The synthesis of a series of adenosine A_3 receptor agonists

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A series of 1′-(6-aminopurin-9-yl)-1′-deoxy-*N*-methyl-β-D-ribofuranuronamides characterised by 2-dialkylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethyl substituents on N6 of interest for screening as selective adenosine A_3 receptor agonists, have been synthesised. This work involved the synthesis of 2-dialkylamino-5-aminomethyl-7-methyloxazolo[4,5-*b*]pyridines and analogues that were coupled with the known 1′-(6-chloropurin-9-yl)-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide. The oxazolo[4,5-*b*]pyridines were synthesized by regioselective functionalisation of 2,4-dimethylpyridine *N*-oxides. The regioselectivities of these reactions were found to depend upon the nature of the heterocycle with 2-dimethylamino-5,7-dimethyloxazolo[4,5-*b*]pyridine-*N*-oxide undergoing regioselective functionalisation at the 7-methyl group on reaction with trifluoroacetic anhydride in contrast to the reaction of 4,6-dimethyl-3-hydroxypyridine-*N*-oxide with acetic anhydride that resulted in functionalisation of the 6-methyl group. To optimise selectivity for the A3 receptor, 5-aminomethyl-7-bromo-2-dimethylamino-4-[(3-methylisoxazol-5-yl)methoxy]benzo[*d*]oxazole was synthesised and coupled with the 1′-(6-chloropurin-9-yl)-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide. The products were found to act as adenosine A_3 agonists but further work is required to optimise potency and selectivity.

Introduction

The G-protein-coupled adenosine receptors are important in regulating a wide range of physiological functions. Specifically A_3 receptor agonists have been identified as being of interest for the treatment of cardiac ischaemia[1] and many compounds have been evaluated for selective A_3 receptor agonist activity.[2] Indeed, *N*6 substituted derivatives of adenosine and analogues have been found to exhibit useful A_3 agonist activity, the *N*6-(iodobenzyl)purinylribofuranuronamide **1**[3a] being an early example, see Figure 1, with many more homologues subsequently synthesized and evaluated.[2,4] In particular, the *N*6-(benzoxazolylmethyl)purinyluronamide **2** was identified as a promising lead.[5] However, concerns about toxicity issues due to the iodine substituent and the possible improvement in selectivity following incorporation of an oxazolopyridine rather than a benzoxazole into the *N*6 substituent, led to the selection of the ribofuranuronamide **3** as the next target for synthesis,[6] see Figure 2. We here report a synthesis of this compound and several of its homologues together with the results of preliminary biological evaluation of these compounds.

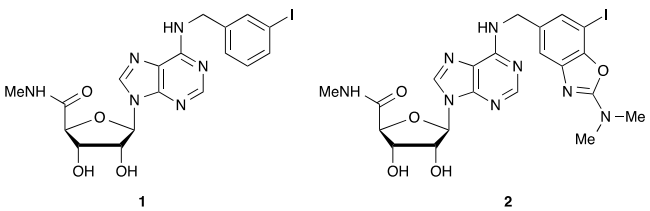


Figure 1 Examples of adenosine A_3 receptor agonists

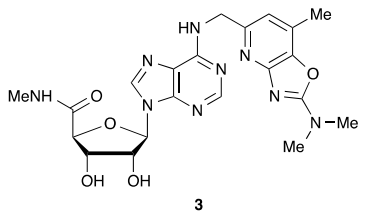


Figure 2 The *N*6-substituted purinylribofuranuronamide **3** selected for evaluation as an A_3 receptor agonist

Results and discussion

Synthesis of oxazolopyridine derived adenosine derivatives

Following well established literature precedent,[2-4] the uronamide **3** was to be prepared from the 2-dimethylamino-5-aminomethyl-7-methyloxazolo[4,5-*b*]pyridine **5** and the known 6-chloropurinyluronamide **4**,[7] the challenge in the work being to develop a synthesis of the oxazolopyridine **5**. Initially it was intended to prepare this oxazolopyridine from 5,7-dimethyl-2-dimethylamino-oxazolopyridine **6** by rearrangement of the corresponding pyridine *N*-oxide. In turn the oxazolopyridine **6** was to be prepared from 5-hydroxy-6-nitro-2,4-lutidine (**7**) that it was intended to prepare from 2,4-lutidine (**8**), see Figure 3.

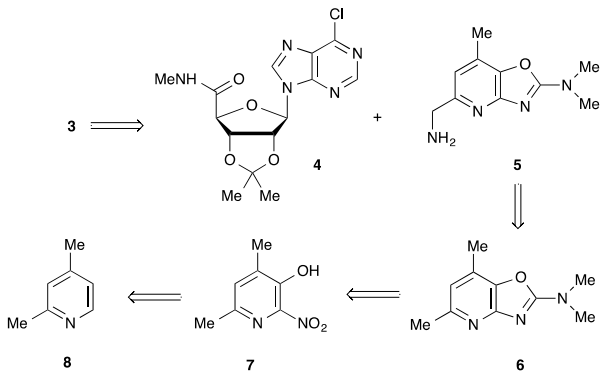
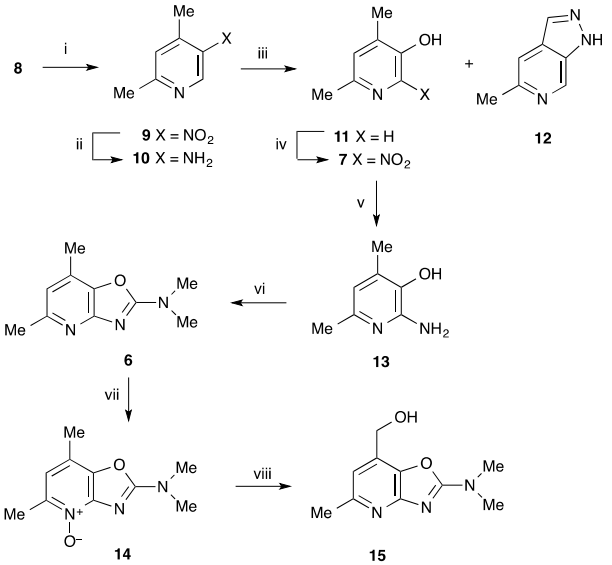


Figure 3 Planned synthesis of the target compound **3**

Nitration of 2,4-lutidine (**8**) using potassium nitrate in fuming sulfuric acid gave a mixture of 5-nitro-2,4-lutidine (**9**) and its 3-nitro isomer from which the required isomer **9** was isolated by fractional distillation albeit in only a low yield.[8a] Hydrogenation gave the 5-amino-2,4-lutidine (**10**) that was converted into the 5-hydroxy-2,4-lutidine (**11**) by diazotisation using sodium nitrite in aqueous sulfuric acid. In this reaction it was important to use just a small excess of sulfuric acid to avoid the formation of the pyrazolopyridine **12**.[9] Nitration of the hydroxylutidine **11** using concentrated nitric and sulfuric acids[10] led to decomposition but the use of ceric ammonium nitrate and sodium bicarbonate in acetonitrile heated under reflux[11] gave the required 5-hydroxy-6-nitro-2,4-lutidine (**7**) in a modest but reproducible yield. Hydrogenation of the nitrolutidine **7** gave the corresponding hydroxyaminolutidine **13** that was converted into the 2-dimethylamino-oxazolopyridine **6** using dichloromethylene-(dimethyl)ammonium chloride, see Scheme 1.



Scheme 1 Synthesis and hydroxylation of the 2-dimethylamino-oxazolopyridine **6** Reagents and conditions (i) fuming H_2SO_4, 0 °C, add KNO_3, heat slowly to 100 °C, 8 h (17%); (ii) H_2, Pd/C, MeOH, rt, 16 h (*ca*. 100%); (iii) aq. H_2SO_4, 0 °C, $NaNO_2$, H_2O, 0 °C, 15 min, reflux 15 min (**11**, 47%; with a slight excess of H_2SO_4); (iv) CAN, $NaHCO_3$, MeCN, reflux, 6 h (42%); (v) H_2, Pd/C, EtOAc, rt, 16 h; (vi) $Cl_2C{=}NMe_2Cl$, DCM, reflux, 5 h; (vii) *m*CPBA, $CHCl_3$, rt, 16 h (78%); (viii) $(CF_3CO)_2O$, DCM, reflux, 16 h (29%).

Oxidation of the oxazolopyridine **6** using *meta*-chloroperoxybenzoic acid gave the *N*-oxide **14**, an X-ray crystal structure confirming that the product was the pyridine *N*-oxide shown, see Figure 4. When this *N*-oxide was reacted with an excess of acetic anhydride, standard conditions for effecting regioselective hydroxylation of a methyl group *ortho* to an *N*-oxide,[8,12] a mixture of several products was obtained. However, the use of trifluoroacetic anhydride in dichloromethane under reflux,[13] followed by saponification, gave a single product **15** in which the methyl group remote from the *N*-oxide had been hydroxylated, albeit in only a modest yield, see Scheme 1.

The regioselectivity of this hydroxylation was initially indicated by the ^1H-^{15}N gHMBC NMR spectrum that showed a three-bond coupling of 5.0 Hz between the remaining aryl methyl group at δ 1.5 and the pyridine nitrogen in contrast to the small coupling of 0.5 Hz between the aryl methylene protons at δ 5.0 and the pyridine nitrogen. This structural assignment was eventually confirmed by X-ray diffraction, see Figure 5.

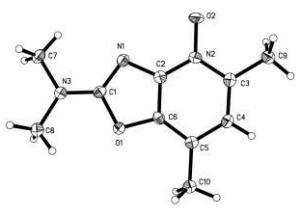


Figure 4 The structure of the *N*-oxide **14** as established by X-ray crystallography

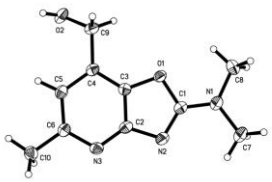


Figure 5 The structure of 2-dimethylamino-7-hydroxymethyl-5-methyloxazolo[4,5-*b*]pyridine (**15**) as established by X-ray crystallography

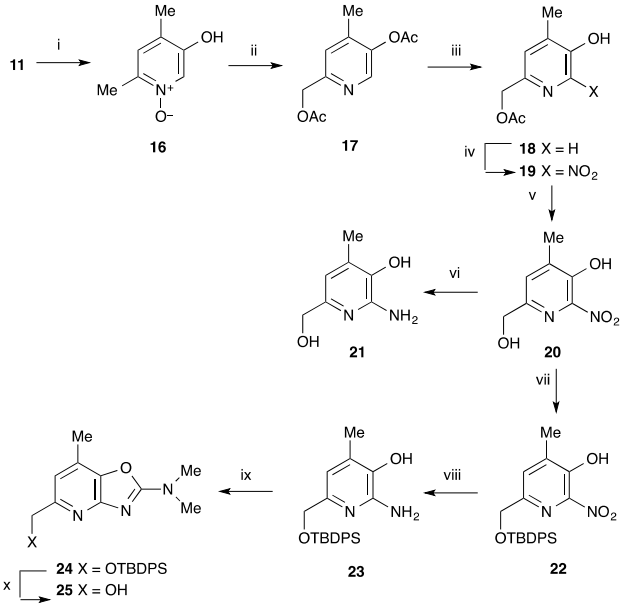
The selective formation of the 7-hydroxymethyloxazolopyridine **15** rather than its 5-hydroxymethyl isomer was unexpected since typically an ortho methyl group is hydroxylated on treatment of a pyridine *N*-oxide with an acyl anhydride.[8] This meant that it was necessary to hydroxylate the ortho methyl group before assembling the oxazolopyridine.

In our hands, oxidation of the 5-hydroxy-2,4-lutidine **11** to its *N*-oxide **16** was carried out using *meta*-chloroperoxybenzoic acid. The conversion of the *N*-oxide **16** into the bis-acetate **17** using acetic anhydride is known and proceded without incident, the structure of the product being assigned according to the literature.[8] Selective deacetylation of the aromatic hydroxyl group was carried out using pyrrolidine in DCM,[14] as sodium hydroxide was less selective and gave a mixture of products, and nitration of the resulting hydroxypyridine **18** to the nitropyridine **19** was best achieved using ceric ammonium nitrate as before. Attempts to reduce the nitropyridine **19** to the corresponding aminopyridine by hydrogenation were complicated by hydrogenolysis of the acetoxy group. To convert the acetoxy group into a less good leaving group, it was saponified to give the alcohol **20** and hydrogenation of this now proceeded uneventfully to give 2-amino-3-hydroxy-6-hydroxymethyl-4-methylpyridine (**21**). However, it transpired that this compound was relatively insoluble in many organic solvents and correspondingly difficult to functionalise. The dihydroxynitropyridine **20** was therefore converted into its mono-*tert*-butyldiphenylsilyl ether **22**. Hydrogenation of this gave the aminopyridine **23** that on treatment with dichloromethylene(dimethyl)ammonium chloride gave the required oxazolopyridine **24**. Desilylation provided the 5-hydroxymethyl-7-methyloxazolo[4,5-*b*]pyridine **25**, see Scheme 2.

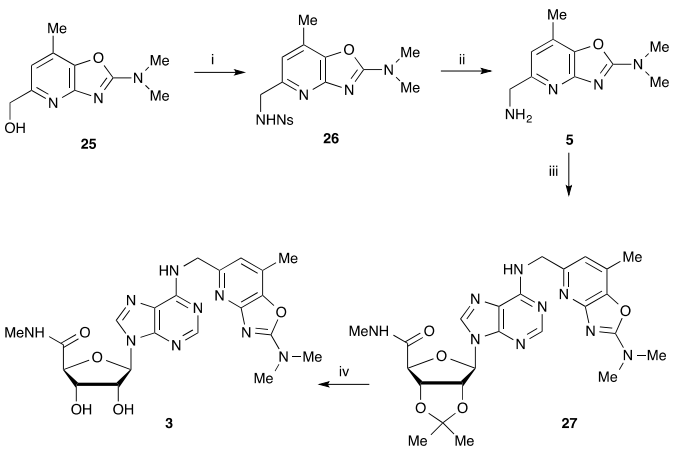
The structures of the products in Scheme 2 were assigned on the basis of the literature precedent for the pyridine *N*-oxide reaction[8] and from spectroscopic data. The 5-hydroxymethyl-7-methyloxazolopyridine **25** was distinctly different from its 7-hydroxmethyl-5-methyl isomer **15** prepared earlier.

