itself. These products are amenable to substitution and coupling reactions in the 2- and 6-positions and, accordingly, provide efficient access to highly functionalized purine nucleosides.

Introduction

Nitrogen-containing heterocycles are ubiquitous in nature, exhibit a wide and varied role in biological systems and are of great pharmaceutical importance, including purine nucleosides such as adenosines and guanosines. However, syntheses of these compounds can be challenging and classically require multiple steps, often in a linear fashion, which reduces efficiency and does not lend itself to a convergent approach to drug discovery. Typically, these steps include protection of functional groups, activation, functionalization (via S_NAr) and deprotection.

Previous work in our group has focused on the synthesis of highly substituted 2-, 6- and/or 5′-substituted adenosines, aimed at generating adenosine receptor (AR) agonists more selective and/or potent at the four distinct receptor subtypes, A_1, A_{2A}, A_{2B} and A_3 receptors. This generally requires numerous steps with incorporation of the 2-halo group occurring via stannylation[1] before nucleophilic substitution can take place at the 6-position from either chloro[2] or O^6-(benzotriazol-1-yl)[3] moieties. However, protection of the hydroxy groups, as well as modifications to the 5′-position of the ribose also needed to be undertaken thereby increasing the sequence as well. Alternatively, we have recently reported a more convergent approach utilising a Vorbrüggen coupling strategy, whereby purine and sugar moieties are independently functionalised before undergoing glycosylation.[4,5] However, this method necessitated the presence of the 2-halo group in the starting purine and greater degree of functionality resulted in often capricious reactions. To this end, we strived towards a more streamlined approach to achieve these highly substituted adenosine analogs.

For a number of years, the versatility and efficiency of phosphonium-mediated coupling of tautomerizable heterocycles,[6] in particular nucleosides, has generated widespread attention.[7–12] Previous work by Lakshman et al.[11] as well as our group[3] has shown that it is possible to convert certain protected guanosine derivatives to the corresponding O^6-(benzotriazol-1-yl)guanosines using BOP and DBU. More specifically, TBS-protected guanosine was found to undergo this conversion in 65% yield, while 2′,3′-isopropylidene-protected guanosine-5′-*N*-ethylcarboxamide gave a 95% yield of the corresponding O^6-(benzotriazol-1-yl) derivative. However, this has not been achieved for unprotected guanosine until now. In a related study, Bae et al.[8] also showed that it was possible to generate O^6-(benzotriazol-1-yl)inosine without protection of the 2′-, 3′- and 5′-hydroxy groups in a yield of 53%. In all cases, these O^6-(benzotriazol-1-yl)purine nucleosides were demonstrated to be highly versatile synthetic intermediates that readily underwent substitution in the 6-position with a range of nucleophiles and could also be elaborated further in the 2-position. In this current study, our aim was to further explore the scope and limitations of this chemistry. The requirement for ribose protection and the efficiency of a range of protecting groups were evaluated in the formation of the O^6-(benzotriazol-1-yl)guanosines **2a**–**f**. The conversion of **2a**–**f** to the corresponding 2-halo derivatives **3**–**5** was also explored.

Results and Discussion

Our initial attempt to synthesize O^6-(benzotriazol-1-yl)-guanosine (**2a**) with BOP and DBU in MeCN was successful, but proceeded in low yield (28%). This was due to poor solubility and the majority of recovered material was unre-

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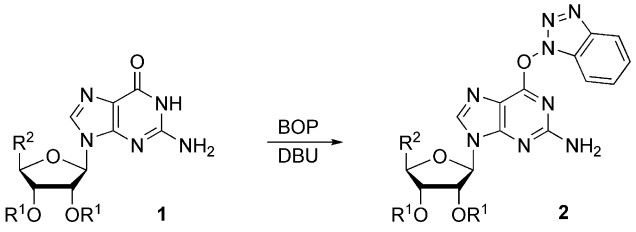
acted guanosine. In a previous study on the conversion of Biginelli 3,4-dihydropyrimidin-2(1*H*)-one to pyrimidines via PyBroP-mediated coupling, the choice of solvent was shown to have significant effect on the isolated yield.[6] Accordingly, we explored the reaction of guanosine with BOP and DBU in a range of solvents and the results are reported in Table 1. This reaction proceeded in low yield in a number of the solvents and guanosine's poor solubility was thought to be a major factor in these outcomes. However, a modest yield of 42% was obtained in DMF and a respectable yield of 59% was obtained when NMP was used as the solvent. Although the O^6-(benzotriazol-1-yl)-substituted guanosine (**2a**) was difficult to extract from NMP due to the water solubility of both species, this problem was largely overcome by submitting the crude reaction mixture directly to a silica column and eluting with a CH_2Cl_2/MeOH gradient (1:0→9:1). This observation of aqueous uptake and poor solubility of inosine was also noted by Bae et al.[8] This outcome is comparable to the previously reported reaction between TBS-protected guanosine and BOP in the presence of DBU (59% vs. 65% yield).[11]

Table 1. Results of the solvent effect for the BOP-mediated reaction on **1**.



a R^1 = H, R^2 = CH_2OH
b R^1 = Ac, R^2 = CH_2OAc
c R^1 = TBS, R^2 = CH_2OTBS
d R^1 = isopropylidene, R^2 = CH_2OH
e R^1 = isopropylidene, R^2 = CONHMe
f R^1 = isopropylidene, R^2 = CONHEt

Entry		R^1	R^2	Solvent	% Yield[a]
1	**1a**	H	CH_2OH	MeCN	28
2	**1a**	H	CH_2OH	NMP	59
3	**1a**	H	CH_2OH	DBU	–
4	**1a**	H	CH_2OH	DMF	42
5	**1a**	H	CH_2OH	CH_2Cl_2	18
6	**1a**	H	CH_2OH	DCE	24
7	**1a**	H	CH_2OH	THF	6
8	**1a**	H	CH_2OH	dioxane	45
9	**1b**	Ac	CH_2OAc	NMP	74
10	**1b**	Ac	CH_2OAc	MeCN	90
11	**1c**	TBS	CH_2OTBS	NMP	69
12	**1c**	TBS	CH_2OTBS	MeCN	75
13	**1d**	2′,3′-IP[b]	CH_2OH	NMP	76
14	**1d**	2′,3′-IP	CH_2OH	MeCN	78
15	**1e**	2′,3′-IP	CONHMe	NMP	55
16	**1e**	2′,3′-IP	CONHMe	MeCN	92
17	**1f**	2′,3′-IP	CONHEt	MeCN	95[3]

[a] Isolated yield after chromatography. [b] IP = isopropylidene.

