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Linear and convergent approaches to 2-substituted adenosine-5′-*N*-alkylcarboxamides

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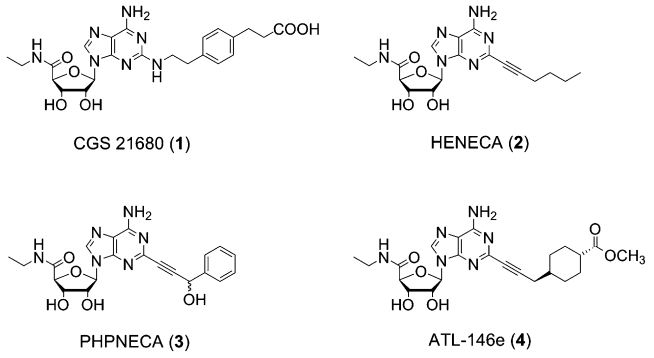
ABSTRACT

Herein we report both linear and convergent pathways for the preparation of 2-alkynyl substituted adenosine-5′-*N*-ethylcarboxamides via the versatile synthetic intermediate, 2-iodoadenosine-5′-*N*-ethylcarboxamide (**13**). The linear approach afforded **13** in an overall yield of 30% from guanosine over eight synthetic steps. The convergent approach was shorter, but proceeded in lower yield (five steps, 20% yield). Both approaches compare favourably with previously reported syntheses of **13**, which has been prepared in 15% yield from guanosine over nine steps. 2-Iodoadenosine-5′-*N*-ethylcarboxamide (**13**) was subsequently converted to HENECA (**2**) and PHPNECA (**3**) to exemplify the utility of this approach for the preparation of potent A_{2A} adenosine receptor agonists. The linear approach was also amenable to the synthesis of 2-fluoropurine ribosides, which were subsequently elaborated into 2-alkylaminoadenosine-5′-*N*-ethylcarboxamides. Furthermore, both of these synthetic approaches are readily amenable to the synthesis of adenosine analogues with varied 2-, 6- and 5′-substitution patterns.

1. Introduction

2-Substituted adenosine-5′-*N*-alkylcarboxamides are an important class of compound, many of which are agonists at the A_{2A} adenosine receptor (A_{2A}AR).[1] The synthesis and cardiovascular activity of 5′-*N*-ethylcarboxamidoadenosine (NECA) was reported in 1980.[2] Further substitution of the 2-position lead to the discovery of 2-[4-(2-carboxyethyl)phenylethyl]amino-5′-*N*-ethylcarboxamide (CGS 21680, **1**),[3] which is selective for the rat A_{2A}AR, and has seen widespread use as a pharmacological tool for the study of this receptor. 2-Alkynyl substituted adenosine-5′-*N*-carboxamides such as 2-(hexyn-1-yl)adenosine-5′-*N*-ethylcarboxamide (HENECA, **2**) and 2-(*R*,*S*)-phenylhydroxypropynyladenosine-5′-*N*-ethylcarboxamide ((*R*,*S*)-PHPNECA, **3**) have also proven to be potent A_{2A}AR agonists.[4,5] More recently, another 2-alkynyl substituted derivative, Apadenoson (ATL-146e, **4**),[6] entered phase III clinical trials as a pharmacologic stress agent for use in myocardial perfusion imaging.

2-Alkynyl adenosine-5′-*N*-ethylcarboxamides such as HENECA (**2**), (*R*,*S*)-PHPNECA (**3**) and ATL-146e (**4**) are typically prepared from 2-iodoadenosine-5′-*N*-ethylcarboxamide (2-iodoNECA) via Sonogashira coupling with the appropriate terminal alkyne.[4–6] 2-IodoNECA was originally synthesised from 2-iodoadenosine in five steps in 26% yield,[4] which was in turn prepared from guanosine in four steps in yields ranging from 45 to 58% yield (i.e., 12–15% over nine steps).[7,8] Herein we report two different and higher yielding synthetic pathways to 2-iodoNECA and the 2-alkynyl derivatives, **2** and **3**. The first of these is a more convergent approach, which features a microwave-assisted Vorbrüggen coupling step to form the purine riboside core. The second synthesis is a linear sequence from guanosine, which employs a new methodology for the amination of the 6-position. Both approaches afforded 2-iodoNECA in fewer synthetic steps and higher overall yield than previously reported methods.



2. Results and discussion

2,6-Dihalopurines, such as 6-chloro-2-iodopurine (**6**), are common intermediates for the synthesis of a range of 2,6-disubstituted

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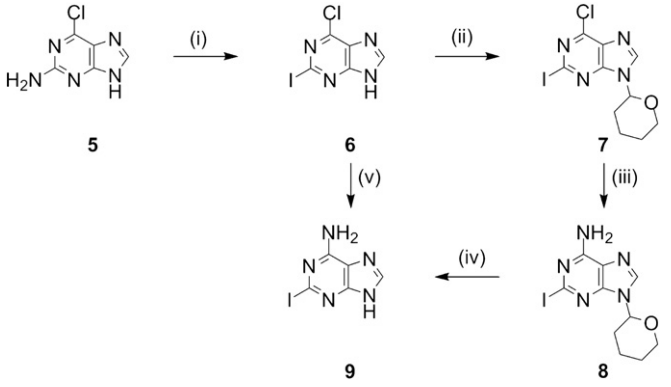
adenosines and purine ribosides. The presence of a 2-iodo moiety is particularly advantageous for the synthesis of 2-alkynyl purines via Sonogashira coupling reactions. The synthesis of 6-chloro-2-iodopurine (**6**) was achieved from commercially available 2-amino-6-chloropurine (**5**) in one high yielding step (73% isolated yield) (Scheme 1). This diazotisation–iodination sequence employed standard reagents (*iso*-amylnitrite, CuI, CH_2I_2, DMF) and microwave irradiation. Preparation of 6-chloro-2-iodopurine (**6**) previously required a multiple step synthesis, such as the five-step process outlined by Taddei et al.[9] In addition to the longer synthetic sequence needed, this approach also required relatively expensive reagents such as 2,2,6,6-tetramethylpiperidine, which were essential for the selective substitution of the 2-position.[10]



Scheme 1. Synthesis of 2-iodo-6-aminopurine. Method A: (i) *iso*-amylnitrite, CuI, CH_2I_2, DMF, MW, 120 °C, 2 h, 73%; (ii) dihydropyran, THF, TsOH, 66 °C, 16 h, 78%; (iii) MeOH/NH_3, 25 °C, 7 days, 90%; (iv) $CuCl_2$, EtOH/H_2O (95:5), 25 °C, 16 h, 89%. Method B: (i) *iso*-amylnitrite, CuI, CH_2I_2, DMF, MW, 120 °C, 2 h, 73%; (v) NH_4Cl, DIPEA, *i*-PrOH, MW, 150 °C, 2 h, 91%.