To complete the synthesis of the uronamide **3**, the hydroxymethyloxazolopyridine **25** had to be converted into its aminomethyl homologue **5**. This was achieved using a Mitsunobu reaction[15] of the alcohol **25** with 2-nitrobenzene sulfonamide to prepare the *N*-alkylsulfonamide **26**. This reaction was complicated by bis-alkylation of the 2-nitrobenzene sulfonamide but was not optimised at this stage. Desulfonylation gave the primary amine **5** and coupling this with the 6-chloropurine **4** gave the *N*6-substituted purinyluronamide **27**. Selective hydrolysis of this acetonide **27** gave the required ribofuranuronamide **3**, see Scheme 3.

The products in Scheme 3 were identified on the basis of their spectrocopic data. Following evaluation of the uronamide **3** for biological activity, *vide infra*, it was decided to prepare homologues for further studies.



Scheme 2 Preparation of the 5-hydroxymethyloxazolopyridine **25** Reagents and conditions (i) *m*CPBA, DCM, rt, 16 h (85%); (ii) Ac_2O, 110 °C, 2.5 h (80%); (iii) pyrrolidine, DCM, rt, 16 h (*ca.* 100%); (iv) CAN, $NaHCO_3$, MeCN, reflux, 5 h (38%); (v) NaOH, MeOH, rt, 1 h; (vi) H_2, Pd/C, EtOAc, rt, 2 h; (vii) ^{t}BuPh$_2$SiCl, imid., DMF, rt, 12 h (75%); (viii) H_2, Pd/C, EtOAc, rt, 16 h; (ix) $Cl_2C{=}NMe_2Cl$, Et_3N, DCM, reflux, 6 h (86%); (x) TBAF, THF, rt, 1 h (92%).

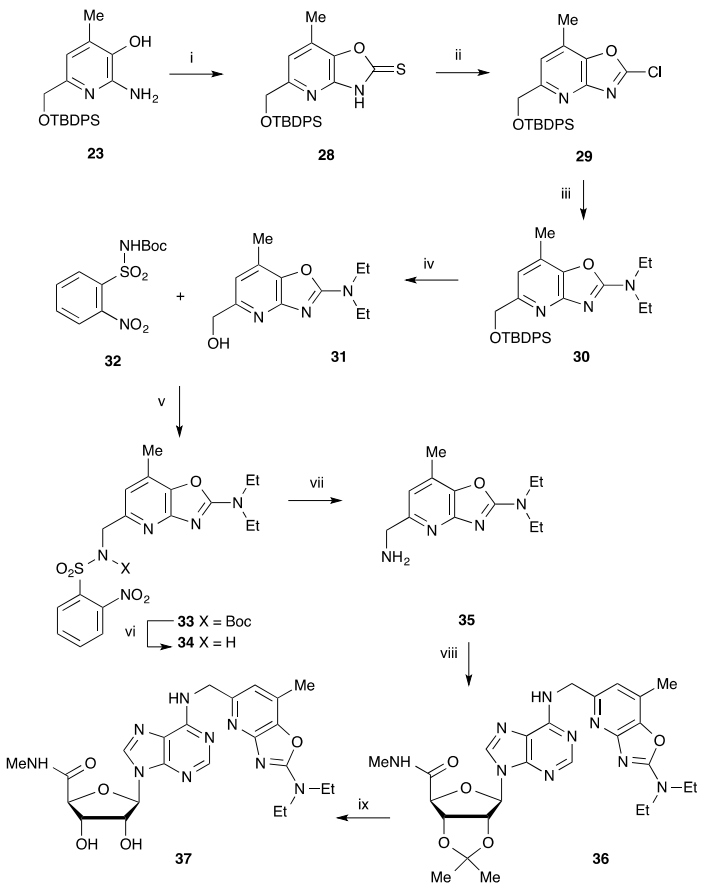


Scheme 3 Completion of a synthesis of the A_3 receptor agonist **3** Reagents and conditions (i) 2-$O_2NC_6H_4SO_2NH_2$, Ph_3P, THF, ^{i}PrO$_2$CN=NCO$_2^i$Pr, rt, 16 h (31%); (ii) PhSH, K_2CO_3, MeCN, rt, 16 h (84%); (iii) **4**, Et_3N, EtOH, 80 °C, 16 h (90%); (iv) aq. HCl, 65 °C, 1 h (76%).

The next compound identified for synthesis was the diethylamino analogue **37**, see Scheme 4. This required the synthesis of the 2-diethylamino-5-aminomethyl-7-methyloxazolo[4,5-*b*]pyridine **35**. As dichloromethylene(diethyl)ammonium chloride was not commercially available at the time, the original synthesis had to be modified. Therefore, following the literature precedent, the aminophenol **23** was converted into the thione **28** using carbon disulfide and potassium hydroxide in ethanol,[16] the product being identified as the thione tautomer by analogy with the literature.[17] The

attempted direct conversion of the thione **28** into the corresponding diethylamino-oxazole using diethylamine delivered unchanged starting material, perhaps because of the volatility of diethylamine. The thione was therefore converted into the 2-chloro-oxazole **29** using thionyl chloride. Displacement of chloride using diethylamine gave the required 2-diethylamino-oxazole **30**[17] that was desilylated to give the alcohol **31**. To avoid the bis-alkylation side-reaction observed during the synthesis of the amine **5**, the Mitsunobu reaction of the alcohol **31** was carried out using the *N*-Boc-protected 2-nitrobenzene sulfonamide **32**.[18] A good yield of the alkylated sulfonamide **33** was obtained and, following removal of the Boc-group, denosylation of the resulting sulfonamide **34**[19] gave the required primary amine **35**, see Scheme 4.

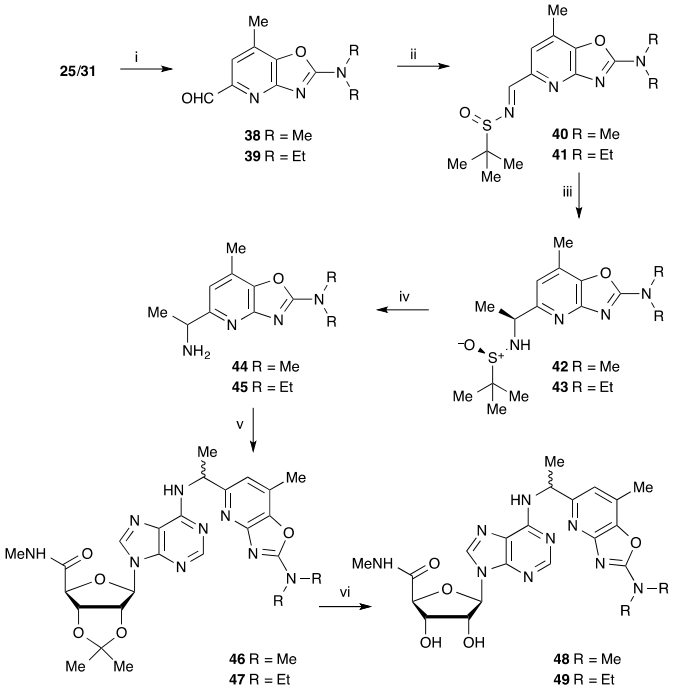
The primary amine **35** was coupled with the 6-chloropurine **4** as before to obtain the *N*6-substituted purinyluronamide **36** and this was deprotected to give the target uronamide **37**, see Scheme 4. The structures of the products in Scheme 4 were assigned using spectroscopic data.



Scheme 4 Synthesis of the diethylamino substituted adenosine uronamide **37** Reagents and conditions (i) CS_2, KOH, EtOH, reflux, 3 h (83%); (ii) $SOCl_2$, Na_2CO_3, benzene, 50 °C, 3 h; (iii) Et_2NH, benzene, rt, 1 h (70% from **28**); (iv) TBAF, THF, rt, 1 h (93%); (v) Ph_3P, THF, DIAD, rt, 16 h (98%); (vi) TFA, rt, 1 h (79%); (vii) PhSH, K_2CO_3, MeCN, rt, 16 h (85%); (viii) **4**, Et_3N, EtOH, reflux, 16 h (55%); (ix) aq. HCl, 65 °C, 1 h (46%).

At this point it was decided to investigate the effect of a methyl substituent on the methylene group attached to *N*6. This introduces a new stereogenic centre but initially mixtures of epimers were prepared for studies of their biological activity although the synthesis that was developed could be modified to control the chirality at this position if required, see Scheme 5.

Oxidation of the alcohols **25** and **31** gave the corresponding aldehydes **38** and **39**. Reaction of these with racemic *tert*-butanesulfinamide gave the racemic sulfinimides **40** and **41**.[20] The reaction of these with methylmagnesium bromide was stereoselective and gave, in each case, essentially a single, albeit racemic, adduct **42** and **43**. The relative configurations of the two stereogenic centres were assigned by analogy with the literature.[21] Methanolysis gave the racemic amines **44** and **45** and these were coupled with the 6-chloropurine **4** to give mixtures of the epimeric purinyluronamides **46** and **47**. A small amount of kinetic resolution was observed in these reactions as the products were found to correspond to 60 : 40 mixtures of the two diastereoisomers. Finally deprotection gave the target compounds **48** and **49**. Again mixtures of epimers were obtained but as the Grignard addition reactions had been highly diastereoselective, the use of enantiomerically enriched *tert*-butanesulfinamide would have delivered one or other of the epimers selectively. The structures shown were assigned to the products in Scheme 5 using spectroscopic data.



Scheme 5 Synthesis of adenosine uronamides **48** and **49** Reagents and conditions (i) Dess-Martin periodinane, DCM, rt, 20 min; (ii) (±)-^{t}BuS(O)NH_2, $CuSO_4$, DCM, rt, 16 h ((**40**, 70% from **25**; **41**, 90% from **31**); (iii) MeMgBr, THF, −78 °C, 1 h (**42**, 76%; **43**, 76%); (iv) aq. HCl, dioxane, MeOH, rt, 30 min (**44**, 83%; **45**, 82%); (v) **4**, Et_3N, EtOH, reflux, 16 h; (vi) aq. HCl, 65 °C, 1 h (**48**, 50% from **44**; **49**, 60% from **45**).

Synthesis of an *N*6-benzoxazolylmethylpurinyluronamide

Although the biological activities of the uronamides **3**, **36**, **48** and **49** were promising, it was decided that further structural changes in the *N*6 substituent were required to achieve the required biological activity and selectivity. The (*N*6-benzoxazolylmethylpurinyl)-uronamide **50** was selected as the next synthetic target, see Figure 4.[6]

This is analogous to the known agonist **2** but with a bromine substituent rather than the labile iodide and an extra hetarylmethoxy substituent to facilitate selective binding.

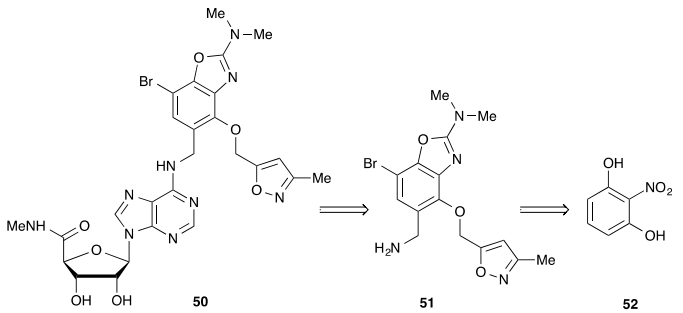
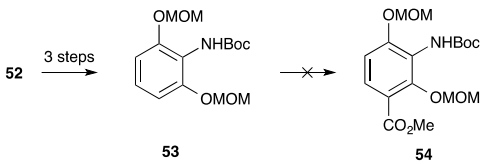


Figure 4 The strategy for the synthesis of the (*N*6-benzoxazolylpurinyl)uronamide **50**

As before it was the synthesis of the heavily substituted benzoxazole **51** that constituted the challenge in preparing uronamide **50**. Embedded within the benzoxazole is a pentasubstituted benzene ring. It was decided to use 2-nitroresorcinol (**52**) as the starting material for this synthesis, see Figure 4. The conversion of this resorcinol into the benzoxazole **51** would require introduction of the bromine and aminomethyl substituents and discrimination between the two hydroxyls so that one could be incorporated into the oxazole and the other one alkylated.

Initial studies involved the known[22] carboxymethylation of the protected aminoresorcinol **53** that was readily available from 2-nitroresorcinol in three steps. However in our hands only complex mixtures of products were obtained using *n*-butyllithium and either Mander's reagent[23] or methyl chloroformate as the electrophile, see Scheme 6.



Scheme 6 Unsuccessful carboxymethylation of the protected resorcinol **53**.

Carboxymethylation of the bis-MOM-protected iodonitroresorcinol **56** using phenylmagnesium bromide to effect halogen-metal exchange followed by reaction of the organometallic intermediate with Mander's reagent is reported to give the regioselectively monodeprotected ester **57**, see Scheme 7.[24] The starting material **56** for this conversion is available in two steps from 2-nitroresorcinol **52**.[24] However, in our hands the reported procedure for the conversion of the iodide **56** into the ester **57** gave a complex mixture of products. Attempts to effect this conversion using different electrophiles were similarly unsuccessful. However, studies into palladium(0) catalysed methoxycarbonylation procedures were more successful.[25,26] The optimum catalyst system was palladium(II) acetate and the hindered electron-rich 2,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane **65** with methanol as the solvent rather than a methanol – *N*,*N*-dimethylformamide mixed solvent system, and gave an excellent yield of the mono-deprotected ester **57** after 12 h at 80 °C, see Scheme 7.

The regioselectivity of the monodeprotection was not confirmed at this stage but the product had NMR data identical to those reported in the literature for isomer **57**.[24]

Bromination of ester **57** was regioselective as would be expected but was accompanied by loss of the remaining MOM-ether and gave the resorcinol **58**. This was slighly disappointing since it meant that discrimination between the two hydroxyl groups had to be carried out. Nevertheless the synthesis was continued in that reduction of the nitro group was achieved using zinc and acetic acid in methanol, conditions known to be compatible with both phenolic and ester groups, to give the aminoresorcinol **59**.

At this point it was decided to investigate the introduction of the oxazole since it was hoped that hydrogen bonding between the ester and the ortho phenolic hydroxyl group would reduce its reactivity relative to the hydroxyl group that was para to the carboxymethyl substituent. In the event, reaction with dichloromethylene-(dimethyl)ammonium chloride gave a single product that was provisionally identified as the required isomer **60**. This structural assignment was confirmed later in the synthesis.

With the assumption that the oxazole was the required regioisomer **60**, the free hydroxyl group was alkylated using 5-hydroxymethyl-3-methylisoxazole under Mitsunobu conditions to provide **61**. Reduction of the ester **61** using lithium aluminium hydride was accompanied by debromination but calcium borohydride[27] was both sufficiently reactive and selective and gave the alcohol **62** in a good yield. Long-range correlation in the ^{1}H NMR spectrum of the alcohol **62** between the two benzylic methylene groups were consistent with the required ortho-orientation of the hydroxymethyl and alkoxy side chains and the structure of the alcohol **62** was finally confirmed by X-ray diffraction, see Figure 5.