We proceeded to investigate the reaction of a number of protected/modified guanosines (**1b**–**1f**) with BOP and DBU in both NMP and MeCN (Table 1). These guanosine derivatives were prepared as described previously,[3,13,14] except in the case of **1e** which was synthesized in an analogous fashion to **1f**.[3] Although, these reactions succeeded in NMP, higher yields were obtained when MeCN was used as the reaction solvent. The difference was particularly significant in the case of **2b** (74% in NMP and 90% in MeCN) and **2e** (55% in NMP and 92% in MeCN). Furthermore, the use of MeCN facilitated the reaction work-up as it could be easily evaporated under reduced pressure prior to a typical extractive work-up. Compounds **2b**–**2f** were readily taken up in an organic phase and were not observed in the aqueous phase, presumably due to the absence of the 2′- and 3′-hydroxy groups, therefore enhancing yields. Another attractive feature when using MeCN was evident in the purification in that chromatography was not typically required (unlike the NMP method), and trituration with H_2O (for **2b** and **2d**–**2f**) or Et_2O (for **2a**) routinely gave pure solids.

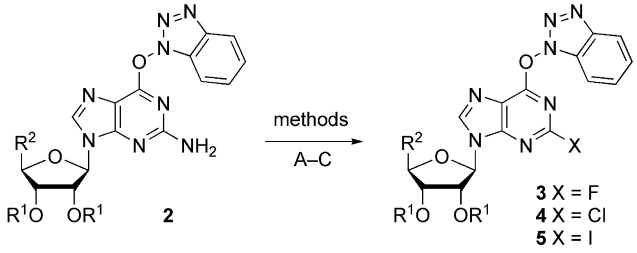
A comparison of the commonly used ribose protecting groups (acetyl, TBS and 2′,3′-isopropylidene), revealed that acetyl-protected guanosine **1b** performed best. This substrate gave a 90% yield of the desired product **2b**, in comparison to yields of 75% and 78% for the TBS and 2′,3′-isopropylidene guanosines, respectively. The 2′,3′-isopropylidene-protected guanosine-5′-*N*-alkylcarboxamides **1e** and **1f** also afforded the desired products in excellent yield (92% and 95%, respectively).

With a series of 2-amino,O^6-(benzotriazol-1-yl) compounds **2a**–**2f** prepared, a range of diazotization/halogenation reactions were undertaken (Table 2).

Fluorination of the nucleosides **2** was achieved using a HF in pyridine complex and *t*BuONO.[15] In the case of **1a**, the reaction was quite capricious and the best result was a yield of 35% of **3a**. This was most likely due to the presence of the free hydroxy groups which invariably reduced the yield. The 5′-hydroxy-containing **3d** also resulted in a poor yield (36%). Deprotection of TBS groups with the fluoride ion is well known and subsequently reaction of **2c** with HF resulted in cleavage of the TBS groups as well as fluorination. However, **3b**, **3e** and **3f** were all fluorinated in good to high yields (59–88%).

The chlorination reaction to produce **4** using TMS-Cl[16] worked well for the hydroxy protected guanosines **2b**, **2c** and **2e**, but failed for **2a** and **2d**. The yields were moderate to high (72–96%), with the 5′-modified methylcarboxamide (**4e**) giving the best result (96%). Changing the solvent from CH_2Cl_2 to MeCN or using $NaNO_2$ in aqueous HCl also failed to produce the 2-chloro analogs, **2a** and **2d**. The presence of unprotected hydroxy groups (**2a** and **2d**) was clearly incompatible with this chlorination reaction. The iodinated compounds **5** were produced using CH_2I_2 and *t*BuONO in MeCN heated by microwave irradiation. All the protecting groups were applicable to this reaction with yields ranging from 56% (**5a**)–96% (**5b**). From the results observed, it was possible to halogenate the unprotected guanosine **2a**, however yields were greatly diminished in comparison to acetyl (**2b**), TBS (**2c**) or amide (**2e**–**2f**) protection and only reproducible in the case of **5a**. Once again, acetyl protecting groups gave the best results, affording yields of 88%, 94%

Table 2. Halogenation reactions of **2a**–**2f**.



a R^1 = H, R^2 = CH_2OH
b R^1 = Ac, R^2 = CH_2OAc
c R^1 = TBS, R^2 = CH_2OTBS
d R^1 = isopropylidene, R^2 = CH_2OH
e R^1 = isopropylidene, R^2 = CONHMe
f R^1 = isopropylidene, R^2 = CONHEt

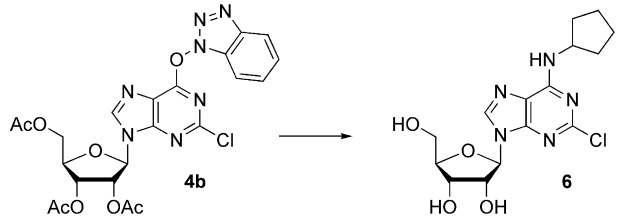
Entry		R^1	R^2	Method[a]	% Yield[b]
1	**2a**	H	CH_2OH	A	35
2	**2a**	H	CH_2OH	B	–[c]
3	**2a**	H	CH_2OH	C	56
4	**2b**	Ac	CH_2OAc	A	88
5	**2b**	Ac	CH_2OAc	B	94
6	**2b**	Ac	CH_2OAc	C	96
7	**2c**	TBS	CH_2OTBS	A	–[c]
8	**2c**	TBS	CH_2OTBS	B	72
9	**2c**	TBS	CH_2OTBS	C	68
10	**2d**	2′,3′-IP[d]	CH_2OH	A	36
11	**2d**	2′,3′-IP	CH_2OH	B	–[c]
12	**2d**	2′,3′-IP	CH_2OH	C	72
13	**2e**	2′,3′-IP	CONHMe	A	74
14	**2e**	2′,3′-IP	CONHMe	B	96
15	**2e**	2′,3′-IP	CONHMe	C	77
16	**2f**	2′,3′-IP	CONHEt	A	59[3]
17	**2f**	2′,3′-IP	CONHEt	C	76[3]

[a] Method A: HF/pyridine, *t*BuONO; Method B: TMS-Cl, *t*BuONO; Method C: CH_2I_2, *t*BuONO. [b] Purified yield after column chromatography. [c] Resulted in decomposition. [d] IP = isopropylidene.

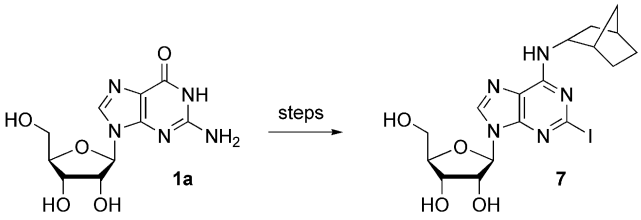
and 96% of the 2-fluoro, 2-chloro and 2-iodo derivatives **3b**, **4b** and **5b**.