The conversion of 6-chloro-2-iodopurine (**6**) to 2-iodoadenine (**9**) was subsequently investigated. Amination of 6-halogenated purines generally requires either a protecting group or a sugar at the *N*-9-position due to their poor solubility in most organic solvents.[9] Accordingly, 6-chloro-2-iodopurine (**6**) was protected as the tetrahydropyran-2-yl derivative (**7**) and reacted with methanolic ammonia at 60 °C. This procedure resulted in the formation of substantial amounts of the corresponding 2,6-diaminopurine. Maximum yields (90%) of 2-iodo-9-(tetrahydropyran-2-yl)adenine (**7**) were achieved by the stirring of the starting materials at 25 °C for 7 days. Deprotection using copper (II) chloride afforded 2-iodoadenine (**9**) in 89% yield. This approach afforded 2-iodoadenine (**9**) in an overall yield of 46% in four steps from 2-amino-6-chloropurine (**5**).

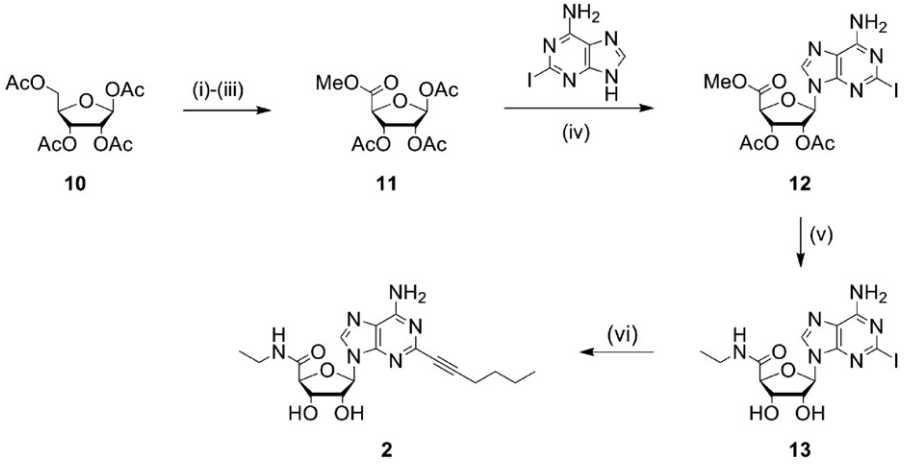
We subsequently found that 6-chloro-2-iodopurine (**6**) could be converted to 2-iodoadenine (**9**) directly without the need for *N*-9 protection using a microwave reactor. The reaction of 6-chloro-2-iodopurine (**6**) with 3.5 equiv of NH_4Cl and a base at 150 °C for 2 h afforded 2-iodoadenine (**9**) in 91% yield. This was the preferred method for the synthesis of 2-iodoadenine (**9**), which was obtained in an overall yield of 66% over two steps from commercially available 2-amino-6-chloropurine (**5**).

2-Iodoadenine (**9**) was subsequently evaluated as a coupling partner for the synthesis of the corresponding adenosines via a Vorbrüggen coupling approach. We recently reported a high yielding synthesis of highly functionalised adenosines, which utilised microwave irradiation in the key Vorbrüggen coupling step.[11] The other coupling partner, methyl 1,2,3-tri-*O*-acetyl-β-D-ribofuronate (**11**), was prepared from commercially available 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranoside (**10**) using the conditions described in this report (Scheme 2). However, the coupling of 2-iodoadenine (**9**) with methyl 1,2,3-tri-*O*-acetyl-β-D-ribofuronate (**11**) afforded a moderate 55% yield of the desired 2-iodoadenosine (**12**). 2-Iodoadenosine-2′,3′-*O*-diacetyl-5′-methylcarboxylate (**12**) was subsequently converted to 2-iodoNECA (**13**) in one step in 61% yield. A Sonogashira coupling reaction of 2-iodoNECA (**9**) with 1-hexyne afforded HENECA (**2**) in six steps in an overall yield of 15%.

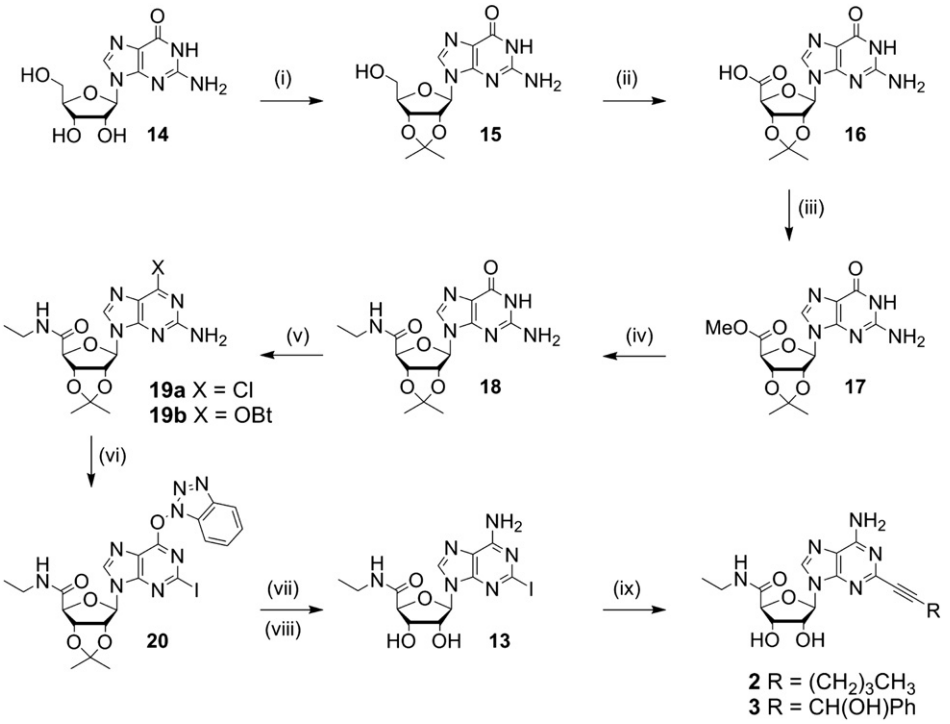
A linear approach from guanosine was also investigated resulting in an eight-step process (Scheme 3) to the common intermediate 2-iodoNECA (**13**) with a superior overall yield of 30%. This process was initiated with the protection of guanosine with an isopropylidene group, followed by oxidation of the 5′-alcohol (**15**) to the corresponding carboxylic acid (**16**) using a BAIB–TEMPO oxidation reaction.[12] Unlike other traditional oxidations, which employ toxic transition metal reagents such as CrO_3, the BAIB–TEMPO oxidation offers mild conditions and produces less toxic by-products.[12]

The introduction of the 5′-*N*-ethylcarboxamide proved to be more challenging than expected. The reaction of the carboxylic acid (**16**) with ethylamine and the carbodiimide activating agent, EDCI, proceeded in low yield. This transformation was ultimately achieved by first forming the corresponding methylcarboxylate (**17**), which was subsequently treated with ethylamine in a reaction bomb for several days to form the carboxamide (**18**). These steps proceeded in yields of 61% and 98%, respectively.