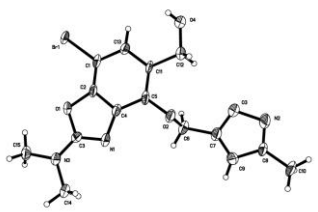
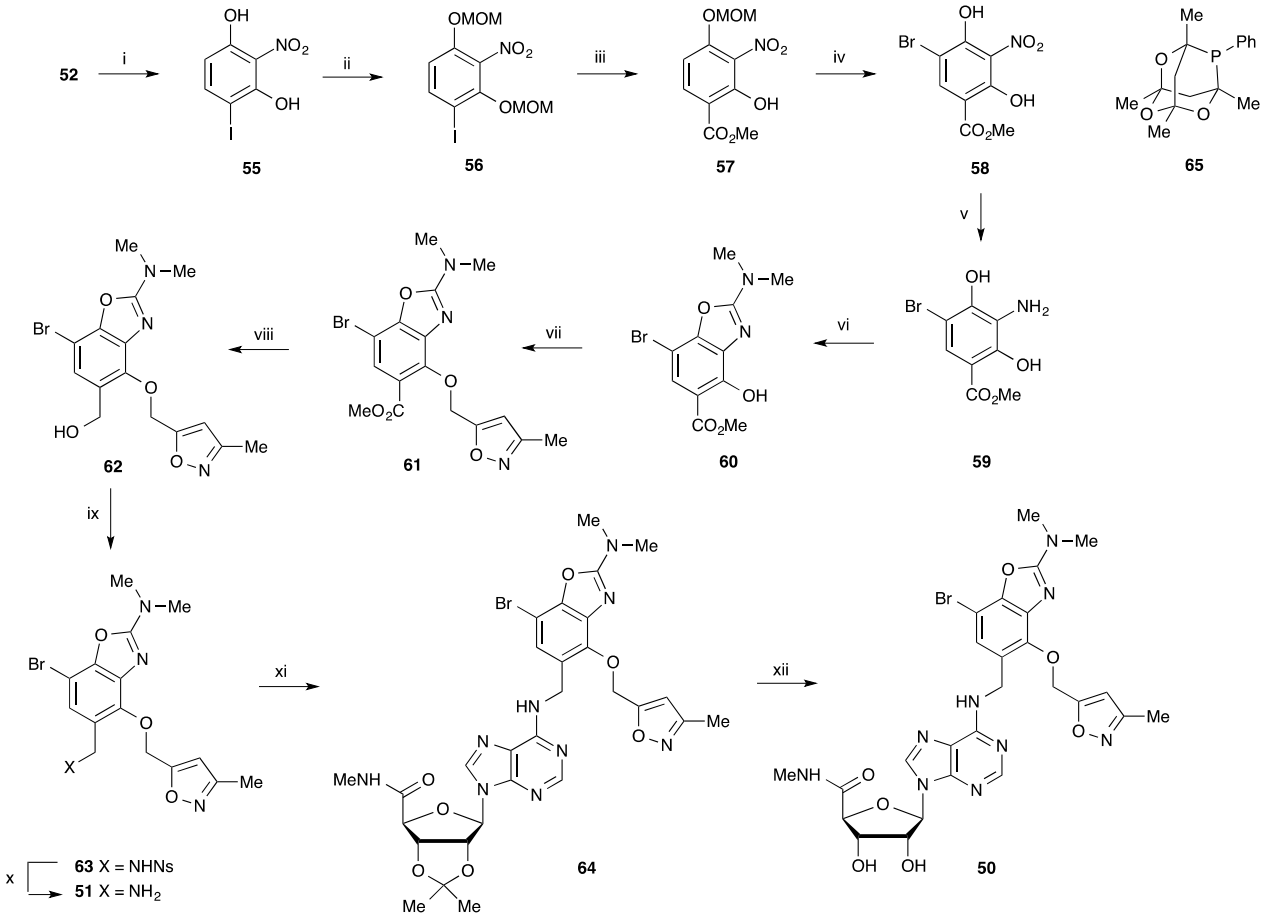


Figure 5 The structure of the alcohol **62** as confirmed by X-ray diffraction

The alcohol **62** was converted into the required primary amine **51** by a Mitsunobu reaction using 2-nitrobenzene sulfonamide, monoalkylation being the major reaction pathway in this hindered system. Denosylation of the intermediate sulfonamide **63** then gave the primary amine **51**. Substitution of the chloride from the 6-chloropurine **4** using the amine **51** proceded uneventfully, and deprotection of the resulting acetonide **64** gave the required *N*6-substituted purinyluronamide **50**.

This potentially selective adenosine A_3 receptor agonist **50** had been prepared in twelve steps from the commercially available resorcinol **62** in an overall yield of 21%. The structures of the products shown in Scheme 7 were consistent with their spectroscopic data, the structures of the benzoxazoles being confirmed by the X-ray crystal structure of the alcohol **62**.



Scheme 7 Synthesis of the adenosine A_3 receptor agonist **50** Reagents and conditions (i) NIS, TFA, rt, 16 h (ca. 100%); (ii) MOMCl, $^{i}Pr_2NEt$, DMF, rt, 1.5 h (96%); (iii) **65**, $Pd(OAc)_2$, Cs_2CO_3, MeOH, CO, 60 °C, 16 h (94%); (iv) Br_2, $CHCl_3$, rt, 48 h (83%); (v) Zn, AcOH, MeOH, rt, 2 min (98%); (vi) ($Cl_2C{=}NMe_2Cl$, Et_3N, DCM, reflux, 2 h (56%); (vii) 5-hydroxymethyl-3-methylisoxazole, Ph_3P, THF, DIAD, 0 °C, then rt, 16 h (99%); (viii) $NaBH_4$, $CaCl_2$, THF, rt, 2 h, add **61**, rt, 48 h (75%); (ix) NsCl, Ph_3P, DIAD, DCM, 0 °C then rt, 16 h (87%); (x) PhSH, K_2CO_3, MeCN, rt, 16 h (98%); (xi) **4,** Et_3N, EtOH, reflux, 18 h (91%); (xii) aq. HCO_2H, rt, 16 h (85%).

Summary and conclusions

Compounds **3**, **36**, **48**, **49** and **50**, were screened for activity as adenosine A3 receptor agonists and were found to demonstrate useful activity.

Of interest in the synthetic work described here is the unexpected regioselectivity of the redox reaction of the pyridine *N*-oxide **14** since usually an ortho-methyl substituent is oxidised in 2,4-dimethylpyridines,[12] as was observed for the analogous reaction of the 5-hydroxy-2,4-dimethylpyridine *N*-oxide **16**. The origin of this unexpected regioselectivity in the reaction of pyridine *N*-oxide **14** is not obvious, but must involve the selective deprotonation of the 7-methyl group to give the *p*-quinoidal intermediate **66** that reacts with trifluoroacetate via an intermolecular process, see Figure 6. Hydrolysis of the resulting product **67** could then deliver the observed product **15**. The oxazole ring clearly has a role in influencing this regioselectivity and may well be protonated or trifluoroacetylated under the reaction conditions. The enhanced acidity of the *p*-methyl group may then be due to an electrostatic effect involving the proximate oxazole ring.

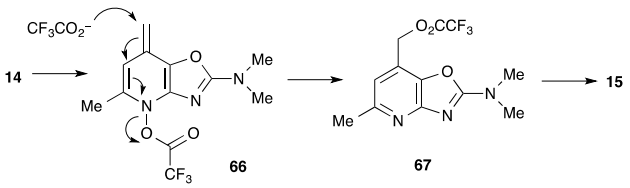


Figure 6 Intermediates that may be involved with the regioselective redox reaction of pyridine *N*-oxide **14**

Other aspects of the syntheses that may be of some interest are the mild conditions used for the nitration of the hydroxypyridines **11** and **18**; the improved conditions of the conversion of iodide **56** into the ester **57**, and the acccompanying regioselective monodeprotection; the regioselective formation of the benzoxazole **60**; and the overall strategies used in the synthesis of the highly substituted pyridine and benzene derivatives used in this work. Further studies leading to the additional development of these adenosine A_3 receptor agonists would be of interest.

Experimental

General experimental details

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Inova 400 and Varian Unity Inova 300 spectrometers with residual non-deuterated solvent as the internal standard. Only distinguishable peaks are reported for minor isomers in isomeric mixtures. IR spectra were recorded on an ATI Mattson Genesis FTIR as thin films produced by evaporation of a dichloromethane solution on sodium chloride plates unless otherwise stated. Mass spectra were recorded on Fison VG Trio 2000 and Kratos Concept spectrometers. Chromatography refers to flash column chromatography using Merck silica gel 60 H (230-300 mesh). Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. Dichloromethane was dried and distilled from calcium hydride under an atmosphere of nitrogen. Ether refers to diethyl ether, which was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. Light petroleum refers to the fraction of petroleum ether distilled between 40-60 °C. Benzene and hexane were dried over sodium metal. Butyllithium (1.6 M in hexanes) was titrated against a solution of propan-2-ol in xylene with 2,2′-bipyridine as an indicator. Triethylamine and di-isopropylamine were dried over potassium hydroxide pellets. Brine refers to saturated aqueous sodium chloride.

4,6-Dimethyl-3-hydroxy-2-nitropyridine (**7**)

Fuming sulfuric acid (147 g, 1.498 mol) was added slowly with stirring to 2,4-lutidine (**8**) (15 g, 140 mmol) cooled in an ice bath. Potassium nitrate (25.5 g, 252 mmol, 1.8 eq) was added slowly, and the reaction mixture gradually heated to 100 °C and maintained at this temperature for 8 h. The reaction mixture was then heated at 120 °C for 8 h. After cooling to rt, the reaction mixture was poured onto ice (300 g), then neutralized to pH 7 using K_2CO_3 and filtered. The filtrate was extracted with chloroform (5 × 300 mL) and the organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure and the residue distilled to give 5-nitro-2,4-lutidine (**9**)[8a] as a pale oil (3.62 g, 17%), b.p. 79 °C (3.73 mm Hg) [lit.[8a] 44 °C (0.17 mm Hg)], R_f 0.60 (Et_2O); ν_{max}/cm^{-1} 2930, 1610, 1557, 1519, 1346 and 838; δ_H (300 MHz, $CDCl_3$) 2.62 and 2.63 (each 3 H, s, CH_3), 7.15 (1 H, s, 3-H) and 9.10 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 20.5, 24.5, 126.9, 143.6, 145.9 and 163.5; *m/z* (ES+) 153.1 (M^+ + 1, 100%).

Palladium on charcoal (10%, 280 mg, 2 mol%) was added to 5-nitro-2,4-lutidine (**9**) (2 g, 13.1 mmol) in methanol (39 mL). The mixture was stirred at rt under hydrogen at atmospheric pressure for 16 h then filtered, and concentrated under reduced pressure to leave 5-amino-2,4-lutidine (**10**)[8a] (1.67 g, ca. 100%) used without purification, R_f 0.13 (10% MeOH/Et_2O); ν_{max}/cm^{-1} 3375, 3338, 3209, 1651, 1612, 1505, 1448, 1242 and 868; δ_H (300 MHz, $CDCl_3$) 2.12 (3 H, s, 4-CH_3), 2.39 (3 H, s, 2-CH_3), 3.37 (2 H, br. s, 3-NH_2), 6.82 (1 H, s, 3-H) and 7.91 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 17.0, 23.4, 124.8, 131.8, 136.3, 139.1 and 148.6; *m/z* (ES+) 123.1 (M^+ + 1, 100%).

Sodium nitrite (1.47 g, 21.3 mmol, 1.1 eq) in water (15 mL) was added over a period of 7 min to 5-amino-2,4-lutidine (**10**) (2.37 g, 19.4 mmol) in aqueous sulfuric acid (4.8%, 37.8 mL) cooled to 0 °C using dry ice/acetone bath. The solution was maintained at 0 °C for 15 min and then heated under reflux for 5 min. After cooling to room temperature, the solution was neutralised to pH 7 with K_2CO_3 and the mixture extracted with methanol in dichloromethane (10%, 10 × 100 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (50% to 90% Et_2O/light petroleum) gave 5-hydroxy-2,4-lutidine (**11**)[8a] as a white solid (1.13 g, 47%), m.p. 146-148 °C (lit.[8a] 146-148 °C), R_f 0.61 (10% MeOH/Et_2O); ν_{max}/cm^{-1} 2922, 2618, 2554, 1612, 1504, 1462, 1423, 1295, 1219 and 946; δ_H (300 MHz, $CDCl_3$) 2.28 (3 H, s, 4-CH_3), 2.46 (3 H, s, 2-CH_3), 6.98 (1 H, s, 3-H) and 8.08 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 16.1, 22.1, 126.5, 134.0, 137.2, 147.8 and 152.4; *m/z* (ES+) 124.2 (M^++ 1, 100%).

Ceric ammonium nitrate (8.90 g, 16.24 mmol, 2.0 eq) was added to 5-hydroxy-2,4-lutidine (**11**) (1.00 g, 8.12 mmol) and $NaHCO_3$ (2.05 g, 24.36 mmol, 3.0 eq) in anhydrous acetonitrile (93 mL) at rt. The mixture was heated under reflux for 6 h then filtered and the filtrate concentrated under reduced pressure. The residue was taken up into water (30 mL) and extracted with dichloromethane (3 × 30 mL). The organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue (10% to 30% Et_2O/light petroleum) gave the *title compound* **7** as yellow solid (577 mg, 42%), R_f 0.63 (Et_2O), m.p. 63-65 °C; ν_{max}/cm^{-1} 3228, 2966, 2933, 1573, 1538, 1479, 1447, 1385, 1360, 1323, 1256, 1229, 1184, 1036, 1019, 913, 896, 807, 772 and 765; δ_H (300 MHz, $CDCl_3$) 2.42 (3 H, s, CH_3), 2.57 (3 H, s, CH_3), 7.36 (1 H, s, 5-H) and 10.45 (1 H, s, 3-OH); δ_C (100 MHz, $CDCl_3$) 15.8, 23.3, 133.0, 141.1, 141.4, 148.3 and 149.0; *m/z* (ES−) 151.2 (M^+ − 1, 100%).