To illustrate the applicability of these intermediates towards our ultimate goal of forming selective and efficacious adenosine analogs we chose to synthesise 2-chloro-N^6-cyclopentyladenosine (CCPA)[17] (**6**) (Scheme 1) and 2-iodo-N^6-(*endo*-norborn-2-yl)adenosine[1] (**7**). The only reported synthesis by Jagtap et al. of CCPA was from 2′,3′,5′-triacetoxy-2,6-dichloropurine riboside using excess cyclopentylamine to give CCPA (**6**) in 76% yield. Typically the 2,6-dichloro analogue is obtained in 3 steps from guanosine, via acetylation and chlorination reactions with $POCl_3$, 3-methyl-1-nitro-1-butene and CCl_4[18] or by Vorbrüggen attachment of 2,6-dichloropurine and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose.[5] In our hands, CCPA (**6**) was obtained in 84% yield from the 2′,3′,5′-tri-*O*-acetyl-O^6-(benzotriazol-1-yl)-2-chloroinosine (**4b**) by reaction with cyclopentylamine and subsequent treatment with NH_3.

Hutchinson, et al.[1] previously required 5 steps to produce 2-iodo-N^6-(*endo*-norborn-2-yl)adenosine (**7**) (Scheme 2) from 6-chloropurine riboside in a yield of 22.6%, This sequence included TBS protection, stannylation, N^6-substitution, iodination and TBS removal. 6-Chloropurine riboside was, in turn, prepared from inosine[19] in three steps and 90% yield (eight steps and 20.4% overall). Applying our method from the inexpensive guanosine **1a** achieves an overall yield of 31.4% in 3 steps, eliminating the toxic by-products of tin, amongst other things.



Scheme 1. Formation of CCPA (**6**).



Scheme 2. Synthesis of 2-iodo-N^6-(*endo*-norborn-2-yl)adenosine (**7**).

Conclusions

In conclusion, we have synthesised the first reported synthesis of unprotected O^6-(benzotriazol-1-yl)guanosine (**2a**) via a BOP/DBU-mediated reaction and have shown the utility of this on protected versions **2b**–**2e** of guanosine. In general, the protected O^6-(benzotriazol-1-yl)guanosines **2b**–**2e** gave higher yields of halogenated products in comparison to the unprotected guanosine **2a**. The O^6-(benzotriazol-1-yl)-substituted guanosines **2** are versatile synthetic intermediates that can be readily elaborated into highly functionalized purine ribosides. A range of nucleophiles can substitute at the 6-position to generate a considerable library of compounds. Further derivatization of the 2-amino group to corresponding fluoro (**3**), chloro (**4**) or iodo (**5**) moieties has been demonstrated by diazotization and nucleophilic attack of the halide, typically in good yield. The use of various protecting groups on the ribose moiety demonstrates the ability to incorporate 5′-modified analogs. The 2-fluoro group is amenable to S_NAr processes, the 2-iodo to a wide range of coupling reactions. Therefore, there is wide scope for derivatization of these synthetically useful intermediates to generate a large variety of analogs. These various 2-halo,O^6-(benzotriazol-1-yl)-substituted purine nucleosides **3**–**5** are now in the process of being elaborated to generate novel adenosine analogs with anticipated greater selectivity and efficacy over the different adenosine receptors (AR), with reduced synthetic steps and greater overall yields.

Experimental Section

General Methods: Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. All microwave reactions took place in a Biotage Initiator Microwave Synthesiser. All NMR spectra were recorded on a Bruker Avance III 400-MHz Ultrashield Plus spectrometer and ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.62 MHz, respectively. Thin-layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F_{254}. Column chromatography was achieved using Merck silica gel 60 (article size 0.063–0.200 μm, 70–230 mesh). High resolution mass spectra were obtained on a Waters LCT Premier XE (TOF) mass spectrometer fitted with an ESI ion source, coupled to a 2795 Alliance Separations Module. LCMS were routinely run to verify reaction outcome using an Agilent 6100 Series Single Quad coupled to an Agilent 1200 Series HPLC. All compounds were of > 95% purity. 2′,3′,5′-Tri-*O*-acetylguanosine (**1b**),[13] 2′,3′,5′-*O*-(*tert*-butyldimethylsilyl)guanosine (**1c**),[14] 2′,3′-*O*-isopropylideneguanosine (**1d**)[3] and 2′,3′-*O*-isopropylideneguanosine-5′-*N*-ethylcarboxamide (**1f**)[3] were synthesised as previously published. Guanosine (**1a**) was purchased from Sigma–Aldrich.

2′,3′-*O*-Isopropylideneguanosine-5′-*N*-methylcarboxamide (1e):[20] Methyl 2′,3′-*O*-isopropylideneguanosine-5′-carboxylate[3] (1.00 g, 2.85 mmol) was suspended in a mixture of MeOH/DMF (9:1) (10 mL) and 2.0 M $MeNH_2$ in THF (8 mL) was added. The mixture was heated in a 10–20 mL Biotage vial in the microwave at 100 °C for 2 h. The solution was then evaporated at reduced pressure to give a yellow gum. To this, was added Et_2O (200 mL) and a white precipitate formed, which was filtered, washed with Et_2O and dried to give **1e** (1.00 g, 100%) as a white solid; m.p. 140–142 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 1.32 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.40 (d, J = 4.7 Hz, 3 H, NHCH_3), 4.48 (d, J = 2.3 Hz, 1 H, 4′-H), 5.24 (dd, J = 6.2, 1.6 Hz, 1 H, 3′-H), 5.37 (dd, J = 6.2, 2.4 Hz, 1 H, 2′-H), 6.10 (d, J = 1.7 Hz, 1 H, 1′-H), 6.40 (br. s, 2 H, NH_2), 7.44 (q, J = 4.3 Hz, 1 H, NHCH$_3$), 7.81 (s, 1 H, 8-H), 10.65 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.0, 25.4, 26.7, 83.1, 83.3, 85.8, 88.8, 112.9, 116.6, 136.4, 150.7, 153.6, 156.7, 169.0 ppm. HR-ESMS calcd. for $C_{14}H_{19}N_6O_5^+$ [M + H] 351.1411, found 351.1422.

***O*^{6}-(Benzotriazol-1-yl)guanosine (2a):** To a mixture of guanosine (**1a**) (100 mg, 0.35 mmol, 1 equiv.), BOP (234 mg, 0.53 mmol, 1.5 equiv.) in NMP (2 mL) was added DBU (132 μL, 0.88 mmol, 2.5 equiv.) dropwise and stirred at 25 °C for 16 h. The resultant solution was then worked up in one of two ways: a) added directly to a column containing a large amount of SiO_2 in DCM and flushed with a significant quantity of DCM (to elute the NMP), before increasing the gradient to DCM/MeOH, 9:1 (R_f = 0.17) to give **2a** (83 mg, 59%). Alternatively, b) added to EtOAc (100 mL), washed with H_2O (3 × 15 mL), dried with $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (DCM/MeOH, 9:1 R_f = 0.17) to give **2a** as a colourless solid (21 mg, 15%); m.p. 156–160 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 3.52–3.57 (m, 1 H, 5′-H), 3.62–3.67 (m, 1 H, 5′-H), 3.92 (q, J = 3.9 Hz, 1 H, 4′-H), 4.13 (d, J = 3.6 Hz, 1 H, 3′-H), 4.50 (dd, J = 10.3, 5.1 Hz, 1 H, 2′-H), 5.07 (t, J = 4.9 Hz, 1 H, 5′-OH), 5.20 (d, J = 4.0 Hz, 1 H, OH), 5.49 (d, J = 5.5 Hz, 1 H, OH), 5.84 (d, J = 5.9 Hz, 1 H, 1′-H), 6.73 (br. s, 2 H, NH_2), 7.51–7.55 (m, 1 H, Ar-H), 7.62–7.67 (m, 1 H, Ar-H), 7.76 (d, J = 8.3 Hz, 1 H, Ar-H), 8.17 (d, J = 8.4 Hz, 1 H, Ar-H), 8.35 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 61.4, 70.4, 73.7, 85.5, 86.8, 109.5, 111.4, 120.0, 125.4, 128.6, 129.4, 140.9, 142.9, 156.8, 158.8, 159.4 ppm. HR-ESMS calcd. for $C_{16}H_{17}N_8O_5^+$ [M + H] 401.1316, found 401.1329.