Activation of the 6-position was initially attempted via halogenation. However, the reaction of **18** with $POCl_3$ in the presence of *N*,*N*-dimethylaniline proved to be capricious and low yielding. Bae



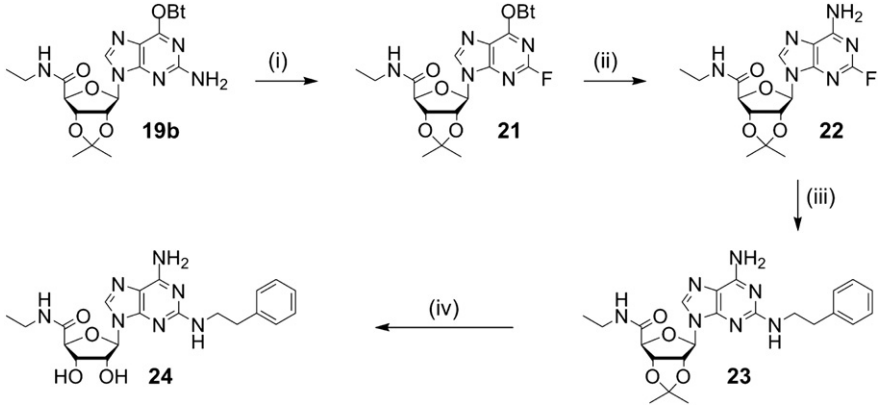
Scheme 2. (i) *Candida rugosa* lipase, 0.1 M sodium phosphate buffer (pH 7.0), 1,4-dioxane, rt 16 h, 91%[11]; (ii) TEMPO, BAIB, MeCN/H_2O (1:1), 25 °C, 16 h, 72%[11]; (iii) EDCI, DMAP, MeOH, 25 °C, 4 h, 92%[11]; (iv) **9**, HMDS, MeCN, $(NH_4)_2SO_4$, MW, 110 °C, 3 h, 55% (v) $EtNH_2$, THF, MW, 110 °C, 3 h, 61%; (vi) THF, Et_3N, CuI, $PdCl_2(PPh_3)_2$, alkyne, 25 °C, 4 days, 76%.



Scheme 3. (i) Acetone, TsOH, $(CH_3)_2C(OCH_3)_2$, 25 °C, 16 h, 94%; (ii) TEMPO, BAIB, MeCN/H_2O (1:1), 25 °C, 16 h, 72%; (iii) $SOCl_2$, MeOH, 0 °C→25 °C, 16 h, 61%; (iv) $EtNH_2$, MeOH/DMF (9:1), 70–75 °C, 3 days, 98%; (v) for X=Cl: $POCl_3$, DMA, Et_4NCl, MeCN, reflux, 1 h, 36%; for X=OBt: BOP, DBU, MeCN, 25 °C, 16 h, 95%; (vi) *t*-BuONO, CH_2I_2, 85 °C, 1 h, 88%; (vii) NH_4OH, MeCN, 25 °C, 3 days, 96%; (viii) TFA, H_2O, 50 °C, 3 h, 93%; (ix) $PdCl_2(PPh_3)_2$, alkyne, Et_3N, CuI, THF, 25 °C, 4 days, 76% for **2**, 56% for **3**.

and Lakshman recently reported that inosine could be converted to the corresponding O^6-(benzotriazol-1-yl) derivative using 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP).[13] These researchers also found that O^6-(benzotriazol-1-yl)inosine reacted cleanly with a variety of nucleophiles, including amines to give the corresponding 6-substituted products. Accordingly, we prepared the O^6-(benzotriazol-1-yl) derivative of 2′,3′-*O*-isopropylideneguanosine-5′-*N*-ethylcarboxamide (**18**) in excellent (95%) yield using the BOP reagent. Diazotisation and iodination of the 2-position produced the versatile synthetic intermediate (**20**), which was well poised for selective substitution of the 2- and 6-positions. A 6-amino substituent was introduced prior to the cleavage of the isopropylidene protecting group to afford 2-iodoadenosine-5′-*N*-ethylcarboxamide (**13**) in high yield. This compound was used to prepare the known A_{2A} agonists, HENECA (**2**) and (*R*,*S*)-PHPNECA (**3**), following Sonogashira coupling with the appropriate alkyne (Scheme 3).

This synthetic approach is also amenable to the incorporation of other substituents in the 2-position. One example, shown in Scheme 4, is the preparation of 2-alkylamino adenosines. In this case, the key 2-amino intermediate **19b** is diazotised and fluorinated prior to the introduction of the 6-amino and 2-phenethylamino groups via nucleophilic aromatic substitution reactions. Cleavage of the isopropylidene protecting group afforded the known A_{2A}AR agonist, 2-phenethylaminoadenosine-5′-*N*-ethylcarboxamide (**24**).



Scheme 4. (i) Pyridine-HF, *t*-BuONO, −20 °C, 20 min, 59%; (ii) NH_4OH, MeCN, 0 °C→25 °C, 2 h, 88%; (iii) phenethylamine, DIPEA, EtOH, 110 °C, 3 days, 47%; (iv) 1 M HCl, 60 °C, 5 h, 80%.

3. Conclusions

In conclusion, we have optimised convergent and linear routes to 2-alkynyladenosine-5′-*N*-alkylcarboxamides. Both routes proceeded via the common synthetic intermediate, 2-iodoNECA (**13**), which was coupled with the appropriately substituted terminal alkyne in the final step. The convergent approach afforded **13** in 20% yield over five-synthetic steps. The linear approach required a longer sequence of reactions, but gave a higher overall yield (30%

yield over eight steps). Both approaches compare favourably with previously reported methods in which **13** has been prepared from guanosine in 12–15% yield over nine steps. 2-IodoNECA (**13**) was subsequently coupled with hexyne and (*R*,*S*)-1-phenyl-2-propyn-1-ol under standard Sonogashira coupling conditions to give HENECA (**2**) and (*R*,*S*)-PHPNECA (**3**), respectively, to exemplify the utility of this chemistry for the preparation of potent A_{2A}AR agonists.