5,7-Dimethyl-2-dimethylamino-oxazolo[4,5-*b*]pyridine (**6**)

A mixture of the nitropyridine **7** (768 mg, 4.60 mmol) and palladium on charcoal (10%, 10 mg, 2 mol%) in ethyl acetate (17 mL) was stirred at rt for 16 h under an atmosphere of hydrogen then filtered through a pad of Celite.® The filtrate was concentrated under reduced pressure to leave 2-amino-3-hydroxy-4,6-dimethylpyridine **13** (660 mg) used without purification, R_f 0.15 (10% MeOH/Et_2O); δ_H (300 MHz, $CDCl_3$) 2.18 and 2.27 (each 3 H, s, CH_3), 6.30 (1 H, s, 5-H) and 6.55 (3 H, br. s, NH_2 and OH); δ_C (75 MHz, $CDCl_3$) 16.4, 21.2, 116.3, 134.7, 139.4, 139.9 and 149.8; *m/z* (ES+) 139 (M^+ + 1, 100%).

A solution of 2-amino-3-hydroxy-4,6-dimethylpyridine **13** (685 mg, 4.96 mmol) and dichloromethylene(dimethyl)ammonium chloride (1.29 g, 7.93 mmol, 1.6 eq) in dry dichloromethane (52 mL) was heated under reflux for 5 h. After cooling, the mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and the mixture extracted with dichloromethane (4 × 30 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **6** as a pale solid (1.05 g) used without purification, R_f 0.38 (10% MeOH/Et_2O), m.p. 128-130 °C (Found: M^+ + H, 192.1134. $C_{10}H_{14}N_3O$ requires *M*, 192.1131); ν_{max}/cm^{-1} 2952, 2925, 1664, 1644, 1567, 1446, 1425, 1379, 1223, 1192, 1142, 1044, 956, 892, 875 and 730. δ_H (300 MHz, $CDCl_3$) 2.39 and 2.53 (each 3 H, s, CH_3), 3.26 [6 H, s, 2-N(CH_3)$_2$] and 6.60 (1 H, s, 6-H); δ_C (125 MHz, $CDCl_3$) 13.6, 22.9, 36.4, 115.6, 125.3, 138.2, 151.9, 156.5 and 163.2; *m/z* (ES+) 405.2 ($2M^+$ + 23, 18%), 383.2 ($2M^+$ + 1, 11) and 192.2 (M^+ + 1, 100).

5,7-Dimethyl-2-dimethylamino-oxazolo[4,5-*b*]pyridine 4-oxide (**14**)

m-Chloroperoxybenzoic acid (77%, 1.60 g, 7.14 mmol, 1.3 eq) was added to the oxazolopyridine **6** (1.05 g, 5.49 mmol) in chloroform (11 mL) and the mixture stirred for 16 h. After concentrated under reduced pressure, chromatography of the residue (5% to 10% MeOH/CH_2Cl_2) gave the *title compound* **14** (1.09 g, 78%), R_f 0.13 (30% MeOH/Et_2O), m.p. 204-206 °C (Found: M^+ + H, 208.1084. $C_{10}H_{14}N_3O_2$ requires *M*, 208.1081); ν_{max}/cm^{-1} 3396, 2927, 1675, 1592, 1464, 1426, 1375, 1358, 1234, 1190, 1118, 943, 891, 748 and 723; δ_H (300 MHz, $CDCl_3$) 2.37 and 2.57 (each 3 H, s, CH_3), 3.29 [6 H, s, 2-N(CH_3)$_2$] and 6.65 (1 H, s, 6-H); *m/z* (ES+) 437.3 ($2M^+$ + 23,

70%), 414.9 ($2M^+ + 1$, 25), 230.1 ($M^+ + 23$, 62) and 208.2 ($M^+ + 1$, 100).

2-Dimethylamino-7-hydroxymethyl-5-methyloxazolo[4,5-*b*]pyridine (15)

Trifluoroacetic anhydride (5.20 mL, 37.21 mmo1, 10.0 eq.) was added to the *N*-oxide **14** (771 mg, 3.72 mmol) in dry dichloromethane (21 mL) and the mixture heated under reflux for l6 h. After concentration under reduced pressure, the solid residue was dissolved in dichloromethane (15 mL). Aqueous potassium carbonate (2 M, 5 mL) was added and the biphasic mixture stirred for 1 h. Water (10 mL) was added and the aqueous phase was extracted with dichloromethane (6 × 15 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (Et_2O% to 10% MeOH/Et_2O) gave the *title compound* **15** as a pale solid (220 mg, 29%), R_f 0.17 (10% MeOH/Et_2O), m.p. 188-190 °C (Found: $M^+ + H$, 208.1088, $C_{10}H_{14}N_3O_2$ requires *M*, 208.1081); ν_{max}/cm^{-1} 3163, 2925, 1664, 1640, 1567, 1399, 1283, 1195, 1043, 891 and 725; δ_H (300 MHz, $CDCl_3$) 2.54 (3 H, s, 5-CH_3), 3.24 [6 H, s, 2-N(CH_3)$_2$], 4.88 (2 H, s, 7-CH_2) and 6.84 (1 H, s, 6-H); δ_C (125 MHz, $CDCl_3$) 22.9, 36.5, 57.5, 112.1, 129.3, 136.0, 152.0, 156.6 and 163.3; *m/z* (ES+) 437.1 ($2M^+ + 23$, 21%) and 208.2 ($M^+ + 1$, 100).

2-Acetoxymethyl-5-hydroxy-4-methylpyridine (18)

m-Chloroperoxybenzoic acid (77%, 2.25 g, 10.5 mmol, 1.1 eq) was added to 2,4-dimethyl-5-hydroxypyridine **8** (1.13 g, 9.17 mmol) in dichloromethane (18 mL) and the mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (Et_2O to 10% MeOH/Et_2O) gave 2,4-dimethyl-5-hydroxypyridine *N*-oxide (**16**)[8a] (1.09 g, 85%), m.p 227-229 °C (lit.[8a] 229 °C), R_f 0.55 (10% MeOH/Et_2O); ν_{max}/cm^{-1} 3390, 2961, 2921, 1514, 1491, 1434, 1310, 1189, 1105, 879 and 844; δ_H (300 MHz, CD_3OD) 2.25 (3 H, s, 4-CH_3), 2.43 (3 H, s, 2-CH_3), 7.26 (1 H, s, 3-H) and 7.89 (1 H, s, 6-H); δ_C (75 MHz, CD_3OD) 13.9, 15.4, 126.1, 127.7, 131.1, 140.2 and 153.0; *m/z* (ES+) 140.1 ($M^+ + 1$, 100%).

A mixture of 2,4-dimethyl-5-hydroxypyridine *N*-oxide (**16**) (1.09 g, 7.8 mmol) and acetic anhydride (20 mL) was heated at 110 °C with stirring for 2.5 h. After cooling and concentration under reduced pressure, chromatography of the residue (30% to 50% Et_2O/light petroleum) gave 5-acetoxy-2-acetoxymethyl-4-methylpyridine (**17**)[8a] as a pale oil (1.40g, 80%), R_f 0.11 (50% Et_2O/light petroleum); ν_{max}/cm^{-1} 1760, 1747, 1609, 1486, 1440, 1371, 1268, 1232, 1218, 1194, 1135, 1048, 1013 and 892; δ_H (300 MHz, $CDCl_3$) 2.16 [3 H, s, 2-$CH_2OC(O)CH_3$], 2.23 [3 H, s, 5-$OC(O)CH_3$], 2.36 (3 H, s, 4-CH_3), 5.18 (2 H, s, 2-CH_2), 7.16 (1 H, s, 3-H) and 8.28 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 16.2, 20.9, 21.2, 66.6, 124.6, 140.5, 143.5, 146.2, 153.2, 169.0 and 170.9; *m/z* (CI+) 224 ($M^+ + 1$, 100%).

Pyrrolidine (215 µL, 2.57 mmol) was added to the bis-acetate **17** (574 mg, 2.57 mmol) in dichloromethane (7.2 mL) and the mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (50% to 100% Et_2O/light petroleum) gave the *title compound* **18** as a pale oil (467 mg, ca. 100%), R_f 0.23 (Et_2O) (Found : $M^+ + Na$, 204.0627. $C_9H_{11}NO_3Na$ requires *M*, 204.0631); ν_{max}/cm^{-1} 3028, 2959, 1747, 1611, 1505, 1455, 1363, 1293, 1229, 1032 and 879; δ_H (300 MHz, $CDCl_3$) 2.10 (3 H, s, CH_3CO), 2.34 (3 H, s, 4-CH_3), 5.16 (2 H, s, 2-CH_2), 7.25 (1 H, s, 3-H) and 8.16 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 16.2, 21.1, 65.9, 126.4, 134.7, 137.2, 145.4, 154.0 and 171.1; *m/z* (ES+) 204 ($M^+ + 23$, 25%) and 182 ($M^+ + 1$, 100).

2-Acetoxymethyl-5-hydroxy-4-methyl-6-nitropyridine (19)

Ceric ammonium nitrate (1.55 g, 2.84 mmol, 1.1 eq) was added to 2-acetoxymethyl-5-hydroxy-4-methylpyridine (**18**) (467 mg, 2.58 mmol), and sodium hydrogen carbonate (346 mg, 4.12 mmol, 1.6 eq) in anhydrous acetonitrile (29 mL) at rt and the mixture stirred under reflux for 5 h. The mixture was filtered, and the filtrate washed with water then extracted with dichloromethane (3 × 20 mL). The organic extracts were dried (Na_2SO_4), and concentrated under reduced presure. Chromatography of the residue (10% to 30% Et_2O/light petroleum) gave the *title compound* **19** as yellow solid (223 mg, 38%), R_f 0.65 (Et_2O), m.p. 84-87 °C (Found: $M^+ + Na$, 249.0489. $C_9H_{10}N_2O_5Na$ requires *M*, 249.0482); ν_{max}/cm^{-1} 3297, 2962, 1744, 1615, 1573, 1543, 1482, 1440, 1410, 1380, 1356, 1322, 1229, 1049, 917 and 773; δ_H (300 MHz, $CDCl_3$) 2.16 (3 H, s, CH_3CO), 2.44 (3 H, s, 4-CH_3), 5.16 (2 H, s, 2-CH_2), 7.55 (1 H, s, 3-H) and 10.19 (1 H, br. s, 5-OH); δ_C (75 MHz, $CDCl_3$) 16.2, 21.1, 65.9, 131.6, 141.2, 142.6, 146.3, 149.6 and 170.8; *m/z* (ES−) 225 ($M^+ - 1$, 100%).

3-Hydroxy-6-hydroxymethyl-4-methyl-2-nitropyridine (20)

Aqueous sodium hydroxide (2 M, 2.21 mL, 4.42 mmol, 2.0 eq) was added to the acetoxymethylpyridine **19** (500 g, 2.21 mmol) in methanol (16 mL) and the mixture was stirred at rt for 1 h. After concentration under reduced pressure, the residue was taken up in water (15 mL) and the solution neutralised using aqueous hydrogen chloride (2 M) and extracted with dichloromethane (6 × 20 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the *title compound* **20** that was used without purification, R_f 0.52 (Et_2O), m.p. 136-139 °C (Found: $M^+ + Na$, 207.0380. $C_7H_8N_2O_4Na$ requires *M*, 207.0376); ν_{max}/cm^{-1} 3321, 2474, 1535, 1478, 1362, 1307, 1257, 1200 and 1089; δ_H (300 MHz, CD_3OD) 2.45 (1 H, s, 4-CH_3), 4.63 (2 H, s, 6-CH_2) and 7.74 (1 H, s, 5-H); δ_C (75 MHz, CD_3OD) 15.0, 63.6, 129.7, 142.5, 147.8 and 151.3; *m/z* (ES+) 207.1 ($M^+ + 23$, 100%) and 185.1 ($M^+ + 1$, 32).

2-Amino-3-hydroxy-6-hydroxymethyl-4-methylpyridine (21)

A mixture of the nitropyridine **20** (52 mg, 0.19 mmol) and palladium on charcoal (10%, 10 mg) in ethyl acetate (15 mL) was stirred at rt for 2 h under an atmosphere of hydrogen. The reaction mixture was then filtered through a pad of Celite® and the filtrate concentrated under reduced pressure to leave the *title compound* **21**, R_f 0.07 (20% MeOH/Et_2O) (Found: $M^+ + H$, 155.0820. $C_7H_{11}N_2O_2$ requires *M*, 155.0815); δ_H (300 MHz, CD_3OD) 2.22 (3 H, s, 4-CH_3), 4.44 (2 H, s, 6-CH_2) and 6.57 (1 H, s, 5-H); *m/z* (CI+) 155 ($M^+ + 1$, 100%) and 154 (93).

6-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxy-4-methyl-2-nitropyridine (22)

tert-Butyldiphenylsilyl chloride (245 µL, 0.94 mmol, 1.05 eq) was added to the hydroxymethylpyridine **20** (165 mg, 0.90 mmol) and imidazole (305 mg, 4.48 mmol, 5 eq) in *N*,*N*-dimethylformamide (3.6 mL) and the mixture was stirred at room temperature for 12 h. Water (20 mL) was added and the mixture was extracted with dichloromethane (6 × 20 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (2% to 10% Et_2O/light petroleum) gave the *title compound* **22** as a yellow solid (285 mg, 75%), R_f 0.63 (Et_2O), m.p. 84-86 °C (Found: $M^+ + H$, 423.1746. $C_{23}H_{27}N_2O_4Si$ requires *M*, 423.1735); ν_{max}/cm^{-1} 3233, 2957, 2929, 2857, 1577, 1540, 1473, 1427, 1409, 1358, 1307, 1263, 1111, 824, 741 and 701; δ_H (300 MHz, $CDCl_3$) 1.18 [9 H, s, $SiC(CH_3)_3$], 2.49 (3 H, s, 4-CH_3), 4.85 (2 H, s, 6-CH_2), 7.39-7.51 (6 H, m, ArH), 7.68-7.72 (4 H, m, ArH), 7.83 (1 H, s, 5-H), 10.47 (1 H, s, OH); δ_C (75 MHz, $CDCl_3$) 16.5, 19.6, 27.2, 66.1, 128.1, 130.0, 130.2, 133.0, 135.8, 142.1, 149.0 and 151.5; *m/z* (ES+) 867.6 ($2M^+ + 23$, 57%), 445.3 ($M^+ + 23$, 75%) and 423.3 ($M^+ + 1$, 100).