2′,3′,5′-Tri-*O*-acetyl-*O*^{6}-(benzotriazol-1-yl)guanosine (2b): To a mixture of 2′,3′,5′-tri-*O*-acetyl-*O*^{6}-(benzotriazol-1-yl)guanosine (**1b**) (1.00 g, 2.44 mmol, 1 equiv.), BOP (1.62 g, 3.66 mmol, 1.5 equiv.) in MeCN (10 mL) was added DBU (913 μL, 6.11 mmol, 2.5 equiv.) dropwise and stirred at 25 °C for 16 h. The resultant solution was then evaporated under reduced pressure to give an orange gum. This was taken up in EtOAc (100 mL) and washed with H_2O (100 mL). The aqueous phase was then re-extracted with EtOAc (100 mL). The combined organic fractions were then washed with H_2O (3 × 50 mL) and satd. NaCl (2 × 10 mL), dried with $MgSO_4$, filtered and the filtrate evaporated under pressure to give a foam (1.35 g). H_2O (500 mL) was added and the mixture was filtered, washed with H_2O to give (**2b**) as a colourless solid (1.16 g, 90%); m.p. 115–118 °C (dec.) ^{1}H NMR ($CDCl_3$): δ = 2.08 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 4.37 (dd, J = 13.0, 6.1 Hz, 1 H, 5′-H), 4.42–4.48 (m, 2 H, 4′-H, 5′-H), 4.94 (br. s, 2 H, NH_2), 5.76 (t, J = 5.0 Hz, 1 H, 3′-H), 5.97 (t, J = 5.1 Hz, 1 H, 2′-H), 6.04 (d, J = 4.8 Hz, 1 H, 1′-H), 7.42–7.56 (m, 3 H, Ar-H), 7.87 (s, 1 H, 8-H), 8.11 (dt, J = 8.4, 0.9 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.6, 20.7, 20.9, 63.1, 70.6, 72.9, 80.1, 86.8, 109.0, 113.9, 120.5, 124.9, 128.8, 129.0, 140.5, 143.5, 155.7, 158.9, 159.9, 169.5, 169.7, 170.7 ppm. HR-ESMS calcd. for $C_{22}H_{23}N_8O_8^+$ [M + H] 527.1633, found 527.1630.

***O*^{6}-(Benzotriazol-1-yl)-2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)guanosine (2c):**[11] Same procedure as for **2b**, from **1c**, (petroleum ether/EtOAc, 4:1 R_f = 0.23) to give **2c** as a colourless solid (856 mg, 75%); m.p. 157–160 °C (dec.) ^{1}H NMR ($CDCl_3$): δ = –0.11 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.84 [s, 9 H, C(CH$_3$)$_3$], 0.93 [s, 9 H, C(CH$_3$)$_3$], 0.97 [s, 9 H, C(CH$_3$)$_3$], 3.80 (dd, J = 11.5, 2.4 Hz, 1 H, 5′-H), 4.00 (dd, J = 11.5, 3.4 Hz, 1 H, 5′-H), 4.13 (dd, J = 6.6, 3.4 Hz, 1 H, 4′-H), 4.31 (t, J = 4.3 Hz, 1 H, 3′-H), 4.48 (t, J = 4.4 Hz, 1 H, 2′-H), 4.73 (br. s, 2 H, NH_2), 5.95 (d, J = 4.5 Hz, 1 H, 1′-H), 7.42–7.46 (m, 1 H, Ar-H), 7.48–7.55 (m, 2 H, Ar-H), 8.11 (dt, J = 8.4, 0.9 Hz, 1 H, Ar-H), 8.23 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.2 (×2), –4.8, –4.6, –4.5, –4.2, 18.1, 18.2, 18.7, 25.8, 25.9, 26.3, 62.6, 71.9, 76.7, 85.4, 88.1, 109.0, 113.4, 120.5, 124.8, 128.6, 129.0, 140.5, 143.6, 156.1, 158.7, 159.5 ppm. HR-ESMS calcd. for $C_{34}H_{59}N_8O_5Si_3^+$ [M + H] 743.3911, found 743.3947.

***O*^{6}-(Benzotriazol-1-yl)-2′,3′-*O*-isopropylideneguanosine (2d):** Same procedure as for **2b**, from **1d**, (DCM/MeOH, 9:1 R_f = 0.49) to give **2d** as a colourless solid (505 mg, 78%); m.p. 187–189 °C (dec.) ^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 3.76 (d, J = 10.7 Hz, 1 H, 5′-H), 3.94 (dd, J = 12.6, 1.5 Hz, 1 H, 5′-H), 4.50 (d, J = 1.4 Hz, 1 H, 4′-H), 4.95 (br. s, 2 H, NH_2), 5.06 (dd, J = 6.0, 1.3 Hz, 1 H, 3′-H), 5.15–5.18 (m, 1 H, 2′-H), 5.77 (d, J = 7.5 Hz, 1 H, OH), 5.83 (d, J = 4.8 Hz, 1 H, 1′-H), 7.42–7.56 (m, 3 H, Ar-H), 7.81 (s, 1 H, 8-H), 8.10 (d, J = 8.1 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 27.7, 63.5, 81.6, 82.8, 86.0, 93.9, 108.9, 114.5, 114.7, 120.5, 125.0, 128.8, 128.9, 141.5, 143.5, 154.7, 158.3, 160.2 ppm. HR-ESMS calcd. for $C_{19}H_{21}N_8O_5^+$ [M + H] 441.1629, found 441.1644.