The linear approach featured an improved procedure for functionalising the 6-position of the purine, which involved activation using 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate and subsequent nucleophilic displacement of the resultant 6-benzotriazol-1-yloxy moiety. The 6-OBt group was introduced in 95% yield, which compares favourably with the modest 35% yield obtained for the phosphorous oxychloride mediated chlorination of this position. This approach was also readily amenable to the introduction of alkylamino functionality in the 2-position via the substitution of **22**.

Both of the synthetic approaches described herein are readily amenable to the preparation of a range of adenosine-5′-*N*-alkylcarboxamides, which are functionalised in the 2- and N^6-positions.

4. Experimental

4.1. General experimental

Starting materials were purchased from either Sigma–Aldrich or Advanced Molecular Technologies and had a purity of 96% or greater. Microwave reactions were performed using a Biotage Initiator 2.0. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer or a Varian Unity Inova 600 MHz spectrometer. Optical rotations were measured on a Jasco P-2000 Polarimeter. Infrared spectra were recorded with a Scimitar Series Varian 800 FT-IR Spectrometer fitted with a PIKE Technologies MIRacle ATR and neat samples were used. Low resolution electrospray mass spectra (LRMS) using electrospray ionisation (ESI) were obtained on a Micromass Platform II spectrometer. Unless otherwise stated, cone voltage was 20 eV. High resolution mass spectra (HRMS) were obtained on a Waters LCT Premier XE (TOF) spectrometer fitted with an electrospray ion source.

4.2. Synthesis of 2-(hexyn-1-yl)adenosine-5′-*N*-ethylcarboxamide (2)[4,14]

Compound **13** (32 mg, 0.074 mmol) was dissolved in THF (10 mL) under an atmosphere of N_2. Et_3N (1 mL) and CuI (10 mg, 0.053 mmol) were added to the solution forming a suspension. The mixture was de-gassed by bubbling N_2 through the reaction mixture for 30 min. Addition of $PdCl_2(PPh_3)_2$ (13 mg, 0.019 mmol), followed promptly by hexyne (17 μL, 0.15 mmol) caused the mixture to change from yellow to black, this was stirred at 25 °C for 16 h before additional $PdCl_2(PPh_3)_2$ (13 mg, 0.019 mmol) and hexyne (17 μL, 0.15 mmol) were added and stirred for a further 3 days. The crude mixture was loaded onto silica gel and purified via column chromatography using gradient elution from DCM to DCM/MeOH (9:1) to yield a tan solid 22 mg (76%), mp: 145–146 °C, (lit.[14] mp 147–150 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ: 0.93 (t, 3H, J=7.2 Hz), 1.13 (t, 3H, J=6.9 Hz), 1.50–1.55 (m, 2H), 1.60–1.66 (m, 2H), 2.43 (t, 2H, J=6.9 Hz), 3.35–3.47 (m, 2H), 4.32 (br s, 1H), 4.39 (br s, 1H), 4.64 (br s, 1H), 4.82 (br s, 2H), 5.97 (d, 1H, J=8.4 Hz), 6.81 (br s, 2H), 8.21 (s, 1H), 8.72 (br s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 13.9, 15.4, 18.3, 21.9, 30.3, 49.0, 73.6, 76.6, 86.2, 88.2, 108.3, 109.5, 117.1, 140.1, 145.9, 156.4, 158.8, 169.7; HRMS (ESI) m/z calcd for $C_{18}H_{25}N_6O_4^+$ [M+H] 389.1932, found: 389.1945.

4.3. Synthesis of (*R*,*S*)-2-(3-phenyl-3-hydroxy-1-propyn-1-yl)adenosine-5′-*N*-ethylcarboxamide ((*R*,*S*)-PHPNECA) (3)[5]

Compound **13** (32 mg, 0.074 mmol) was dissolved in THF (10 mL) under an atmosphere of N_2. Et_3N (1 mL) and CuI (10 mg, 0.053 mmol) were added to the solution forming a suspension, the mixture was de-gassed by bubbling N_2 through the reaction mixture for 30 min. Addition of $PdCl_2(PPh_3)_2$ (13 mg, 0.019 mmol), followed promptly by (*R*,*S*)-1-phenyl-2-propyn-1-ol (19 μL, 0.15 mmol) caused the mixture to change from yellow to black, this was stirred at 25 °C for 16 h before more $PdCl_2(PPh_3)_2$ (13 mg, 0.019 mmol) and (*R*,*S*)-1-phenyl-2-propyn-1-ol (19 μL, 0.15 mmol) were added and stirred for a further 4 days. The crude mixture was loaded onto silica gel and purified via column chromatography using gradient elution from DCM to DCM/MeOH (4:1) to yield a grey solid (18 mg, 56%), mp: 146–147 °C, (lit.[5] mp 135–137 °C dec); ^{1}H NMR (300 MHz, CD_3OD) δ: 0.95 (t, 3H, J=7.2 Hz), 2.95–3.06 (m, 2H), 4.16 (s, 1H), 4.33 (s, 1H), 4.60 (s, 1H), 5.53 (s, 1H), 5.69 (s, 1H), 5.97 (s, 1H), 7.39–7.45 (m, 5H), 8.44 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 14.8, 34.1, 64.3, 83.6, 84.2, 85.9, 86.6, 91.9, 112.4, 116.6, 126.5, 127.9, 128.4, 137.1, 139.8, 152.2, 153.0, 156.3, 169.0; HRMS (ESI) m/z calcd for $C_{21}H_{23}N_6O_5^+$ [M+H] 439.1724, found: 437.1731.

4.4. Synthesis of 2-iodo-6-chloropurine (6)[9]

In a 10–20 mL microwave tube, 2-amino-6-chloropurine (**5**) (200 mg, 1.20 mmol) was dissolved in DMF (8 mL). CuI (23 mg, 0.12 mmol), CH_2I_2 (1.5 mL) and *iso*-amylnitrite (800 μL, 6.00 mmol) were added and the reaction mixture was heated to 120 °C for 2 h in the microwave. The solvents were evaporated under reduced pressure and the resultant oil loaded onto a silica gel plug ($\sim$100 g), the impurities were removed by eluting with 500 mL of hexane/EtOAc (4:1), elution of the product was achieved using EtOAc (500 mL) leaving a brown oil, which was triturated with hexane/EtOAc (4:1) and a few drops of conc. HCl to yield a cream powder (242 mg, 73%), mp: 210 °C dec, (lit.[9] mp 200 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.63 (s, 1H), 13.87 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 117.7, 129.7, 147.1, 147.4, 156.1; HRMS (ESI) m/z calcd for $C_5H_3ClIN_4^+$ [M+H] 280.9085, found: 280.9094.