2-Amino-6-*tert*-butyldiphenylsilyloxymethyl-3-hydroxy-4-methylpyridine (**23**)

A mixture of the nitropyridine **22** (285 mg, 0.67 mmol) and palladium on charcoal (10%, 14 mg, 2 mol%) in ethyl acetate (2.5 mL) was stirred at rt for 16 h under an atmosphere of hydrogen. The reaction mixture was then filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give the *title compound* **23** (290 mg) used without further purification, R_f 0.21 (Et_2O), m.p. 131–133 °C (Found: $M^+ + H$, 393.1999. $C_{23}H_{29}N_2O_2Si$ requires *M*, 393.1993); ν_{max}/cm^{-1} 3478, 3377, 2957, 2930, 2857, 1623, 1474, 1427, 1162, 1113, 823, 740 and 702; δ_H (300 MHz, $CDCl_3$) 1.13 [9 H, s, $SiC(CH_3)_3$], 2.18 (3 H, s, 4-CH_3), 4.64 (2 H, s, 6-CH_2), 5.02 (3 H, br. s, 2-NH_2 and 3-OH), 6.71 (1 H, s, 5-H), 7.35-7.47 (6 H, m, ArH) and 7.69-7.72 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 16.1, 19.6, 27.2, 65.7, 113.4, 128.0, 130.0, 133.1, 133.6, 135.1, 135.8, 137.2 and 149.1; *m/z* (ES+) 393.3 ($M^+ + 1$, 100%).

5-*tert*-Butyldiphenylsilyloxymethyl-2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridine (**24**)

A solution of the pyridine **23** (265 mg, 0.67 mmol), dichloromethylene(dimethyl)ammonium chloride (175 mg, 1.08 mmol, 1.6 eq), and triethylamine (301 µL, 2.16 mmol, 3.2 eq) in dry dichloromethane (7.1 mL) was heated under reflux for 6 h. After cooling, the solution was poured into saturated aqueous sodium bicarbonate (20 mL) and the mixture extracted with dichloromethane (4 × 20 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% MeOH/CH_2Cl_2) gave the *title compound* **24** as a pale oil (260 mg, 86%), R_f 0.16 (Et_2O) (Found: $M^+ + H$, 446.2257. $C_{26}H_{32}N_3O_2Si$ requires *M*, 446.2258); ν_{max}/cm^{-1} 2952, 2931, 2857, 2359, 2346, 1660, 1570, 1428, 1386, 1139, 1112, 1089, 894 and 837; δ_H (300 MHz, $CDCl_3$) 1.17 [9 H, s, $SiC(CH_3)_3$], 2.48 (3 H, s, 7-CH_3), 3.25 [6 H, s, 2-$N(CH_3)_2$], 4.90 (2 H, s, 5-CH_2), 7.13 (1 H, s, 6-H), 7.37-7.48 (6 H, m, ArH) and 7.73-7.76 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 15.2, 19.6, 27.2, 37.7, 67.0, 113.9, 126.7, 128.0, 129.9, 133.8, 135.8, 140.3, 155.6, 157.7 and 164.6; *m/z* (ES+) 446.4 ($M^+ + 1$, 100%).

2-Dimethylamino-5-hydroxymethyl-7-methyloxazolo[4,5-*b*]pyridine (**25**)

Tetrabutylammonium fluoride in tetrahydrofuran (1 M, 0.7 mL, 0.70 mmol, 1.2 eq) was added to the silyl ether **24** (260 mg, 0.58 mmol) in tetrahydrofuran (10 mL) at rt and the solution stirred for 1 h. After concentration under reduced pressure, chromatography of the residue 10% MeOH/CH_2Cl_2) gave the *title compound* **25** as a white solid (111 mg, 92%), R_f 0.24 (10% MeOH/Et_2O), m.p. 203-205 °C (Found: $M^+ + H$, 208.1084. $C_{10}H_{14}N_3O_2$ requires *M*, 208.1081); ν_{max}/cm^{-1} 3235, 2925, 2873, 1662, 1644, 1574, 1403, 1383, 1136, 1064, 895, 837, 776 and 726; δ_H (300 MHz, CD_3OD) 2.47 (3 H, s, 7-CH_3), 3.26 [6 H, s, 2-$N(CH_3)_2$], 4.65 (2 H, s, 5-CH_2) and 7.00 (1 H, s, 6-H); δ_C (75 MHz, CD_3OD) 13.5, 36.5, 64.5, 114.6, 127.8, 140.3, 155.3, 157.2 and 164.8; *m/z* (ES+) 437.0 ($2M^+ + 23$, 20%), 230.1 ($M^+ + 23$, 22) and 208.2 ($M^+ + 1$, 100%).

***N*-(2-Dimethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethyl) 2-nitrobenzenesulfonamide** (**26**)

Di-*iso*propylazodicarboxylate (104 µL, 0.53 mmol, 1.3 eq) was added to 2-nitrobenzenesulfonamide (123 mg, 0.61 mmol, 1.5 eq), triphenylphosphine (139 mg, 0.53 mmol, 1.3 eq) and the alcohol **25** (84.2 mg, 0.41 mmol) in tetrahydrofuran (10 mL) and the reaction mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (Et_2O to 10% MeOH/Et_2O) gave the *title compound* **26** (50 mg, 31%), R_f 0.36 (10% MeOH/Et_2O) (Found: $M^+ + H$, 392.1027. $C_{16}H_{18}N_5O_5S$ requires *M*, 392.1023); ν_{max}/cm^{-1} 3330, 3094, 3031, 1664, 1572, 1540, 1430, 1393, 1372, 1341, 1291, 1167, 895, 854, 782 and 733; δ_H (300 MHz, $CDCl_3$) 2.38 (3 H, s, 7-CH_3), 3.26 [6 H, s, 2-$N(CH_3)_2$], 4.38 (2 H, d, *J* 5.4 Hz, 5-CH_2), 6.43 (1 H, m, NH), 6.73 (1 H, s, 6-H), 7.64-7.71 (2 H, m, ArH), 7.84 (1 H, m, ArH) and 8.13 (1 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 14.9, 37.8, 48.7, 116.1, 125.4, 127.0, 131.1, 132.7, 133.5, 133.9, 140.6, 148.2, 149.5, 158.1, 164.8; *m/z* (ES+) 450.3 (85%), 414.2 ($M^+ + 23$, 18) and 392.2 ($M^+ + 1$, 100). The bis-alkylated sulfonamide, bis-*N*-(2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethyl) 2-nitrobenzenesulfonamide was also isolated (Found: $M^+ + H$, 581.1917. $C_{26}H_{29}N_8O_6S$ requires *M*, 581.1925); ν_{max}/cm^{-1} 3417, 2960, 2928, 1729, 1664, 1568, 1543, 1390, 1287, 1163, 1075, 894, 791 and 734; δ_H (300 MHz, $CDCl_3$) 2.34 (6 H, s, 2 × 7-CH_3), 3.27 [12 H, s, 2 × 2-$N(CH_3)_2$], 4.79 (4 H, s, 2 × 5-CH_2), 6.83 (2 H, s, 2 × 6-H), 7.50-7.64 (3 H, m, ArH) and 8.15 (1 H, m, ArH); *m/z* (ES+) 581.4 ($M^+ + 1$, 100%).

5-Aminomethyl-2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridine (**5**)

A mixture of the sulfonamide **26** (50 mg, 0.13 mmol), thiophenol (039 µL, 0.38 mmol, 3.0 eq) and potassium carbonate (70 mg, 0.51 mmol) in acetonitrile (2.1 mL) was stirred at rt for 16 h. Direct chromatography (10% to 20% MeOH/CH_2Cl_2/1% Et_3N) gave the *title compound* **5** as a pale oil (22 mg, 84%), R_f 0.57 (20% MeOH/CH_2Cl_2) (Found: $M^+ + H$, 207.1232. $C_8H_{13}N_7$ requires *M*, 207.1227); ν_{max}/cm^{-1} 3368, 2928, 1667, 1572, 1431, 1394, 1288, 1220, 1142, 896 and 733; δ_H (300 MHz, CD_3OD) 2.46 (3 H, s, 7-CH_3), 3.27 [6 H, s, 2-$N(CH_3)_2$], 3.93 (2 H, br s, 5-CH_2) and 6.88 (1 H, s, 6-H); δ_C (75 MHz, CD_3OD) 13.4, 36.6, 45.3, 115.8, 127.8, 140.5, 153.0, 157.5 and 164.8; *m/z* (ES+) 207.2 ($M^+ + 1$, 100%).

1′-[6-(2-Dimethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethylamino)-9*H*-purin-9-yl]-2′,3′-*O*-isopropylidene-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (**27**)

A solution of 6-chloropurine-2′,3′-*O*-isopropylidene-*N*-methyluronamide **4** (38 mg, 0.11 mmol), amine **5** (22 mg, 0.11 mmol) and triethylamine (30 µL, 0.21 mmol, 2.0 eq) in ethanol (1.1 mL) was stirred at 80 °C for 16 h then comcentrated under reduced pressure. Chromatography of the residue (20% to 30% MeOH/Et_2O/1% Et_3N) gave the *title compound* **27** as a white solid (51 mg, 90%), R_f 0.27 (20% MeOH/Et_2O), m.p. >250 °C (dec.) (Found: $M^+ + Na$, 546.2178. $C_{24}H_{29}N_9O_5Na$ requires *M*, 546.2184); ν_{max}/cm^{-1} 3380, 2986, 2939, 1652, 1644, 1621, 1615, 1574, 1480, 1430, 1393, 1333, 1290, 1266, 1213, 1157, 1092, 977, 895, 869, 851, 797 and 734; δ_H (500 MHz, CD_3OD) 1.27 and 1.44 (each 3 H, s, CH_3), 2.19 (3 H, s, NHCH_3), 2.20 (3 H, s, 7″-CH_3), 3.08 [6 H, s, 2″-$N(CH_3)_2$], 4.50 (1 H, d, *J* 1.0 Hz, 4′-H), 4.68 (2 H, br. s, 5″-CH_2), 5.32 (1 H, dd, *J* 6.0, 1.0 Hz, 2′-H), 5.44 (1 H, dd, *J* 6.0, 2.0 Hz, 3′-H), 6.19 (1 H, d, *J* 1.0 Hz, 1′-H), 6.69 (1 H, s, 6″-H), 8.06 (1 H, s, 8-H) and 8.07 (1 H, s, 2-H); δ_C (75 MHz, CD_3OD) 8.14, 13.5, 24.3, 24.7, 26.0, 36.6, 84.0, 84.2, 87.4, 91.4, 113.8, 115.2, 119.7, 127.6, 140.2, 141.0, 147.7, 152.5, 152.7, 154.8, 157.5, 164.8 and 171.1; *m/z* (ES+) 655.8 (100%), 562.7 ($M^+ + 39$, 2) and 546.6 ($M^+ + 23$, 26).

1′-[6-(2-Dimethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethylamino)-9*H*-purin-9-yl]-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (**3**)

A solution of the acetonide **27** (51 mg, 0.10 mmol) in aqueous hydrogen chloride (1 M, 793 µL) was stirred at 65 °C for 1 h. After cooling, saturated aqueous sodium hydrogen carbonate was added until pH 7 and the mixture was concentrated under reduced pressure. Chromatography of the residue (CH_2Cl_2 to 10% MeOH/CH_2Cl_2/1%

Et_3N) gave the *title compound* **3** as a white solid (35 mg, 76%), R_f 0.17 (20% MeOH/Et_2O), m.p. >228 °C (dec.) (Found: M^+ + H, 484.2055. $C_{21}H_{26}N_9O_5$ requires *M*, 484.2051); ν_{max}/cm^{-1} 3336, 3241, 3086, 2938, 1660, 1618, 1573, 1483, 1399, 1385, 1371, 1330, 1294, 1283, 1232, 1226, 1192, 1136, 1099, 1050, 898, 851, 797, 745 and 732; δ_H (500 MHz, DMSO-d_6) 2.38 (3 H, s, 7″-CH_3), 2.78 (3 H, d, *J* 4.8 Hz, NHCH_3), 3.21 [6 H, s, 2″-N(CH_3)$_2$], 4.21 (1 H, td, *J* 4.3, 1.3 Hz, 3′-H), 4.38 (1 H, d, *J* 0.8 Hz, 4′-H), 4.67 (1 H, td, *J* 6.9, 4.8 Hz, 2′-H), 4.80 (2 H, br. d, *J* 5.0 Hz, 5″-CH_2), 5.67 (1 H, d, *J* 6.3 Hz, 2′-OH), 5.84 (1 H, d, *J* 4.3 Hz, 3′-OH), 6.05 (1 H, d, *J* 7.6 Hz, 1′-H), 6.81 (1 H, s, 6″-H), 8.35 (1 H, s, 2-H), 8.47 (1 H, br. t, *J* 5.0 Hz, 6-NH), 8.53 (1 H, s, 8-H) and 9.01 (1 H, q, *J* 4.5 Hz, NHCO); δ_C (100 MHz, DMSO-d_6) 14.3, 25.3, 37.0, 44.6, 72.0, 73.1, 84.7, 87.8, 113.9, 120.1, 126.1, 139.3, 140.7, 148.1, 152.5, 153.0, 154.6, 157.2, 164.0 and 169.8; *m/z* (ES+) 506.2 (M^+ + 23, 3%) and 484.3 (M^+ + 1, 100).

5-*tert*-Butyldiphenylsilyloxymethyl-7-methyloxazolo[4,5-*b*]pyridine-2(3*H*)-thione (28)

Carbon disulfide (0.468 mL, 7.7 mmol) was added to the aminopyridine **23** (200 mg, 0.509 mmol) and potassium hydroxide (65 mg, 1.16 mmol) in ethanol (1.42 mL) at rt and the mixture heated under reflux for 3 h then concentrated under reduced pressure. The residue was partitioned between aqueous hydrogen chloride (5 M, 10 mL) and ethyl acetate (4 × 15 mL), and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure to yield the *title compound* **28** a yellow solid (184 mg, 83 %), R_f 0.37 (50 % Et_2O/light petroleum), m.p. 166.4-168.2 °C (Found: M^+ + H, 435.1550. $C_{24}H_{27}O_2N_2SSi$ requires *M*, 435.1557); ν_{max}/cm^{-1} 3070, 2930, 2857, 1654, 1613, 1488, 1449, 1427, 1391, 1378, 1289, 1269, 1180, 1114, 906, 835, 822, 739 and 701; δ_H (300 MHz, $CDCl_3$) 1.20 [9 H, s, SiCCH_3)$_3$], 2.53 (3 H, s, 7-CH_3), 5.19 (2 H, s, 5-CH_2), 7.36-7.51 (7 H, m, ArH) and 7.71-7.77 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 15.3, 19.6, 27.3, 66.5, 117.7, 128.1, 130.2, 130.8, 133.2, 135.9, 140.8, 145.7, 156.6 and 181.1; *m/z* (ES−) 433.5 (M^+ − 1, 100 %).