***O*^{6}-(Benzotriazol-1-yl)-2′-3′-*O*-isopropylideneguanosine-5′-*N*-methylcarboxamide (2e):** Same procedure as for **2b**, from **1e**, (DCM/MeOH, 9:1 R_f = 0.50) to give **2e** as a colourless solid (1.07 g, 92%); m.p. 195–198 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 1.34 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.35 (d, J = 4.5 Hz, 3 H, NHCH_3), 4.55 (d, J = 2.1 Hz, 1 H, 4′-H), 5.37 (dd, J = 6.1, 1.3 Hz, 1 H, 2′-H), 5.44 (dd, J = 6.1, 2.2 Hz, 1 H, 3′-H), 6.25 (d, J = 1.4 Hz, 1 H, 1′-

H), 6.67 (br. s, 2 H, NH_2), 7.48–7.56 (m, 2 H, Ar-H, CONH), 7.63–7.72 (m, 2 H, Ar-H), 8.18 (d, J = 8.4 Hz, 1 H, Ar-H), 8.21 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.0, 25.3, 26.6, 83.2 (×2), 86.2, 89.1, 109.2, 111.0, 112.8, 120.0, 125.2, 128.5, 129.2, 141.7, 142.8, 156.1, 158.7, 159.2, 168.9 ppm. HR-ESMS calcd. for $C_{20}H_{22}N_9O_5^+$ [M + H] 468.1738, found 468.1745.

***O*^{6}-(Benzotriazol-1-yl)-2′-3′-*O*-isopropylideneguanosine-5′-*N*-ethylcarboxamide (2f):**[3] Same procedure as for **2b**, from **1f**, to give **2f** as a yellow foam (95%); m.p. 140–141 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 0.68 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.35 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.78–2.92 (m, 2 H, CH_2CH_3), 4.52 (d, J = 2.1 Hz, 1 H, 4′-H), 5.40 (d, J = 6.0 Hz, 1 H, 3′-H), 5.51 (dd, J = 2.1, 6.0 Hz, 1 H, 2′-H), 6.28 (s, 1 H, 1′-H), 6.65 (s, 2 H, NH_2), 7.46 (t, J = 6.0 Hz, 1 H, CONH), 7.52–7.56 (m, 1 H, Ar-H), 7.65 (d, J = 3.9 Hz, 2 H, Ar-H), 8.17 (d, J = 8.4 Hz, 1 H, Ar-H), 8.21 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 14.4, 25.5, 27.0, 33.5, 83.7 (× 2), 87.0, 89.6, 109.5, 111.5, 133.1, 120.4, 125.7, 128.9, 129.6, 142.4, 143.3, 156.5, 159.1, 159.5, 168.6 ppm. HR-ESMS calcd. for $C_{21}H_{24}N_9O_5^+$ [M + H] 482.1895, found 482.1901.

***O*^{6}-(Benzotriazol-1-yl)-2-fluoroinosine (3a):** *O*^{6}-(Benzotriazol-1-yl)-guanosine (**2a**) (94 mg, 0.23 mmol) was dissolved in pyridine (1 mL) and cooled in an ice/salt bath. To this was added, 70% HF in pyridine (2 mL) dropwise, followed by *t*BuONO (140 μL, 1.17 mmol) dropwise with vigorous stirring. The reaction was stirred at this temperature for 20 min before being poured onto ca. 100 mL of ice/water and stirred for 30 min. The resultant precipitate was filtered and thoroughly washed with water to give **3a** as a colourless solid (33 mg, 35%); m.p. 189–192 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 3.56–3.62 (m, 1 H, 5′-H), 3.68–3.73 (m, 1 H, 5′-H), 3.99 (q, J = 3.9 Hz, 1 H, 4′-H), 4.18 (dd, J = 9.4, 4.8 Hz, 1 H, 3′-H), 4.53 (dd, J = 10.5, 5.2 Hz, 1 H, 2′-H), 5.08 (t, J = 5.4 Hz, 1 H, OH), 5.28 (d, J = 5.4 Hz, 1 H, OH), 5.61 (d, J = 5.9 Hz, 1 H, 5′-OH), 5.96 (d, J = 5.1 Hz, 1 H, 1′-H), 7.56–7.60 (m, 1 H, Ar-H), 7.67–7.71 (m, 1 H, Ar-H), 7.86 (d, J = 8.3 Hz, 1 H, Ar-H), 8.23 (d, J = 8.4 Hz, 1 H, Ar-H), 8.91 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 60.9, 69.9, 74.0, 85.7, 88.3, 109.5, 117.8 (d, J = 5.0 Hz), 120.0, 125.6, 128.3, 129.6, 142.7, 145.7 (d, J = 3.0 Hz), 155.8 (d, J = 17.6 Hz), 156.0 (d, J = 214.2 Hz), 159.6 (d, J = 17.0 Hz) ppm. HR-ESMS calcd. for $C_{16}H_{15}FN_7O_5^+$ [M + H] 404.1113, found 404.1109.

2′,3′,5′-Tri-*O*-acetyl-*O*^{6}-(benzotriazol-1-yl)-2-fluoroinosine (3b): Same procedure as for **3a**, from **2b**, (DCM/MeOH, 9:1 R_f = 0.75) to give **3b** (440 mg, 88%); m.p. 132–133 °C (dec.) ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 4.35–4.46 (m, 2 H, 5′-H, 5′-H), 4.48 (dd, J = 7.2, 4.0 Hz, 1 H, 4′-H), 5.56 (dd, J = 5.6, 4.3 Hz, 1 H, 3′-H), 5.83 (t, J = 5.6 Hz, 1 H, 2′-H), 6.19 (d, J = 5.6 Hz, 1 H, 1′-H), 7.46–7.53 (m, 2 H, Ar-H), 7.56–7.60 (m, 1 H, Ar-H), 8.15 (dt, J = 8.4, 0.9 Hz, 1 H, Ar-H), 8.23 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5, 20.6, 20.9, 70.6, 73.2, 81.0, 86.8, 108.5, 118.6 (d, J = 5.1 Hz), 120.8, 125.2, 128.7, 129.3, 143.5, 143.7 (d, J = 3.2 Hz), 155.6 (d, J = 16.8 Hz), 157.4 (d, J = 222.3 Hz), 161.1 (d, J = 16.4 Hz), 169.5, 169.7, 170.4 ppm. HR-ESMS calcd. for $C_{22}H_{21}FN_7O_8^+$ [M + H] 530.1430, found 530.1440.

***O*^{6}-(Benzotriazol-1-yl)-2-fluoro-2′,3′-*O*-isopropylideneinosine (3d):** Same procedure as for **3a**, from **2d**, (DCM/MeOH, 9:1 R_f = 0.57) to give **3d** as a colourless solid (35 mg, 36%); m.p. 195–199 °C (dec.) ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 3.82 (m, 2 H, 5′-H, OH), 3.97 (d, J = 11.1 Hz, 1 H, 5′-H), 4.51 (s, 1 H, 4′-H), 5.08 (dd, J = 6.1, 1.8 Hz, 1 H, 3′-H), 5.17 (dd, J = 6.0, 4.3 Hz, 1 H, 2′-H), 6.02 (d, J = 4.2 Hz, 1 H, 1′-H), 7.46–7.50 (m, 2 H, Ar-H), 7.55–7.59 (m, 1 H, Ar-H), 8.14 (d, J = 8.4 Hz, 1 H, Ar-H) 8.27 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.3, 27.6, 63.2, 81.4, 83.7, 86.6, 93.3, 108.5, 114.8, 119.1 (d, J = 5.0 Hz), 120.9, 125.3, 128.7, 129.3, 143.5, 144.9 (d, J = 3.0 Hz), 154.9 (d, J = 16.4 Hz), 157.1 (d, J = 223.7 Hz), 161.1 (d, J = 16.4 Hz) ppm. HR-ESMS calcd. for $C_{19}H_{19}FN_7O_5^+$ [M + H] 444.1426, found 444.1445.