4.5. Synthesis of 2-iodo-6-chloro-9-(tetrahydropyran-2-yl)-purine (7)[9]

The purine **6** (1.00 g, 3.57 mmol) was dissolved in THF (10 mL) under an atmosphere of N_2. 3,4-Dihydro-2*H*-pyran (1.30 mL, 14.30 mmol) and *p*-toluenesulfonic acid (68 mg, 0.36 mmol) were added and the reaction mixture heated to reflux overnight. Upon cooling, H_2O (100 mL) was added and the product extracted using EtOAc (3×100 mL). The organic fractions were combined, washed with H_2O (100 mL), brine (100 mL), then dried using Na_2SO_4. The solvents were removed under reduced pressure to yield an oil. Trituration with hexane afforded a yellow solid (1.03 g, 78%), mp: 112–114 °C, (lit.[9] mp 112–113 °C dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41–1.45 (m, 3H), 1.65–1.88 (m, 2H), 1.94–2.00 (m, 1H), 3.79 (t, 1H, J=9.6 Hz), 4.19 (d, 1H, J=12.3 Hz), 5.77 (d, 1H, J=10.5 Hz), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.1, 24.7, 31.9, 68.9, 82.4, 116.6, 131.5, 143.4, 150.0, 151.6; HRMS (ESI) m/z calcd for $C_{10}H_{11}ClIN_4O^+$ [M+H] 364.9661, found: 364.9675.

4.6. Synthesis of 2-iodo-9-(tetrahydropyran-2-yl)adenine (8)

A solution of **7** (500 mg, 1.37 mmol) in MeOH (10 mL) was cooled to 0 °C in a pressure tube. Gaseous NH_3 was slowly bubbled through this solution for 30 min before the tube was sealed and stirred at room temperature for 7 days. The solvents were removed under reduced pressure and the resultant solid was purified on

a silica gel column using EtOAc as the eluent (R_f=0.57) to yield the desired product as a white powder (427 mg, 90%), mp: 209–210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.45–1.48 (m, 2H), 1.76–1.80 (m, 2H), 1.97–2.03 (m, 2H), 3.68–3.72 (m, 2H), 5.55 (d, 1H, J=10.8 Hz), 7.67 (s, 2H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 22.8, 25.0, 30.8, 68.2, 81.2, 119.0, 121.5, 139.3, 149.8, 156.4; HRMS (ESI) m/z calcd for $C_{10}H_{13}IN_5O^+$ [M+H] 346.0159, found: 346.0163.

4.7. Synthesis of 2-iodoadenine (9)

4.7.1. Method A. To a solution of **8** (173 mg, 0.48 mmol) in 95:5 EtOH/H_2O (25 mL), $CuCl_2$ (13 mg, 0.10 mmol) was added and the reaction mixture stirred at reflux overnight. Upon cooling, the reaction mixture was evaporated to dryness to afford a green solid. This solid was suspended in a 1 M HCl solution (50 mL) then filtered, resulting in 115 mg (89%) of a tan solid as the product, mp: 258–260 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.56 (br s, 2H), 8.04 (s, 1H), 12.98 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 117.2, 121.0, 139.9, 152.6, 155.9; HRMS (ESI) m/z calcd for $C_5H_5IN_5^+$ [M+H] 261.9584, found: 261.9585.

4.7.2. Method B. Purine (**6**) (150 mg, 0.53 mmol), NH_4Cl (100 mg, 1.87 mmol), DIPEA (1.5 mL) and *i*-PrOH (3.5 mL) were added to 2–5 mL microwave vial and heated at 150 °C for 2 h. The mixture was cooled to room temperature, filtered and the filtrate evaporated under reduced pressure. To this oil, H_2O (100 mL) was added and the precipitate that formed was collected by filtration and washed with H_2O to give a yellow solid (**9**) (127 mg, 91%).

4.8. Synthesis of 2-iodoadenosine-2′,3′-*O*-diacetyl-5′-methylcarboxylate (12)

2-Iodo-6-aminopurine (**9**) (50 mg, 0.19 mmol), $(NH_4)_2SO_4$ (6 mg, 0.05 mmol) and hexamethyldisilazane (5 mL) in anhydrous MeCN (2 mL) were heated under reflux for 2 h under an atmosphere of N_2. After evaporation at reduced pressure, the residue was taken up in anhydrous 1,2-dichloroethane (DCE) (2 mL) and added to a stirred solution of methyl 1,2,3-tri-*O*-acetyl-β-D-ribofuronate (**11**) (73 mg, 0.24 mmol) in anhydrous DCE (3 mL) in a 2–5 mL microwave vial and capped under N_2. After 5 min stirring, TMS triflate (45 μL, 0.25 mmol) was added dropwise and the mixture was heated in the microwave at 90 °C for 20 min. This was then added to a mixture of a saturated solution of $NaHCO_3$ (50 mL) and DCM (50 mL) and extracted into the organic phase. The aqueous layer was then extracted with DCM (2×20 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and the filtrate evaporated under reduced pressure to afford a yellow oil (89 mg). Purification was achieved using a silica gel column using gradient elution from 1:1 hexane/EtOAc to neat EtOAc to give a colourless oil (**12**) (53 mg, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3H), 2.22 (s, 3H), 3.87 (s, 3H), 4.74 (d, 1H, J=1.5 Hz), 5.70–5.75 (m, 2H), 6.09 (br s, 2H), 6.36–6.40 (m, 1H), 8.34 (s, 1H). ESMS calcd for $C_{15}H_{17}IN_5O_7^+$ [M+H] 506.0, found: 505.8.