5-*tert*-Butyldiphenylsiloxymethyl-2-diethylamino-7-methyloxazolo[4,5-*b*]pyridine (30)

Thionyl chloride (12.6 µL, 0.15 mmol) was added to a suspension of the thione **28** (50 mg, 0.1 mmol) and sodium carbonate (18 mg, 0.15 mmol) in benzene (0.13 mL) at 0 ºC and the reaction mixture warmed to 50 °C for 3 h then allowed to cool to rt. Diethylamine (66 µL, 0.55 mmol) was added dropwise and the reaction mixture stirred at rt for 1 h. The mixture was partitioned between water (10 mL) and Et_2O (4 × 15 mL). The organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure. Chromatography of the residue (Et_2O to10 % MeOH/Et_2O) gave the *title compound* **30** as a pale oil which solidified upon storage (37 mg, 70 %), R_f 0.38 (50 % Et_2O/ light petroleum), m.p. 90.3-91.6 °C (Found: M^+ + H, 474.2567. $C_{28}H_{36}O_2N_3Si$ requires *M*, 474.2571); ν_{max}/cm^{-1} 3067, 2959, 2929, 2890, 2855, 2355, 1655, 1565, 1461, 1445, 1427, 1389, 1361, 1138, 1112, 1082, 968, 822 and 700; δ_H (300 MHz, $CDCl_3$) 1.19 [9 H, s, Si$(CH_3)_3$], 1.33 (6 H, t, *J* 7.1 Hz, 2 × NCH$_2$CH_3), 2.49 (3 H, s, 7-CH_3), 3.65 (4 H, q, *J* 7.1 Hz, 2 × NCH_2CH$_3$), 4.92 (2 H, s, 5-CH_2), 7.13 (1 H, s, 6-H), 7.35-7.47 (6 H, m, ArH) and 7.74-7.79 (4 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 13.7, 15.3, 19.6, 27.2, 43.2, 67.0, 113.7, 126.5, 128.0, 129.9, 133.8, 135.8, 140.0, 155.5, 157.8 and 163.9; *m/z* (ES+) 947.6 (2M^+ + 1, 24 %) and 474.4 (M^+ + 1, 100).

2-Diethylamino-5-hydroxymethyl-7-methyloxazolo[4,5-*b*]pyridine (31)

Tetrabutylammonium fluoride in tetrahydrofuran (1 M, 0.8 mL, 0.77 mmol) was added to the silyl ether **30** (303 mg, 0.64 mmol) in tetrahydrofuran (10.7 mL) and the reaction mixture stirred for 1 h at rt. After concentration under reduced pressure, the residue was partitioned between water (20 mL) and Et_2O (4 × 20 mL). The organic extracts were dried (Na_2SO_4) and concntrated under reduced pressure. Chromatography of the residue (Et_2O to10 % MeOH/Et_2O) gave the *title compound* **31** as a pale oil (139 mg, 93 %), R_f 0.45 (10 % MeOH/Et_2O) (Found: M^+ + H, 236.1396. $C_{12}H_{18}O_2N_3$ requires *M*, 236.1394); ν_{max}/cm^{-1} 3309, 2974, 2934, 2360, 2340, 1650, 1636, 1570, 1448, 1388, 1363, 1205, 1137, 1071, 968, 876, 778, and 734; δ_H (500 MHz, $CDCl_3$) 1.23 (6 H, t, *J* 7.3 Hz, 2 × NCH$_2$CH_3), 2.32 (3 H, s, 7-CH_3), 3.55 (4 H, q, *J* 7.3 Hz, 2 × NCH_2CH$_3$), 4.61 (2 H, s, 5-CH_2) and 6.57 (1 H, s, 6-H); δ_C (125 MHz, $CDCl_3$) 13.4, 14.7, 43.0, 64.1, 113.7, 126.8, 139.8, 153.7, 157.3 and 163.6; *m/z* (ES+) 236.2 (M^+ + 1, 100%).

***N*-(2-Diethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-yl)methyl-*N*-*tert*-butoxcarbonyl 2-nitrophenylsulfonamide (33)**

Di-*iso*propylazo dicarboxylate (22 µL, 0.11 mmol) was added to the alcohol **31** (20 mg, 0.087 mmol), sulfonamide **32** (39 mg, 0.13 mmol) and triphenylphosphine (29 mg, 0.11 mmol) in tetrahydrofuran (2.2 mL) at rt and the reaction mixture stirred for 16 h. After concentration under reduced presssure, chromatography of the residue (Et_2O) gave the *title compound* **33** as a pale oil (44 mg, 98 %), R_f 0.24 (Et_2O) (Found: M^+ + H, 520.1860. $C_{23}H_{30}O_7N_5S$ requires *M*, 520.1860); ν_{max}/cm^{-1} 2979, 1735, 1652, 1640, 1565, 1544, 1365, 1149 and 1123; δ_H (300 MHz, $CDCl_3$) 1.30 [9 H, s, C$(CH_3)_3$], 1.33 (6 H, t, *J* 7.2 Hz, 2 × NCH$_2$CH_3), 2.44 (3 H, s, 7-CH_3), 3.67 (4 H, q, *J* 7.2 Hz, 2 × NCH_2CH$_3$), 5.11 (2 H, s, 5-CH_2), 6.87 (1 H, s, 6-H), 7.76-7.84 (3 H, m, ArH) and 8.52-8.60 (1 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 13.7, 15.1, 28.0, 43.2, 52.5, 85.2, 114.1, 124.6, 126.6, 132.1, 133.7, 133.9, 134.3, 140.1, 148.1, 150.8, 151.7, 158.1 and 164.0; *m/z* (ES+) 1061.5 (2M^+ + 23, 80 %), 542.3 (M^+ + 23, 78) and 520.4 (M^+ + 1, 100%).

***N*-(2-Diethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-yl)methyl 2-nitrobenzenesulfonamide (34)**

Sulfonamide **33** (102 mg, 0.2 mmol) was dissolved in trifluoroacetic acid (0.51 mL) and the solution stirred at rt for 1 h. Ethyl acetate was added and the mixture was partitioned between saturated aqueous sodium bicarbonate (5 mL) and Et_2O (5 x 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (Et_2O to 10 % MeOH/Et_2O) gave the *title compound* **34** as a pale yellow oil (64 mg, 79 %) R_f 0.1 (Et_2O) (Found: M^+ + H, 420.1330. $C_{18}H_{22}O_5N_5S$ requires *M*, 420.1336); ν_{max}/cm^{-1} 2978, 2360, 1655, 1640, 1568, 1540, 1445, 1393, 1363, 1207, 1167, 1081, 970, 853, 785 and 734; δ_H (300 MHz, $CDCl_3$) 1.32 (6 H, t, *J* 7.2 Hz, 2 × NCH$_2$CH_3), 2.39 (3 H, s, 7-CH_3), 3.64 (4 H, q, *J* 7.2 Hz, 2 × NCH_2CH$_3$), 4.38 (2 H, d, *J* 2.7 Hz, 5-CH_2), 6.41 (1 H, br. t, *J* 2.7 Hz, NH), 6.72 (1 H, s, 6-H), 7.63-7.71 (2 H, m, ArH), 7.85 (1 H, m, ArH) and 8.10 (1 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 13.6, 14.9, 43.3, 48.8, 115.9, 125.5, 126.7, 131.1, 132.6, 133.4, 134.1, 140.3, 149.4, 158.2 and 164.0; *m/z* (ES+) 839.4 (2M^+ + 1, 30 %), 442.3 (M^+ + 23, 37) and 420.3 (M^+ + 1, 100).

5-Aminomethyl-2-diethylamino-7-methyloxazolo[4,5-*b*]pyridine (35)

Thiophenol (17 µL, 0.25 mmol) was added to a suspension of the sulfonamide **34** (24 mg, 0.084 mmol) and potassium carbonate (31 mg, 0.34 mmol) in acetonitrile (0.95 mL) at rt and the reaction mixture was stirred for 16 h. After concentration under reduced pressure, chromatography of the residue (10 % MeOH/CH_2Cl_2 containing 1 % NEt_3) gave the *title compound* **35** as a pale yellow oil (12 mg, 85 %), R_f 0.1 (10 % MeOH/Et_2O) (Found: M^+ + H, 235.1558. $C_{12}H_{19}ON_4$ requires *M*, 235.1553); ν_{max}/cm^{-1} 3369, 2976,

1651, 1567, 1448, 1392, 1364, 1319, 1209, 1083, 1027, 877, 786 and 732; δ_H (300 MHz, $CDCl_3$) 1.29 (6 H, t, *J* 7.2 Hz, 2 × NCH_2CH_3), 2.38 (3 H, s, 7-CH_3), 3.62 (4 H, q, *J* 7.2 Hz, 2 × NCH_2CH_3), 4.22 (2 H, s, 5-CH_2), 5.28 (2 H, br. s, NH_2) and 6.77 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 13.6, 14.9, 43.3, 47.0, 115.2, 126.7, 140.0, 155.0, 158.2 and 163.8; *m/z* (ES+) 257.2 (M^+ + 23, 52 %) and 235.2 (M^+ + 1, 100).

1′-[6-(2-Diethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-ylmethylamino)-9*H*-purin-9-yl]-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (37)

The chloropurine **4** (17 mg, 0.049 mmol) was added to the amine **35** (12 mg, 0.049 mmol) and triethylamine (13.7 µL, 0.1 mmol) in ethanol (0.5 mL) and the reaction mixture heated under reflux for 16 h. Concentration by distillation under reduced pressure gave the 2′,3′-*O*-isopropylidene-1-deoxy-*N*-methyl-β-D-ribofuranuronamide **36** as an oil (15 mg, 55 %), R_f 0.41 (10 % MeOH/ Et_2O) (Found: M^+ + H, 552.2684. $C_{26}H_{34}N_9O_5$ requires *M*, 552.2677); δ_H (500 MHz, $CDCl_3$) 1.24 (6 H, t, *J* 7.0 Hz, 2 × NCH_2CH_3), 1.32 and 1.54 (each 3 H, s, CH_3), 2.31 (3 H, s, 7′′-CH_3), 2.53 (3 H, d, *J* 3.0 Hz, $NHCH_3$), 3.55 (4 H, q, *J* 7.0 Hz, 2 × NCH_2CH_3), 4.62 (1 H, s, 4′-H), 4.80 (2 H, m, 5′′-CH_2), 5.28 (2 H, m, 2′-H and 3′-H), 5.98 (1 H, s, 1′-H), 6.69 (1 H, s, 6′′-H), 7.10 (1 H, br. s, 6-NH), 7.22 (1 H, br. s, $NHCH_3$), 7.73 (1 H, s, 2-H) and 8.27 (1 H, br. s, 8-H); δ_C (125 MHz, $CDCl_3$) 13.4, 14.7, 25.1, 25.6, 27.1, 30.3, 43.1, 45.3, 82.5, 83.7, 85.8, 92.1, 114.4, 115.4, 120.8, 126.6, 139.3, 140.0, 151.0, 153.2, 154.9, 157.9, 163.6 and 169.5; *m/z* (ES+) 574.4 ((M^+ + 23, 100%) and 552.7 (20). This was immediately dissolved in aqueous hydrogen chloride (1 M, 1.5 mL) and the mixture stirred at 65 °C for 1 h. The mixture was neutralised to pH 7 using saturated aqueous sodium hydrogen carbonate then concentrated under reduced pressure. Chromatography of the residue (CH_2Cl_2 to 20 % MeOH/CH_2Cl_2) gave the *title compound* **37** as a white solid (12 mg, 46 %), R_f 0.1 (20 % MeOH/DCM) (Found: M^+ + H, 512.2373. $C_{23}H_{30}O_5N_9$ requires *M*, 512.2364); δ_H (500 MHz, DMSO-d_6) 1.23 (6 H, t, *J* 6.9 Hz, 2 × NCH_2CH_3), 2.33 (3 H, s, 7′′-CH_3), 2.73 (3 H, d, *J* 4.4 Hz, $NHCH_3$), 3.57 (4 H, q, *J* 6.9 Hz, 2 × NCH_2CH_3), 4.16 (1 H, m, 3′-H), 4.33 (1 H, s, 4′-H), 4.62 (1 H, m, 2′-H), 4.74 (2 H, d, *J* 4.7 Hz, 5′′-CH_2), 5.61 (1 H, d, *J* 6.3 Hz, 2′-OH), 5.78 (1 H, d, *J* 4.4 Hz, 3′-OH), 6.00 (1 H, d, *J* 7.5 Hz, 1′-H), 6.76 (1 H, s, 6′′-H), 8.30 (1 H, s, 2-H), 8.42 (1 H, br s, 6-NH), 8.47 (1 H, s, 8-H) and 8.96 (1 H, m, $NHCH_3$); *m/z* (ES+) 533.8 (M^+ + 23, 85 %) and 512.2 (M^+ + 1, 100).

(±)-5-[(*E*)-*tert*-Butylsulfinyliminomethyl]-2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridine (40)

Dess-Martin periodinane (399 mg, 0.94 mmol) was added to the alcohol **25** (130 mg, 0.63 mmol) in dichloromethane (4.5 mL) and the solution stirred for 20 min at rt. The reaction mixture was concentrated under reduced pressure to give an oil, R_f 0.36 (10 % MeOH/Et_2O), that was dissolved in dichloromethane (1.6 mL). Anhydrous copper sulphate (200 mg, 1.25 mmol) and racemic *tert*-butanesulfinamide (84 mg, 0.69 mmol) were added and the mixture was stirred at rt for 16 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue (0.5% to 2 % MeOH/CH_2Cl_2) gave the *title compound* **40** as a pale oil (135 mg, 70 %), R_f 0.43 (10 % MeOH/Et_2O) (Found: M^+ + Na, 331.1195. $C_{14}H_{20}O_2N_4NaS$ requires *M*, 331.1199); ν_{max}/cm^{-1} 2927, 1664, 1600, 1558, 1430, 1393, 1285, 1188, 1138, 1085, 891, 772 and 732; δ_H (500 MHz, $CDCl_3$) 1.21 [9 H, s, $C(CH_3)_3$], 2.40 (3 H, s, 7-CH_3), 3.21 (6 H, s, 2 × NCH_3), 7.47 (1 H, s, 6-H) and 8.57 (1 H, s, 5-CH); δ_C (125 MHz, $CDCl_3$) 14.7, 22.1, 22.7, 57.8, 118.7, 126.4, 142.7, 147.6, 158.6 and 164.0; *m/z* (ES+) 331 (M^+ + 23, 100 %).