***O*^{6}-(Benzotriazol-1-yl)-2-fluoro-2′,3′-*O*-isopropylideneinosine-5′-*N*-methylcarboxamide (3e):** Same procedure as for **3a**, from **2e**, (DCM/MeOH, 9:1 R_f = 0.45) to give **3e** (40 mg, 74%). ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 2.72 (d, J = 4.9 Hz, 3 H, $NHCH_3$), 4.75 (d, J = 2.0 Hz, 1 H, 4′-H), 5.25 (dd, J = 6.2, 3.4 Hz, 1 H, 2′-H), 5.30 (dd, J = 6.2, 2.1 Hz, 1 H, 3′-H), 6.13 (d, J = 3.4 Hz, 1 H, 1′-H), 6.73 (d, J = 4.4 Hz, 1 H, CONH), 7.46–7.52 (m, 2 H, Ar-H), 7.58 (ddd, J = 8.6, 6.9, 0.9 Hz, 1 H, Ar-H), 8.15 (dd, J = 8.4, 0.9 Hz, 1 H, Ar-H), 8.17 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.2, 25.9, 27.3, 82.5, 83.2, 85.5, 92.2, 108.4, 115.4, 118.9 (d, J = 5.1 Hz), 120.9, 125.3, 128.7, 129.4, 143.6, 144.7 (d, J = 3.2 Hz), 155.1 (d, J = 16.5 Hz), 157.3 (d, J = 223.5 Hz), 161.3 (d, J = 16.5 Hz), 168.7 ppm. HR-ESMS calcd. for $C_{20}H_{20}FN_8O_5^+$ [M + H] 471.1535, found 471.1535.

***O*^{6}-(Benzotriazol-1-yl)-2-fluoro-2′,3′-*O*-isopropylideneinosine-5′-*N*-ethylcarboxamide (3f):**[3] Same procedure as for **3a**, from **2f**, to give **3f** (59%); m.p. 140–145 °C (dec.) ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 1.11 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.35 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.70–2.95 (m, 2 H, CH_2CH_3), 4.61 (s, 1 H, 4′-H), 5.38 (d, J = 4.8 Hz, 1 H, 3′-H), 5.44 (d, J = 4.8 Hz, 1 H, 2′-H), 6.45 (s, 1 H, 1′-H), 7.59 (t, J = 6.3 Hz, 1 H, CONH), 7.65–7.80 (m, 3 H, Ar-H), 8.22 (d, J = 9.5 Hz, 1 H, Ar-H), 8.76 (s, 1 H, 8-H) ppm. ^{13}C NMR (300 MHz, CD_3OD): δ = 14.2, 25.0, 27.0, 34.0, 82.7, 83.2, 85.8, 91.8, 108.3, 115.0, 118.6, 120.7, 125.3, 128.5, 129.3, 143.4, 144.9, 155.1 (J = 16.4 Hz), 157.1 (J = 221.8 Hz), 160.0 (J = 16.4 Hz), 167.9 ppm. HR-ESMS calcd. for $C_{21}H_{22}N_8O_5F^+$ [M + H] 485.1692, found 485.1699.

2′,3′,5′-Tri-*O*-acetyl-*O*^{6}-(benzotriazol-1-yl)-2-chloroinosine (4b): A solution of *t*BuONO (689 μL, 5.79 mmol) in DCM (30 mL) was added TMS-Cl (368 μL, 2.90 mmol) at 0 °C. To this was added drop wise **2b** (305 mg, 0.58 mmol), dissolved in DCM (30 mL), then stirred at 0 °C for 1 h. The solution was then diluted with more DCM (40 mL), washed with H_2O (20 mL), saturated $NaHCO_3$ (20 mL), dried with $MgSO_4$ and evaporated at reduced pressure. The residue was purified by column chromatography (DCM/MeOH, 9:1 R_f = 0.66) to give **4e** (297 mg, 94%). ^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 4.39 (d, J = 3.7 Hz, 2 H, 5′-H, 5′-H), 4.46 (dd, J = 7.9, 3.8 Hz, 1 H, 4′-H), 5.56 (dd, J = 5.5, 4.4 Hz, 1 H, 3′-H), 5.80 (t, J = 5.6 Hz, 1 H, 2′-H), 6.23 (d, J = 5.6 Hz, 1 H, 1′-H), 7.43–7.50 (m, 2 H, Ar-H), 7.53–7.57 (m, 1 H, Ar-H), 8.11 (dt, J = 8.4, 0.8 Hz, 1 H, Ar-H), 8.25 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 20.9, 63.0, 70.6, 73.3, 80.9, 86.7, 108.6, 119.2, 120.7, 125.1, 128.7, 129.1, 143.5, 143.6, 153.2, 155.1, 159.4, 169.5, 169.6, 170.3. HR-ESMS calcd. for $C_{22}H_{21}ClN_7O_5^+$ [M + H] 546.1135, found 546.1160.

***O*^{6}-(Benzotriazol-1-yl)-2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-2-chloroinosine (4c):** Same procedure as for **4b**, from **2c**, (petroleum ether/EtOAc, 4:1 R_f = 0.45) to give **4c** as a colourless foam (50 mg, 72%). ^{1}H NMR ($CDCl_3$): δ = –0.12 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.85 [s, 9 H, $C(CH_3)_3$], 0.93 [s, 9 H, $C(CH_3)_3$], 0.96 [s, 9 H, $C(CH_3)_3$], 3.81 (dd, J = 11.6, 2.4 Hz, 1 H, 5′-H), 4.06 (dd, J = 11.6, 3.8 Hz, 1 H, 5′-H), 4.17 (dt, J = 4.1, 2.6 Hz, 1 H, 4′-H), 4.32 (t, J = 4.4 Hz, 1 H, 3′-H), 4.55 (t, J = 4.2 Hz, 1 H, 2′-H), 6.05 (d, J = 4.1 Hz, 1 H, 1′-H), 7.43–7.50 (m, 2 H, Ar-H),

7.55 (ddd, J = 8.3, 6.7, 0.9 Hz, 1 H, Ar-H), 8.13 (dt, J = 8.4, 0.9 Hz, 1 H, Ar-H), 8.58 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.3, –5.2, –4.8, –4.7, –4.6, –4.2, 18.0, 18.2, 18.7, 25.8, 26.0, 26.2, 62.1, 71.4, 76.4, 85.5, 89.5, 108.7, 119.2, 120.8, 125.1, 128.9, 129.1, 143.6, 144.6, 152.8, 155.0, 159.2 ppm. HR-ESMS calcd. for $C_{34}H_{57}ClN_7O_5Si_3^+$ [M + H] 762.3412, found 762.3424.