4.9. Synthesis of 2-iodoadenosine-5′-*N*-ethylcarboxylamide (13)[4]

4.9.1. Method A. Compound **12** (53 mg, 0.11 mmol) and ethylamine (1 mL, 2.0 M solution in THF) were combined in THF (2 mL) and heated (microwave) at 110 °C for 3 h. The solvents were removed under reduced pressure leaving a dark oil. Purification was achieved using a silica gel column using gradient elution from EtOAc to 89:10:1 EtOAc/acetone/NH_4OH to yield a tan solid (**13**) (28 mg, 61%), mp: 214–216 °C dec, (lit.[4] mp 232–234 °C dec); ^{1}H NMR (300 MHz, CD_3OD) δ: 1.27 (t, 3H, J=7.2 Hz), 3.40–3.55 (m, 2H), 4.36 (dd, 1H, J=2.0, 5.0 Hz), 4.44 (d, 1H, J=2.0 Hz), 4.75 (dd, 1H, J=5.0, 7.1 Hz), 5.97 (d, 1H, J=7.1 Hz), 8.22 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 15.3, 34.0, 73.1, 73.4, 84.7, 87.5, 119.6, 121.6, 140.4, 150.3, 156.4, 169.6; HRMS (ESI) m/z calcd for $C_{12}H_{16}IN_6O_4^+$ [M+H] 435.0272, found: 435.0284.

4.9.2. Method B. A solution of **20** (300 mg, 0.51 mmol), NH_4OH (28%) in MeCN (20 mL) was stirred at 25 °C for 3 days. The reaction mixture was evaporated to dryness, then dissolved in EtOAc (100 mL), washed with H_2O (5×100 mL) and dried over $MgSO_4$. Evaporation of the filtrate afforded a yellow foam as the pure protected product (231 mg, 96%). This compound was subsequently dissolved in TFA (3 mL) and H_2O (0.5 mL) and stirred at 50 °C for 3 h. This reaction mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL) and then basified with solid $NaHCO_3$. The organic layer was separated and washed with H_2O (3×100 mL), brine (50 mL), dried over $MgSO_4$ and the filtrate was evaporated to afford a white solid (207 mg, 93%).

4.10. Synthesis of 2′,3′-*O*-isopropylideneguanosine (15)[15]

Guanosine (**14**) (15.00 g, 53.0 mmol) was stirred in acetone (600 mL). *p*-Toluenesulfonic acid (9.15 g, 53.0 mmol) and 2,2-dimethoxypropane (150 mL) were added and the reaction mixture was stirred overnight at 25 °C. The reaction mixture was evaporated to dryness and then dissolved in H_2O (100 mL). Solid $NaHCO_3$ (4.45 g, 53.0 mmol) was added cautiously portion wise and the solution was stirred for 2 h. Saturated $NaHCO_3$ (100 mL) was added and the solution was stirred for a further 2 h. The suspension was filtered and the product washed with cold H_2O (2×50 mL) to yield a white solid (16.05 g, 94%), mp: 260–262 °C dec, (lit.[15] mp 292 °C dec); $[\alpha]_D^{24}$ −30.5 (*c* 0.93, DMSO) (lit.[15] $[\alpha]_D$ −36.3 (*c* 4.98, DMF)). IR ν 3427, 3322, 3206, 2729, 1717, 1629, 1375, 1213, 1071, 861; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.33 (s, 3H), 1.53 (s, 3H), 3.49–3.59 (m, 2H), 4.11–4.15 (m, 1H), 4.97 (dd, 1H, J=3.0, 6.2 Hz), 5.02 (br s, 1H), 5.20 (dd, 1H, J=2.5, 6.2 Hz), 5.94 (d, 1H, J=2.5 Hz), 6.49 (br s, 2H), 7.92 (s, 1H), 10.66 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.7, 27.5, 62.1, 81.7, 84.0, 87.1, 88.9, 113.5, 117.2, 136.4, 151.2, 154.2, 157.3; HRMS (ESI) m/z calcd for $C_{13}H_{18}N_5O_5^+$ [M+H] 324.1302, found: 324.1303.

4.11. Synthesis of 2′,3′-*O*-isopropylideneguanosine-5′-carboxylic acid (16)

2′,3′-*O*-Isopropylideneguanosine (**15**) (2.5 g, 7.73 mmol), TEMPO (302 mg, 1.93 mmol) and bis(acetoxy)iodobenzene (BAIB) (5.48 g, 17.0 mmol) were combined in MeCN/H_2O (1:1, 100 mL) and stirred overnight at 25 °C. Acetone (50 mL) was added followed by Et_2O (250 mL) and the mixture stirred for a further 2 h. The mixture was filtered and the solid washed with a further 100 mL of Et_2O resulting in an orange solid (1.88 g, 72%), mp: 210–212 °C dec. IR ν 3340, 1634, 1383, 1056, 865, 772; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.45 (s, 3H), 1.51 (s, 3H), 4.63 (s, 1H), 5.33 (d, 1H, J=6.0 Hz), 5.59 (d, 1H, J=6.0 Hz), 6.12 (s, 1H), 6.40 (s, 2H), 7.78 (s, 1H), 10.60 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 25.4, 27.1, 84.3, 84.4, 86.5, 89.6, 112.9, 116.8, 137.0, 151.4, 154.1, 157.4, 172.4; MS (ESI) m/z calcd for $C_{13}H_{16}N_5O_6^+$ [M+H] 338.1, found: 338.1.

4.12. Synthesis of 2′,3′-*O*-isopropylideneguanosine-5′-methylcarboxylate (17)

A suspension of the carboxylic acid (**16**) (3.00 g, 8.89 mmol) in MeOH (400 mL) was stirred at 0 °C for 30 min. $SOCl_2$ (3.22 mL, 44.50 mmol) was slowly added and the reaction mixture left to warm to room temperature overnight. A solution of saturated $NaHCO_3$ (20 mL) was cautiously added, followed by solid $NaHCO_3$ portion wise over several hours until the solid $NaHCO_3$ was suspended in the mixture. Silica gel was added to the reaction mixture

and the mixture evaporated to dryness, this was loaded onto a plug of silica and the product extracted using 800 mL of DCM/MeOH (9:1) to yield a white solid (1.90 g, 61%), mp: 203–205 °C dec; $[\alpha]_D^{24}$ +24.5 (*c* 0.73, DMSO). IR *ν* 3441, 3158, 2990, 2717, 1702, 1637, 1603, 1385, 1212, 1101, 865, 781; ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 1.25 (s, 3H), 1.46 (s, 3H), 3.38 (s, 3H), 4.73 (d, 1H, *J*=1.5 Hz), 5.25 (d, 1H, *J*=6.0 Hz), 5.69 (dd, 1H, *J*=1.5, 6.0 Hz), 6.15 (s, 1H), 6.37 (br s, 2H), 7.75 (s, 1H), 10.60 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 25.3, 26.8, 52.1, 84.0, 84.8, 86.4, 90.0, 112.8, 117.2, 137.7, 151.1, 153.7, 157.2, 170.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}N_5O_6^+$ [M+H] 352.1252, found: 352.1262.