(±)-5-[(*E*)-*tert*-Butylsulfinyliminomethyl]-2-diethylamino-7-methyl-oxazolo[4,5-*b*]pyridine (41)

Following the procedure outlined for the synthesis of imine **40**, alcohol **31** (116 mg, 0.5 mmol) in dichloromethane (3.5 mL) and the Dess-Martin periodinane (315 mg, 0.74 mmol) gave the aldehyde **39**, R_f 0.5 10 % MeOH. This aldehyde without purification, in dichloromethane (1.24 mL), anhydrous copper sulphate (158 mg, 0.99 mmol) and racemic *tert*-butanesulfinamide (66 mg, 0.54 mmol), after chromatography (0.5% to 2 % MeOH/CH_2Cl_2) gave the *title compound* **41** as a pale yellow oil (150 mg, 90 %), R_f 0.57 (10 % MeOH/Et_2O) (Found: M^+ + H, 337.1704 $C_{16}H_{25}O_2N_4S$ requires *M*, 337.1693); ν_{max}/cm^{-1} 3434, 2971, 2361, 1647, 1601, 1553, 1450, 1393, 1210, 1138, 1084, 872 and 769; δ_H (500 MHz, $CDCl_3$) 1.21 [9 H, s, $C(CH_3)_3$], 1.24 (6 H, t, *J* 7.2 Hz, 2 × NCH_2CH_3), 2.40 (3 H, s, 7-CH_3), 3.58 (4 H, q, *J* 7.2 Hz, 2 × NCH_2CH_3), 7.45 (1 H, s, 6-H) and 8.56 (1 H, s, 5-CH); δ_C (75 MHz, $CDCl_3$) 13.6, 15.0, 22.9, 43.4, 58.1, 118.8, 126.5, 142.7, 147.7, 158.9 and 164.2; *m/z* (ES+) 337.2 (M^+ + 1, 100 %).

5-{(*RS*)-1-[(*RS*)-*tert*-Butylsulfinylamino]ethyl}-2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridine (42)

Methylmagnesium bromide in ether (3 M, 0.51 mL, 1.6 mmol) was added dropwise to the sulfinimine **40** (132 mg, 0.43 mmol) in tetrahydrofuran (4.3 mL) at –78 ºC. The reaction mixture was stirred at -78 °C for 1 h and then saturated aqueous ammonium chloride (5 mL) was added. The mixture was extracted with ethyl acetate (6 × 5 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (CH_2Cl_2 to 4% MeOH/CH_2Cl_2) gave the *title compound* **42** as a pale oil (119 mg, 76 %), R_f 0.1 (EtOAc) (Found: M^+ + H, 325.1691. $C_{15}H_{25}O_2N_4S$ requires *M*, 325.1693); ν_{max}/cm^{-1} 3234, 2927, 1667, 1570, 1430, 1389, 1290, 1190, 1145, 1063 and 894; δ_H (500 MHz, $CDCl_3$) 1.16 [9 H, s, $C(CH_3)_3$], 1.42 (3 H, d, *J* 6.6 Hz, 5-$CHCH_3$), 2.31 (3 H, s, 7-CH_3), 3.16 (6 H, s, 2 × NCH_3), 4.42 (1 H, quin, *J* 6.6 Hz, 5-CH), 4.51 (1 H, d, *J* 6.3 Hz, NH) and 6.64 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 15.0, 22.4, 23.0, 24.2, 37.7, 56.4, 115.2, 126.9, 140.4, 157.4, 158.0 and 164.7; *m/z* (ES+) 325 (M^+ + 1, 100 %).

5-{(*RS*)-1-[(*RS*)-*tert*-Butylsulfinylamino]ethyl}-2-diethylamino-7-methyloxazolo[4,5-*b*]pyridine (43)

Following the procedure outlined for the synthesis of amine **42**, the sulfinimine **41** (150 mg, 0.45 mmol) in tetrahydrofuran (4.45 mL) and methylmagnesium bromide in ether (3 M, 0.53 mL, 1.6 mmol), after chromatography (CH_2Cl_2 to 4 % MeOH/CH_2Cl_2), gave the *title compound* **43** as a pale yellow oil (119 mg, 76 %), R_f 0.1 (EtOAc) (Found: M^+ + Na, 375.1834. $C_{17}H_{28}O_2N_4NaS$ requires *M*, 375.1825); ν_{max}/cm^{-1} 2974, 1654, 1565, 1388 and 1069; δ_H (500 MHz, $CDCl_3$) 1.15 [9 H, s, $C(CH_3)_3$], 1.22 (6 H, t, *J* 7.2 Hz, 2 × NCH_2CH_3), 1.43 (3 H, d, *J* 6.6 Hz, 5-$CHCH_3$), 2.31 (3 H, s, 7-CH_3), 3.55 (4 H, q, *J* 7.2 Hz, 2 × NCH_2CH_3), 4.40 (1 H, quin, *J* 6.7 Hz, 5-CH), 4.49 (1 H, d, *J* 6.9 Hz, NH) and 6.62 (1 H, s, 6-H); δ_C NMR (125 MHz, $CDCl_3$) 12.4, 13.7, 21.7, 22.9, 42.0, 54.6, 55.4, 113.7, 125.4, 138.9, 156.0, 156.9 and 162.6; *m/z* (ES+) 374.9 (M^+ + 23, 100 %).

(±)-5-(1-Aminoethyl)-2-dimethylamino-7-methyloxazolo[4,5-*b*]pyridine (44)

Hydrogen chloride in dioxane (4 M, 0.61 mL, 2.4 mmol) was added to the sulfinamide **42** (132 mg, 0.407 mmol) in MeOH (4.1 mL) and the reaction mixture was stirred at rt for 30 min. Saturated aqueous sodium bicarbonate was added until the mixture was basic. After concentration under reduced pressure, chromatography of the residue (CH_2Cl_2 to 3% MeOH/CH_2Cl_2 with 0.5% NEt_3) gave the *title compound* **44** as a pale waxy solid (74 mg, 83 %), R_f 0.3 (10 %/

MeOH/DCM) (Found: M^+ + H, 221.1397. $C_{11}H_{17}ON_4$ requires *M*, 221.1397); ν_{max}/cm^{-1} 3365, 2920, 2361, 1659, 1572, 1431, 1392, 896 and 734; δ_H (300 Mz, $CDCl_3$) 1.49 (3 H, d, *J* 6.6 Hz, 5-CHC*H*$_3$), 2.41 (3 H, s, 7-CH_3), 3.01 (2 H, br. s, NH_2), 3.27 (6 H, s, 2 × NCH_3), 4.15 (1 H, br. q, *J* 6.7 Hz, 5-CH) and 6.72 (1 H, s, 6-H); δ_C (75 MHz $CDCl_3$) 15.0, 24.5, 37.7, 52.4, 114.4, 126.8, 140.2, 157.9, 159.8 and 164.6; *m/z* (ES+) 441.5 ($2M^+$ + 1, 16 %) and 221.1 (M^+ + 1, 100).

(±)-5-(1-Aminoethyl)-2-diethylamino-7-methyloxazolo[4,5-*b*]pyridine (45)

Following the procedure outlined for the synthesis of amine **44**, sulfinamide **43** (110 mg, 0.313 mmol) in MeOH (3.1 mL) and hydrogen chloride in dioxane (4 M, 0.47 mL, 1.88 mmol), after chromatography (CH_2Cl_2 to 3% MeOH/CH_2Cl_2 with 0.5 % NEt_3) gave the *title compound* **45** as a pale oil (64 mg, 82 %), R_f 0.2 (10%/ MeOH/CH_2Cl_2) (Found: M^+ + H, 249.1705. $C_{13}H_{21}ON_4$ requires *M*, 249.1710); ν_{max}/cm^{-1} 3356, 2973, 1652, 1565, 1447, 1387 and 1081; δ_H (500 MHz, $CDCl_3$) 1.21 (6 H, t, *J* 7.1 Hz, 2 × NCH_2CH_3), 1.41 (3 H, d, *J* 6.6 Hz, 5-CHC*H*$_3$), 2.32 (3 H, s, 7-CH_3), 3.12 (2 H, br. s, NH_2), 3.55 (4 H, q, *J* 7.1 Hz, 2 × NCH_2CH_3), 4.08 (1 H, br. q, *J* 6.3 Hz, 5-CH) and 6.61 (1 H, s, 6-H); δ_C (75 MHz, $CDCl_3$) 13.4, 14.7, 24.7, 42.9, 52.3, 113.7, 126.2, 139.5, 157.9, 160.5 and 163.6; *m/z* (ES+) 249 (M^+ + 1, 100 %).

1′-{6-[(*RS*)-1-(2-Dimethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-yl)ethylamino]-9*H*-purin-9-yl}-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (48)

The chloropurine **4** (111 mg, 0.313 mmol) was added to the amine **44** (69 mg, 0.313 mmol) and triethylamine (87 μL, 0.626 mmol) in ethanol (3.1 mL) and the reaction mixture was stirred under reflux for 16 h. Concentration under reduced pressure gave 2′,3′-*O*-isopropylidene-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide **46** as a pale oil, R_f 0.38 (20% MeOH/Et_2O) (Found: M^+ + H, 538.2523. $C_{25}H_{32}N_9O_5$ requires *M*, 538.2521); *m/z* (ES+) 538.1 (M^++ 1, 100 %). This was immediately dissolved in aqueous hydrogen chloride (1 M, 1.5 mL). The reaction mixture stirred at 65 °C for 1 h and saturated aqueous sodium bicarbonate was added until the reaction mixture was neutral. After concentration under reduced pressure, chromatography of the residue (CH_2Cl_2 to 20% MeOH/CH_2Cl_2) gave the *title compound* **48** as a white solid (77 mg, 50 %), R_f 0.6 (20% MeOH/DCM), m.p. 171-173 °C (Found: M^+ + H, 498.2206. $C_{22}H_{28}O_5N_9$ requires *M*, 498.2208); δ_H (500 MHz, DMSO-d_6) 1.55 (3 H, d, *J* 6.9 Hz, 5′′-CHC*H*$_3$), 2.35 (3 H, s, 7′′-CH_3), 2.71 (3 H, m, NHC*H*$_3$), 3.17 (6 H, s, 2 × NCH_3), 4.16 (1 H, m, 3′-H), 4.32 (1 H, s, 4′-H), 4.61 (1 H, m, 2′-H), 5.47 (1 H, m, 5′′-CH), 5.54 (1 H, br. d, *J* 6.0 Hz, 2′-OH), 5.72 (1 H, d, *J* 4.5 Hz, 3′-OH), 5.98 (1 H, d, *J* 7.3 Hz, 1′-H), 6.91 (1 H, s, 6′′-H), 8.10 (1 H, m, 6-NH), 8.29 (1 H, s, 2-H), 8.46 (1 H, s, 8-H), 8.87 (1 H, m, N*H*CH$_3$); *m/z* (ES+) 995.5 ($2M^+$ + 1, 17 %) and 498.4 (M^+ + 1, 100).

1′-{6-[(*RS*)-1-(2-Diethylamino-7-methyloxazolo[4,5-*b*]pyridin-5-yl)ethylamino]-9*H*-purin-9-yl}-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (49)

Following the procedure outlined for the synthesis of the adenosine uronamide **48**, the amine **45** (64 mg, 0.258 mmol) and triethylamine (72 μL, 0.52 mmol) in ethanol (2.6 mL) together with the chloropurine **4** (92 mg, 0.258 mmol) gave the 2′,3′-*O*-isopropylidene-1-deoxy-*N*-methyl-β-D-ribofuranuronamide **47** as a pale oil (120 mg, 82 %), R_f 0.25 (10% MeOH/Et_2O) (Found: M^+ + Na, 588.2645. $C_{27}H_{35}N_9O_5Na$ requires *M*, 588.2653); ν_{max}/cm^{-1} 3348, 2977, 1654, 1613, 1565, 1381, 1213, 1088, 871, 756 and 733; δ_H (500 MHz, $CDCl_3$) 1.25 (6 H, t, *J* 7.0 Hz, 2 × NCH_2CH_3), 1.30 and 1.54 (each 3 H, s, CH_3), 1.54 (3 H, d, *J* 4.5 Hz, 5′′-CHC*H*$_3$), 2.33 (3 H, s, 7′′-CH_3), 2.57 (3 H, narrow m, NHC*H*$_3$), 3.57 (4 H, m, 2 x NCH_2CH_3), 4.61 (1 H, s, 4′-H), 5.24 (2 H, m, 2′-H and 3′-H), 5.44 (1 H, m, 5′′-H), 5.95 (1 H, s, 1′-H), 6.69 (1 H, s, 6′′-H), 7.01 and 7.22 (each 1 H, m, NH), 7.69 (1 H, s, 2-H) and 8.23 (1 H, s, 8-H); δ_C (75 MHz, $CDCl_3$) 13.6, 15.0, 23.1, 25.4, 25.8, 27.4, 43.3, 51.0, 82.7, 83.9, 85.9, 92.3, 114.7, 115.1, 126.8, 139.3, 140.2, 153.4, 154.4, 156.1, 158.2, 163.9 and 169.8; *m/z* (ES+) 588.5 (M^+ + 23, 100%). This residue with aqueous hydrogen chloride (1 M, 1.5 mL) as before, after chromatography (CH_2Cl_2 to 20% MeOH/CH_2Cl_2) gave the *title compound* **49** as a white solid (80 mg, 60 %), R_f 0.58 (20% MeOH/CH_2Cl_2), m.p. 143-146 °C (Found: M^+ + H, 526.2532. $C_{24}H_{32}O_5N_9$ requires *M*, 526.2521); δ_H (500 MHz, DMSO-d_6) 1.28 (6 H, t, *J* 7.1, 2 × NCH_2CH_3), 1.60 (3 H, d, *J* 6.9, 5′′-CHC*H*$_3$), 2.39 (3 H, s, 7′′-CH_3), 2.77 (1.2 H, d, *J* 4.5 Hz, NHC*H*$_3$), 2.78 (1.8 H, d, *J* 4.4 Hz, NHC*H*$_3$), 3.62 (4 H, q, *J* 7.1 Hz, 2 × NCH_2CH_3), 4.21 (1 H, s, 3′-H), 4.38 (1 H, s, 4′-H), 4.66 (1 H, m, 2′-H), 5.51 (1 H, m, 5′′-C*H*CH$_3$), 5.64 (1 H, d, *J* 6.0 Hz, 2′-OH), 5.81 (1 H, s, 3′-OH), 6.04 (1 H, d, *J* 7.6, 1′-H), 6.95 (1 H, s, 6′′-H), 8.10 (1 H, d, *J* 6.9 Hz, 6-NH), 8.35 (1 H, s, 2-H), 8.53 (1 H, s, 8-H), 8.95 (0.4 H, q, *J* 4.5 Hz, N*H*CH$_3$) and 8.97 (0.6 H, q, *J* 4.4 Hz, N*H*CH$_3$); *m/z* (ES+) 526 (M^+ + 1, 100 %).