O^6-(Benzotriazol-1-yl)-2-chloro-2′,3′-*O*-isopropylideneinosine-5′-*N*-methylcarboxamide (4e): Same procedure as for **4b**, from **2e**, (DCM/MeOH, 9:1 R_f = 0.65) to give **4e** as a colourless solid (757 mg, 96%); m.p. 188–191 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 1.35 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 2.32 (d, J = 4.6 Hz, 3 H, NHCH_3), 4.66 (d, J = 1.9 Hz, 1 H, 4′-H), 5.36 (d, J = 6.1, 2.1 Hz, 1 H, 3′-H), 5.42 (dd, J = 6.1, 1.2 Hz, 1 H, 2′-H), 6.46 (d, J = 1.3 Hz, 1 H, 1′-H), 7.56–7.60 (m, 2 H, Ar-H, CONH), 7.67–7.72 (m, 1 H, Ar-H), 7.75–7.78 (m, 1 H, Ar-H), 8.23 (d, J = 8.5 Hz, 1 H, Ar-H), 8.78 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 25.0, 25.3, 26.6, 83.3 (× 2), 86.6, 90.1, 109.2, 113.0, 118.4, 120.1, 125.6, 128.2, 129.6, 142.7, 146.8, 150.4, 155.4, 158.3, 168.6 ppm. HR-ESMS calcd. for $C_{20}H_{20}ClN_8O_5^+$ [M + H] 487.1240, found 487.1254.

O^6-(Benzotriazol-1-yl)-2-iodoinosine (5a): O^6-(Benzotriazol-1-yl)-guanosine (**2a**) (50.6 mg, 0.107 mmol) was suspended in MeCN (2 mL) in a 2–5 mL Biotage microwave vial. Diiodomethane (250 μL) and isopentylnitrite (68 μL, 0.506 mmol) were added and the microwave vial capped. The mixture was heated in the microwave at 90 °C for 1h. The solution was then added to EtOAc (30 mL) and washed with satd. $NaHCO_3$ (25 mL). The aqueous phase was re-extracted with EtOAc (15 mL), the combined organic extracts combined and washed subsequently with satd. $NaHCO_3$ (15 mL), H_2O (15 mL) and satd. NaCl (10 mL). The organic phase was dried with $MgSO_4$, filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (DCM/MeOH, 9:1 R_f = 0.23) to give **5a** as a pale yellow solid (36 mg, 56%); m.p. 179–182 °C (dec.) ^{1}H NMR ([D$_6$]DMSO): δ = 3.52–3.62 (m, 1 H, 5′-H), 3.64–3.72 (m, 1 H, 5′-H), 3.98 (q, J = 4.0 Hz, 1 H, 4′-H), 4.17 (dd, J = 8.6, 4.6 Hz, 1 H, 3′-H), 4.54 (q, J = 5.4 Hz, 1 H, 2′-H), 5.06 (t, J = 5.2 Hz, 1 H, 5′-OH), 5.29 (d, J = 5.1 Hz, 1 H, OH), 5.59 (d, J = 5.8 Hz, 1 H, OH), 5.99 (d, J = 5.4 Hz, 1 H, 1′-H), 7.55–7.60 (m, 1 H, Ar-H), 7.66–7.70 (m, 1 H, Ar-H), 7.83 (d, J = 8.3 Hz, 1 H, Ar-H), 8.22 (d, J = 8.4 Hz, 1 H, Ar-H), 8.81 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 61.0, 70.1, 74.0, 85.9, 88.0, 109.5, 117.3, 119.0, 120.0, 125.5, 128.4, 129.5, 142.7, 145.0, 155.1, 156.8 ppm. HR-ESMS calcd. for $C_{16}H_{15}IN_7O_5^+$ [M + H] 512.0174, found 512.0178.

2′,3′,5′-Tri-*O*-acetyl-O^6-(benzotriazol-1-yl)-2-iodoinosine (5b): Same procedure as for **5a**, from **2b**, (DCM/MeOH, 19:1 R_f = 0.45) to give **5b** (61 mg, 96%). ^{1}H NMR ($CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 4.39 (dd, J = 3.8, 1.9 Hz, 2 H, 5′-H, 5′-H), 4.47 (dd, J = 7.8, 4.3 Hz, 1 H, 4′-H), 5.58 (dd, J = 5.5, 4.5 Hz, 1 H, 3′-H), 5.79 (dd, J = 5.5 Hz, 1 H, 2′-H), 6.22 (d, J = 5.4 Hz, 1 H, 1′-H), 7.44–7.50 (m, 2 H, Ar-H), 7.56 (ddd, J = 8.2, 6.8, 0.9 Hz, 1 H, Ar-H), 8.12 (dd, J = 7.6, 0.8 Hz, 1 H, Ar-H), 8.16 (s, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5, 20.6, 21.0, 63.0, 70.7, 73.4, 80.9, 86.8, 108.7, 116.3, 120.0, 120.7, 125.1, 128.7, 129.1, 143.0, 143.5, 154.6, 157.7, 169.5, 169.7, 170.4 ppm. HR-ESMS calcd. for $C_{22}H_{21}IN_7O_8^+$ [M + H] 638.0491, found 638.0504.

O^6-(Benzotriazol-1-yl)-2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)-2-iodoinosine (5c): Same procedure as for **5a**, from **2c**, (petroleum ether/EtOAc, 4:1 R_f = 0.46) to give **5c** (44 mg, 68%). ^{1}H NMR ($CDCl_3$): δ = –0.07 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.86 [s, 9 H, $C(CH_3)_3$], 0.92 [s, 9 H, $C(CH_3)_3$], 0.95 [s, 9 H, $C(CH_3)_3$], 3.81 (dd, J = 11.6, 2.4 Hz, 1 H, 5′-H), 4.06 (dd, J = 11.5, 3.9 Hz, 1 H, 5′-H), 4.15–4.18 (m, 1 H, 4′-H), 4.31 (t, J = 4.6 Hz, 1 H, 3′-H), 4.53 (t, J = 4.0 Hz, 1 H, 2′-H), 6.03 (d, J = 3.8 Hz, 1 H, 1′-H), 7.44–7.49 (m, 2 H, Ar-H), 7.53–7.57 (m, 1 H, Ar-H), 8.13 (d, J = 8.3 Hz, 1 H, Ar-H), 8.50 (s, 1 H, 8-H) ppm. ^{1}H NMR ($CDCl_3$): δ = –5.3, –5.1, –4.7, –4.6, –4.5, 4.1, 18.1, 18.2, 18.7, 25.9, 26.0, 26.3, 61.9, 71.1, 76.2, 85.2, 89.7, 108.7, 115.5, 120.1, 120.7, 125.0, 128.9, 129.0, 143.6, 144.0, 154.4, 157.4 ppm. HR-ESMS calcd. for $C_{34}H_{57}IN_7O_5Si_3^+$ [M + H] 854.2768, found 854.2780.