4.13. Synthesis of 2′,3′-*O*-isopropylideneguanosine-5′-*N*-ethylcarboxamide (18)

2′,3′-*O*-Isopropylideneguanosine-5′-methylcarboxylate (**17**) (3.00 g, 8.54 mmol), ethylamine (2.0 M in THF, 25 mL) and MeOH/DMF (9:1, 20 mL) were combined in a 150 mL bomb reactor and heated to 70–75 °C for 3 days. Upon cooling the solvents were evaporated and the crude reaction mixture purified on a silica gel column using gradient elution from DCM to DCM/MeOH (9:1) to yield a tan solid (3.05 g, 98%), mp: 199–200 °C dec; $[\alpha]_D^{24}$ −4.30 (*c* 0.93, DMSO). IR *ν* 3316, 3157, 2934, 2755, 1694, 1659, 1598, 1531, 1381, 1084, 865, 781; ^{1}H NMR (300 MHz, CD_3OD) *δ*: 0.79 (t, 3H, *J*=7.2 Hz), 1.36 (s, 3H), 1.58 (s, 3H), 2.85–3.10 (m, 2H), 4.63 (d, 1H, *J*=1.8 Hz), 5.41 (d, 1H, *J*=6.0 Hz), 5.72 (dd, 1H, *J*=1.8, 6.0 Hz), 6.23 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) *δ*: 14.4, 25.5, 27.0, 33.6, 83.6, 83.9, 86.6, 89.4, 113.1, 117.0, 137.1, 151.1, 154.0, 157.3, 168.7; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}N_6O_5^+$ [M+H] 365.1568, found: 365.1581.

4.14. Synthesis of 2-amino-6-chloropurin-9-yl-2′,3′-*O*-isopropylidene-5′-*N*-ethylcarboxamide (19a)[16]

Under inert conditions Et_4NCl (200 mg, 1.21 mmol) and guanosine-2′,3′-*O*-isopropylidene-5′-*N*-ethylcarboxamide (**18**) (200 mg, 0.55 mmol) were dried under vacuum for 16 h. To this, freshly distilled DMA (100 μL, 0.86 mmol) and MeCN (20 mL) were added and the reaction mixture was cooled to 0 °C, distilled $POCl_3$ (500 μL, 2.0 mmol) was added and the reaction mixture heated to reflux for 1 h. The reaction mixture was evaporated to dryness under reduced pressure. The resultant oil was diluted with $CHCl_3$ (100 mL) and to this was added ice water (100 mL) cautiously followed by a satd soln of $NaHCO_3$ (100 mL). The organic fraction was separated and the aqueous phase washed with $CHCl_3$ (2×100 mL). The organic fractions were combined and dried over $MgSO_4$, evaporated and adsorbed on a silica gel column. The product was purified using gradient elution (DCM to 9:1 DCM/methanol) to yield a brown oil as the product (75 mg, 36%). R_f=0.50 DCM/MeOH (9:1); ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 0.76 (t, 3H, *J*=7.2 Hz), 1.41 (s, 3H), 1.60 (s, 3H), 2.86–3.11 (m, 2H), 4.72 (d, 1H, *J*=1.8 Hz), 5.31 (d, 1H, *J*=6.0 Hz), 5.69 (dd, 1H, *J*=1.8, 6.0 Hz), 5.97 (s, 1H), 6.10 (t, 1H, *J*=5.5 Hz), 6.49 (br s, 2H), 7.93 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 14.0, 25.3, 27.0, 34.7, 85.3, 89.7, 92.4, 114.6, 124.9, 144.5, 151.8, 154.3, 161.3, 171.7; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}ClN_6O_4^+$ 383.1229, found 383.1231.

4.15. Synthesis of O^6-(benzotriazol-1-yl)-2′,3′-*O*-isopropylideneguanosine-5′-*N*-ethylcarboxamide (19b)

Compound **18** (500 mg, 1.37 mmol) was suspended in MeCN (30 mL). BOP (911 mg, 2.06 mmol) and DBU (308 μL, 2.06 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (200 mL) and washed with H_2O (5×100 mL), brine (50 mL), dried over $MgSO_4$ and evaporated to yield a yellow foam as the product (629 mg, 95%), mp: 140–141 °C. IR *ν* 3398, 1641, 1572, 1376, 1205, 1093, 835; ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 0.68 (t, 3H, *J*=7.2 Hz), 1.35 (s, 3H), 1.52 (s, 3H), 2.78–2.92 (m, 2H), 4.52 (d, 1H, *J*=2.1 Hz), 5.40 (d, 1H, *J*=6.0 Hz), 5.51 (dd, 1H, *J*=2.1, 6.0 Hz), 6.28 (s, 1H), 6.65 (br s, 2H), 7.46 (t, 1H, *J*=6.0 Hz), 7.52–7.56 (m, 1H), 7.65 (m, 2H), 8.17 (d, 1H, *J*=8.4 Hz), 8.21 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) *δ*: 14.4, 25.5, 27.0, 33.5, 2×83.7, 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; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_9O_5^+$ [M+H] 482.1895, found: 482.1901.

4.16. Synthesis of 2-fluoro-O^6-(benzotriazol-1-yl)-2′,3′-*O*-isopropylideneinosine-5′-*N*-ethylcarboxamide (20)

Compound **19** (200 mg, 0.42 mmol) was dissolved in dry MeCN (3 mL). CH_2I_2 (1 mL) and *t*-BuONO (200 μL, 1.66 mmol) were added and the reaction mixture was heated to 65–70 °C for 4 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with H_2O (3×100 mL). The crude reaction mixture was purified on a silica gel column using gradient elution from DCM to DCM/MeOH (9:1) to yield a tan solid 190 mg (76%), mp: 195–196 °C dec; $[\alpha]_D^{24}$ +23.7 (*c* 0.92, DMSO). IR *ν* 3293, 3098, 2991, 1655, 1557, 1384, 1205, 1084, 747; ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 0.61 (t, 3H, *J*=7.2 Hz), 1.35 (s, 3H), 1.53 (s, 3H), 2.78–2.92 (m, 2H), 4.60 (d, 1H, *J*=1.5 Hz), 5.31–5.39 (m, 2H), 6.45 (s, 1H), 7.55–7.59 (m, 2H), 7.67–7.69 (m, 2H), 8.21 (d, 1H, *J*=8.4 Hz), 8.65 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) *δ*: 14.6, 25.5, 27.0, 33.5, 83.8, 83.9, 87.5, 90.3, 109.5, 113.3, 117.5, 119.3, 120.5, 125.9, 128.7, 130.0, 143.2, 146.8, 155.3, 157.1, 168.3; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}IN_8O_5^+$ [M+H] 593.0752, found: 593.0750.

4.17. Synthesis of 2-fluoro-O^6-(benzotriazol-1-yl)-2′,3′-*O*-isopropylideneinosine-5′-*N*-ethylcarboxamide (21)

Pyridine (520 μL) was cooled to −30 °C, and 70% HF in pyridine (2.7 mL) added with stirring. Compound **19b** (500 mg, 1.04 mmol) was added and stirred until dissolution occurred. The temperature was allowed to rise to −20 °C and *t*-BuONO (520 μL, 5.82 mmol) added slowly dropwise. The reaction mixture was maintained at −20 °C with stirring for 20 min, and then poured over ice. The resulting precipitate was collected via vacuum filtration, rinsed with H_2O and dried in vacuo to yield a beige solid (298 mg, 59%), mp: 140–145 °C dec. IR *ν* 3401, 3098, 2986, 1628, 1588, 1378, 1199, 1085, 743; ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 1.11 (t, 3H, *J*=7.2 Hz), 1.35 (s, 3H), 1.52 (s, 3H), 2.70–2.95 (m, 2H), 4.61 (d, 1H, *J*=1.8 Hz), 5.38 (dd, 1H, *J*=1.8, 6.0 Hz), 5.44 (d, 1H, *J*=6.0 Hz), 6.45 (s, 1H), 7.59 (t, 1H, *J*=6.3 Hz), 7.65–7.80 (m, 3H), 8.22 (d, 1H, *J*=9.5 Hz), 8.76 (s, 1H); ^{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; ESMS calcd for $C_{21}H_{22}N_8O_5F^+$ [M+H] 485.2, found: 485.4.

4.18. 2-Fluoroadenosine-2′,3′-*O*-isopropylidene-5′-*N*-ethylcarboxamide (22)

To a stirred solution of **21** (600 mg, 1.24 mmol) in MeCN (6 mL) at 0 °C was added 28% ammonia solution (500 μL). The solution was allowed to rise to room temperature and stirring was continued for 2 h. The solvent was removed in vacuo, and the residue partitioned between H_2O and EtOAc. The aqueous phase was extracted into EtOAc (×3) and the combined organic phase was washed with H_2O and brine, dried over $MgSO_4$ and evaporated to afford the crude product. Purification was achieved via column chromatography (silica gel) using EtOAc as the eluent to yield a pale yellow solid (399 mg, 88%), mp: 182–185 °C dec; $[\alpha]_D^{23}$ −31.6 (*c* 0.67, $CHCl_3$). IR *ν* 3290, 3141, 1672, 1373, 1205, 1089, 1053, 858; ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 0.67 (t, 3H, *J*=7.2 Hz), 1.34 (s, 3H), 1.52 (s, 3H), 2.70–2.97 (m, 2H), 4.54 (s, 1H), 5.37 (br s, 2H), 6.29 (s, 1H), 7.52 (t, *J*=5.4 Hz, 1H), 7.87 (br s, 2H), 8.21 (s, 1H); ^{13}C NMR (300 MHz,

CD_3OD) δ: 14.3, 25.4, 27.2, 33.5, 83.5, 83.6, 86.5, 89.8, 113.4, 117.8, 141.0, 150.7 (J=20.1 Hz), 158.1 (J=21.1 Hz), 158.8 (J=203.2 Hz), 168.5; MS (ESI) m/z calcd for $C_{15}H_{20}N_6O_4F^+$ [M+H] 367.2, found: 367.6.

4.19. 2-(Phenethyl-2-amino)adenosine-2′,3′-*O*-isopropylidene-5′-*N*-ethylcarboxamide (23)[17]

A solution of **22** (50 mg, 0.137 mmol), phenylethyl-2-amine (33 mg, 0.273 mmol) and DIPEA (200 μL) in EtOH (2 mL) was stirred in a sealed reaction vessel at 110 °C for 3 days. The crude mixture was evaporated onto silica gel and purified by column chromatography using EtOAc as the eluent (30 mg, 47%), mp: 185–187 °C; ^{1}H NMR (300 MHz, CD_3OD) δ: 0.61 (t, 3H, J=7.2 Hz), 1.38 (s, 3H), 1.59 (s, 3H), 2.70–2.85 (m, 2H), 2.85–2.95 (m, 2H), 3.44–3.54 (m, 1H), 3.69–3.80 (m, 1H), 4.61 (s, 1H), 5.58 (d, 1H, J=6.0 Hz), 5.63 (d, 1H, J=6.0 Hz), 6.22 (s, 1H), 7.15–7.32 (m, 5H), 7.88 (s, 1H); ^{13}C NMR (300 MHz, MeOD) δ: 12.3, 23.8, 25.2, 33.1, 35.1, 42.3, 83.6, 84.1, 87.9, 91.1, 112.8, 113.0, 125.7, 128.0, 128.5, 138.1, 139.8, 151.0, 156.1, 159.3, 170.1; MS (ESI) m/z calcd for $C_{23}H_{30}N_7O_4^+$ [M+H] 468.2, found: 468.4.

4.20. 2-(Phenethyl-2-amino)adenosine-5′-*N*-ethylcarboxamide (24)[17]

A solution of **23** (30 mg, 0.064 mmol) in 1 M HCl (10 mL) was stirred for 5 h at 60 °C. The solution was cooled, basified with $NaHCO_3$, and extracted with EtOAc (×4). The organic phase washed with brine, dried over $MgSO_4$ and evaporated to yield pure **24** (22 mg, 80%), mp: 104–106 °C, (lit.[17] mp 115–118 °C dec); ^{1}H NMR (300 MHz, CD_3OD) δ: 1.06 (t, 3H, J=7.2 Hz), 2.90 (t, 2H, J=7.2 Hz), 3.07–3.20 (m, 1H), 3.21–3.33 (m, 1H), 3.48–3.60 (m, 1H), 3.60–3.71 (m, 1H), 4.40 (d, 1H, J=2.7 Hz), 4.51 (dd, 1H, J=2.7, 4.8 Hz), 5.02 (dd, 1H, J=4.8, 6.3 Hz), 5.93 (d, 1H, J=6.3 Hz), 7.15–7.34 (m, 5H), 7.99 (s, 1H); ^{13}C NMR (600 MHz, MeOD) δ: 14.9, 35.4, 37.1, 44.5, 73.5, 74.9, 85.7, 90.3, 115.0, 127.4, 129.7, 130.1, 139.4, 141.3, 153.3, 157.7, 161.3, 172.2; HRMS (ESI) m/z calcd for $C_{20}H_{26}N_7O_4^+$ [M+H]$^+$ 428.2041, found: 428.2037.

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