O^6-(Benzotriazol-1-yl)-2-iodo-2′,3′-*O*-isopropylideneinosine (5d): Same procedure as for **5a**, from **2d**, (DCM/MeOH, 9:1 R_f = 0.54) to give **5d** (44 mg, 72%). ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 3.83 (t, J = 10.4 Hz, 1 H, 5′-OH), 3.98 (d, J = 12.6 Hz, 1 H, 5′-H), 4.16 (d, J = 9.3 Hz, 1 H, 5′-H), 4.52 (d, J = 1.8 Hz, 1 H, 4′-H), 5.10 (dd, J = 6.0, 1.6 Hz, 1 H, 3′-H), 5.16–5.19 (m, 1 H, 2′-H), 5.95 (d, J = 4.7 Hz, 1 H, 1′-H), 7.45–7.51 (m, 2 H, Ar-H), 7.55–7.59 (m, 1 H, Ar-H), 8.10 (s, 1 H, 8-H), 8.14 (d, J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 27.7, 63.3, 81.5, 83.2, 86.4, 93.8, 108.6, 114.8, 116.0, 120.8, 121.1, 125.2, 128.8, 129.2, 143.6, 144.5, 154.1, 158.0 ppm. HR-ESMS calcd. for $C_{19}H_{19}IN_7O_5^+$ [M + H] 552.0487, found 552.0493.

O^6-(Benzotriazol-1-yl)-2-iodo-2′,3′-*O*-isopropylideneinosine-5′-*N*-methylcarboxamide (5e): Same procedure as for **5a**, from **2e**, (DCM/MeOH, 9:1 R_f = 0.49) to give **5e** (48 mg, 77%). ^{1}H NMR ([D$_6$]-DMSO): δ = 1.35 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 2.32 (d, J = 4.6 Hz, 3 H, NHCH_3), 4.63 (d, J = 1.9 Hz, 1 H, 4′-H), 5.36 (dd, J = 6.1, 2.1 Hz, 1 H, 3′-H), 5.39 (dd, J = 6.2, 0.8 Hz, 1 H, 2′-H), 6.45 (d, J = 0.7 Hz, 1 H, 1′-H), 7.51 (q, J = 4.2 Hz, 1 H, CONH), 7.55–7.60 (m, 1 H, Ar-H), 7.66–7.76 (m, 2 H, Ar-H), 8.23 (d, J = 8.4 Hz, 1 H, Ar-H), 8.66 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 25.0, 25.4, 26.6, 83.3, 83.4, 86.8, 89.9, 109.2, 113.0, 117.0, 118.9, 120.1, 125.5, 128.3, 129.5, 142.7, 146.1, 154.9, 156.7, 168.6 ppm. HR-ESMS calcd. for $C_{20}H_{20}IN_8O_5^+$ [M + H] 579.0596, found 579.0607.

2-Iodo-N^6-(*endo*-norborn-2-yl)adenosine (7):[1] O^6-(Benzotriazol-1-yl)-2-iodoinosine (**5a**) (69.6 mg, 0.14 mmol) was suspended in *t*BuOH (3 mL) in a 2–5 mL Biotage microwave vial. DIPEA (119 μL, 0.68 mmol) and (±)-*endo*-2-norbornylamine hydrochloride (30 mg, 0.20 mmol) were added and the microwave vial capped. The mixture was heated in the microwave at 80 °C for 3 h. The yellow solution was evaporated and purified by column chromatography (DCM/MeOH, 9:1 R_f = 0.31) to give **7** (63 mg, 95%). ^{1}H NMR (MeOD): δ = 0.97–1.05 (m, 1 H, CH), 1.32–1.44 (m, 3 H, CH, CH_2), 1.52–1.72 (m, 3 H, CH, CH_2), 2.08–2.18 (m, 2 H, CH_2), 2.25 (br. s, 1 H, CH), 2.59 (br. s, 1 H, CH), 3.74 (dd, J = 12.5, 2.9 Hz, 1 H, 5′-H), 3.88 (dd, J = 12.5, 2.6 Hz, 1 H, 5′-H), 4.15 (q, J = 2.5 Hz, 1 H, 4′-H), 4.31 (dd, J = 5.0, 3.0 Hz, 1 H, 3′-H), 4.35 (br. s, 1 H, NHCH), 4.67 (t, J = 5.6 Hz, 1 H, 2′-H), 5.89 (d, J = 6.1 Hz, 1 H, 1′-H), 8.15 (s, 1 H, 8-H) ppm. ^{13}C NMR (MeOD): δ = 22.4, 30.7, 37.9, 38.1, 39.1, 41.5, 53.7, 63.3, 72.4, 75.4, 87.9, 91.1, 120.9, 121.0, 141.0, 149.5, 155.4 ppm. HR-ESMS calcd. for $C_{17}H_{23}IN_5O_4^+$ [M + H] 488.0789, found 488.0804.

2-Chloro-N^6-cyclopentyladenosine (6):[17] 2′,3′,5′-Tri-*O*-acetyl-O^6-(benzotriazol-1-yl)-2-chloroinosine (**4b**) (91 mg, 0.17 mmol) was dissolved in MeCN (3 mL) in a 2–5 mL Biotage microwave vial. To this was added cyclopentylamine (82 μL, 0.83 mmol) and stirred at 25 °C for 2 h, at which time all starting material was completely consumed by LCMS. To this solution was added NH_4OH (500 μL), the microwave vial capped and heated in the microwave at 80 °C for 2h. The solution was evaporated at reduced pressure and the residue purified by column chromatography (DCM/MeOH, 9:1 R_f = 0.30) to give **6** (52 mg, 84%). ^{1}H NMR (MeOD): δ = 1.61–1.74 (m, 4 H, CH_2, CH_2), 1.79–1.86 (m, 2 H, CH_2), 2.08–2.14 (m, 2 H,

CH_2), 3.77 (dd, J = 12.5, 2.9 Hz, 1 H, 5′-H), 3.91 (dd, J = 12.5, 2.6 Hz, 1 H, 5′-H), 4.17 (q, J = 2.8 Hz, 1 H, 4′-H), 4.33 (dd, J = 5.1, 3.0 Hz, 1 H, 3′-H), 4.53–4.56 (m, 1 H, NH*CH*), 4.69 (dd, J = 6.0, 5.2 Hz, 1 H, 2′-H), 5.92 (d, J = 6.1 Hz, 1 H, 1′-H), 8.25 (s, 1 H, 8-H) ppm. ^{13}C NMR (MeOD): δ = 24.7, 33.7, 53.6, 63.3, 72.4, 75.4, 87.9, 91.0, 120.1, 141.4, 150.2, 155.4, 156.2 ppm. HR-ESMS calcd. for $C_{15}H_{21}ClN_5O_4^+$ [M + H] 370.1277, found 370.1283.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of **1e**, **2a**–**2e**, **3a**–**3e**, **4b**–**4e**, **5a**–**5e**, **6** and **7**.

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