1,3-Dihydroxy-4-iodo-2-nitrobenzene (55)[24]

N-Iodosuccinimide (3.16 g, 12.9 mmol) was added slowly to the nitroresorcinol **52** (2.00 g, 12.9 mmol) in trifluoroacetic acid (50 mL, 0.65 mol) at 0 °C and the reaction mixture was stirred at rt for 16 h, then poured onto ice water (30 mL). The mixture was extracted with toluene (3 × 10 mL) and the organic extracts were washed with saturated sodium bisulphite, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **55** (3.60 g, 100 %) as an orange solid, R_f 0.57 (20% EtOAc/light petroleum), m.p. 140 - 148 °C; (Found: M^+ – H, 279.9112. $C_6H_3NO_4I$ requires *M*, 279.9112); δ_H (300 MHz, DMSO-d_6) 6.43 (1 H, d, *J* 9.0 Hz, 6-H), 7.63 (1 H, d, *J* 9.0 Hz, 5-H), 10.50 (1 H, br. s, 1-OH) and 11.01 (1 H, br. s, 3-OH); *m/z* (ES–) 280 (M^+ – 1, 100 %).

1-Iodo-2,4-bis(methoxymethoxy)-3-nitrobenzene (56)[24]

N,*N*-Di-isopropylethylamine (16.0 mL, 0.092 mol) and chloromethyl methyl ether (6.51 mL, 0.086 mol) were added sequentially at 0 °C to the resorcinol **55** (8.60 g, 0.031 mol) in *N*,*N*-dimethylformamide (100 mL) and the reaction mixture stirred at rt for 1.5 h. Brine (250 mL) was added and the mixture was extracted with ether (3 × 250 mL). The organic extracts were washed with aqueous sodium hydroxide (2 M, 3 × 200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **56** (10.9 g, 96%) as a yellow solid, R_f 0.37 (20 % EtOAc/light petroleum), m.p. 82 - 84 °C; δ_H (300 MHz, $CDCl_3$) 3.41 and 3.47 (each 3 H, s, OCH_3), 5.06 and 5.15 (each 2 H, s, CH_2), 6.82 (1 H, d, *J* 9.0 Hz, 5-H) and 7.72 (1 H, d, *J* 9.0 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 56.8, 58.1, 82.2, 95.2, 101.0, 113.9, 138.3, 140.5, 149.6 and 149.7; *m/z* (ES+) 391.8 (M^+ + 23, 100 %).

Methyl 2-hydroxy-4-methoxymethoxy-3-nitrobenzoate (57)[24]

1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (79 mg, 0.27 mmol), palladium(II) acetate (61 mg, 0.27 mmol) and caesium carbonate (264 mg, 0.81 mmol) were added to the iodide **56** (200 mg, 0.542 mmol) in methanol (3.6 mL) and the reaction mixture de-gassed, then stirred at 60 °C under an atmosphere of carbon monoxide for 16 h. Saturated aqueous ammonium chloride (5 mL) was added and the mixture extracted with ethyl acetate (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% EtOAc/light petroleum) gave the title compound **57** (130 mg, 94 %) as a white solid, R_f 0.2 (20 % EtOAc/light petroleum), mp 124 - 125

°C; (Found: M^+ - H, 256.0464. $C_{10}H_{10}NO_7$ requires *M*, 256.0452); δ_H (300 MHz, $CDCl_3$) 3.42 (3 H, s, CH_2OCH_3), 3.90 (3 H, s, CO_2CH_3), 5.22 (2 H, s, CH_2), 6.71 (1 H, d, *J* 9.0 Hz, 5-H), 7.81 (1 H, d, *J* 9.0 Hz, 6-H) and 11.32 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 52.8, 56.9, 94.8, 105.8, 107.6, 131.5, 132.4, 154.0, 154.5 and 169.4; *m/z* (ES−) 256 ($M^+ - 1$, 100 %).

Methyl 5-bromo-2,4-dihydroxy-3-nitrobenzoate (**58**)
Bromine (0.22 mL, 0.0043 mol) was added dropwise to the ester **57** (1.09 g, 4.24 mmol) in chloroform (50 mL) and the reaction mixture stirred at rt for 48 h. The mixture was then washed with saturated aqueous sodium bisulphite (50 mL) and water (2 × 50 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Re-crystallisation of the residue from light petroleum/ethyl acetate gave the *title compound* **58** (0.99 g, 83 %) as a yellow crystalline solid, R_f 0.23 (20 % EtOAc/light petroleum); m.p. 137 °C (Found: C, 33.09; H, 1.61; N, 4.81; Br, 27.21. $C_8H_5NO_6Br$ requires C, 32.90; H, 2.07; N, 4.80; Br. 27.36: Found: $M^+ - H$, 289.9297. $C_8H_5NO_6{}^{79}Br$ requires *M*, 289.9305); ν_{max}/cm^{-1} 3080, 2957,1670, 1584, 1533, 1436, 1339, 1253, 1138, 966, 895, 818, 793 and 775; δ_H (300 MHz, $CDCl_3$) 3.93 (3 H, s, CO_2CH_3), 8.20 (1 H, s, 6-H), 11.37 (1 H, s, 2-OH) and 12.64 (1 H, s, 4-OH); δ_C (100 MHz, $CDCl_3$) 53.3, 101.0, 106.6, 126.1, 139.2, 157.1, 158.9 and 169.0; *m/z* (ES−) 292 ($M^+ - 1$, 70%), 290 ($M^+ - 1$, 63), 260 (100) and 258 (98).

Methyl 3-amino-5-bromo-2,4-dihydroxybenzoate (**59**)
Concentrated acetic acid (0.8 mL) and zinc (67 mg, 1.02 mmol) were added sequentially to the nitro compound **58** (50.0 mg, 0.171 mmol) in methanol (3.3 mL) and the resulting mixture was stirred at rt for 2 min. After filtering through a plug of silica, the filtrate was diluted with water (5 mL) and brine (5 mL) then extracted with ethyl acetate (3 × 10 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (5 mL) and water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed (10% EtOAc in light petroleum) to give the *title compound* **59** (44 mg, 98 %) as a white solid, R_f 0.37 (30 % EtOAc/light petroleum), m.p. 160 °C (Found: $M^+ - H$, 261.9530. $C_8H_7NO_4{}^{81}Br$ requires *M*, 261.9543); ν_{max}/cm^{-1} 3181, 2949, 2916, 2848, 1666, 1623, 1548, 1522, 1430, 1340, 1256, 1200, 1150, 1089, 1015, 981, 890, 796 and 778; δ_H (400 MHz, $CDCl_3$) 3.85 (3 H, s, CO_2CH_3), 7.38 (1 H, s, 6-H) and 10.79 (1 H, s, OH); *m/z* (ES−) 262 ($M^+ - 1$, 98%), 260 ($M^+ - 1$, 100), 230 (15) and 228 (13).

Methyl 7-bromo-2-dimethylamino-4-hydroxybenz[*d*]oxazole-5-carboxylate (**60**)
Triethylamine (80 µL, 0.574 mmol) and dichloromethylene(dimethyl)ammonium chloride (28 mg, 0.172 mmol) were added to the aminophenol **59** (30 mg, 0.114 mmol) in dichloromethane (2 mL) and the reaction mixture was heated under reflux for 2 h. After cooling to rt, the mixture was washed with saturated aqueous sodium bicarbonate (10 mL) and extracted with dichloromethane (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed (10% EtOAc in light petroleum) to give the *title compound* **60** (20 mg, 56 %) as a white solid, R_f 0.17 (30 % EtOAc/light petroleum), m.p. 95 – 97 °C (Found: $M^+ + H$, 314.9972. $C_{11}H_{12}N_2O_4{}^{79}Br$ requires *M*, 314.9975); ν_{max}/cm^{-1} 3224, 2952, 1651, 1435, 1311, 1220, 1160, 1078, 1014, 978, 887, 788 and 731; δ_H (400 MHz, $CDCl_3$) 3.17 (6 H, s, 2 × NCH_3), 3.89 (3 H, s, CO_2CH_3), 7.62 (1 H, s, 6-H) and 10.95 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 37.9, 52.5, 91.2, 109.7, 124.5, 132.9, 151.0, 151.3, 162.2 and 170.1; *m/z* (ES−) 315 ($M^+ - 1$,100%) and 313 ($M^+ - 1$, 83).

Methyl-7-bromo-2-dimethylamino-4-(3-methylisoxazol-5 ylmethoxy)benz[*d*]oxazole-5-carboxylate (**61**)
5-Hydroxymethyl-3-methylisoxazole (43 mg, 0.38 mmol) and triphenylphosphine (125 mg, 0.477 mmol) were added to the phenol **60** (100 mg, 0.317 mmol) in tetrahydrofuran (10 mL) and the mixture cooled to 0 °C. Di-isopropyl azodicarboxylate (93.5 µL, 0.476 mmol) in tetrahydrofuran (5 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed (10% EtOAc in light petroleum) to give the *title compound* **61** as a white solid (130 mg, 99 %), R_f 0.33 (50 % EtOAc/light petroleum), m.p. 106 - 110 °C (Found: $M^+ + H$, 410.0347. $C_{16}H_{17}N_3O_5{}^{79}Br$ requires *M*, 410.0346); ν_{max}/cm^{-1} 2945, 1696, 1651, 1618, 1428, 1404, 1380, 1339, 1303, 1251, 1189, 1165, 1027, 978, 897, 885, 857, 798, 781 and 716; δ_H (400 MHz, $CDCl_3$) 2.30 (3 H, s, 3′-CH_3), 3.24 (6 H, s, 2 × NCH_3), 3.89 (3 H, s, CO_2CH_3), 5.73 (2 H, s, CH_2), 6.26 (1 H, s, 4′-H) and 7.64 (1 H, s, 6-H); δ_C (100 MHz, $CDCl_3$) 11.5, 37.7, 52.3, 65.2, 94.3, 103.9, 119.9, 126.0, 135.8, 145.8, 150.6, 159.8, 161.7, 165.7 and 168.4; *m/z* (ES+) 434 ($M^+ + 23$, 63%) and 432 ($M^+ + 23$, 76), 412 ($M^+ + 1$, 90) and 410 ($M^+ + 1$, 100).

7-Bromo-2-dimethylamino-5-hydroxymethyl-4-(3-methylisoxazol-5 ylmethoxy)benz[*d*]oxazole (**62**)
A mixture of sodium borohydride (46 mg, 1.22 mmol) and calcium chloride (54 mg, 0.487 mmol) in tetrahydrofuran (2 mL) was stirred at rt for 2 h before adding the ester **61** (100 mg, 0.244 mmol). The resulting mixture was stirred at rt for 48 h and the pH was adjusted to 7 using aqueous hydrogen chloride (1 M). The mixture was concentrated under reduced pressure and the residue was chromatographed (40% EtOAc in light petroleum) to give the *title compound* **62** as a white solid (70 mg, 75 %), R_f 0.27 (50 % EtOAc/light petroleum), m.p. 140 – 142 °C (Found: M^+ + Na, 404.0227. $C_{15}H_{16}N_3O_4Na^{79}Br$ requires *M*, 404.0217); ν_{max}/cm^{-1} 3352, 3139, 2934, 1649, 1616, 1593, 1432, 1377, 1271, 1248, 1226, 1194, 1092, 1067, 1017, 960. 892, 801, 753 and 722; δ_H (400 MHz, $CDCl_3$) 2.04 (1 H, m, OH), 2.20 (3 H, s, 3′-CH_3), 3.15 (6 H, s, 2 × NCH_3), 4.54-4.58 (2 H, m, 5′′-CH_2), 5.69 (2 H, s, OCH_2), 6.03 (1 H, s, 4′-H) and 7.00 (1 H, s, 6-H); δ_C (100 MHz, $CDCl_3$) 11.4, 37.7, 61.4, 63.7, 93.6, 104.2, 123.2, 128.5, 134.2, 143.0, 148.1, 159.8, 161.5 and 168.2; *m/z* (ES+) 406 ($M^+ + 23$, 100%) and 404 ($M^+ + 23$, 92 %).

***N*-[7-Bromo-2-dimethylamino-4-(3-methylisoxazol-5-ylmethoxy)benz[*d*]oxazol-5-yl]methyl 2-nitrobenzenesulfonamide** (**63**)
2-Nitrobenzene sulphonamide (222 mg, 1.10 mmol) and triphenylphosphine (72 mg, 0.275 mmol) were added to the alcohol **62** (70 mg, 0.183 mmol) in dichloromethane (14 mL) and the mixture cooled to 0 °C. Di-isopropyl azodicarboxylate (54.1 µL, 0.275 mmol) in dichloromethane (3.5 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (10% to 30% EtOAc/light petroleum) gave the *title compound* **63** as a pale yellow oil (90 mg, 87 %), R_f 0.2 (50 % EtOAc/light petroleum) (Found: $M^+ + 1$, 566.0344, $C_{21}H_{21}{}^{79}BrN_5O_7S$ requires *M*, 566.0340); ν_{max}/cm^{-1} 3364, 3265, 2931, 1655, 1617, 1588, 1537, 1483, 1433, 1359, 1345, 1268, 1246, 1168, 1123, 1099, 1035, 897, 859, 782, 738 and 720; δ_H (500 MHz, $CDCl_3$) 2.20 (3 H, s, 3′-CH_3), 3.10 (6 H, s, 2 × NCH_3), 4.18 (2 H, d, *J* 6.5 Hz, 5-CH_2), 5.60 (2 H, s, OCH_2), 5.99 (1 H, t, *J* 6.5 Hz, NH), 6.04 (1 H, s, 4′-H), 6.75 (1 H, s, 6-H), 7.51 and 7.54 (each 1 H, m, 4′′-H, 5′′-H), 7.68 (1 H, m, 6′′-H) and 7.92 (1 H, m, 3′′- H); δ_C (125 MHz, $CDCl_3$) 11.4, 37.7, 44.2, 63.6, 92.9, 104.4, 122.8, 124.1, 125.2, 131.1, 132.5, 133.1, 133.7, 134.3, 143.1, 147.4, 148.3, 159.8, 161.4 and 167.7; *m/z* (ES−) 566 ($M^+ - 1$, 100%) and

564 ($M^+ - 1$, 99).

5-Aminomethyl-7-bromo-2-dimethylamino-4-(3-methylisoxazol-5- ylmethoxy)benz[*d*]oxazole (51)

Thiophenol (49 μL, 0.477 mmol) and potassium carbonate (88 mg, 0.636 mmol) were added to the sulfonamide **63** (90 mg, 0.16 mmol) in acetonitrile (10 mL) and the reaction mixture was stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (1% MeOH/CH_2Cl_2 with a drop of Et_3N) gave the *title compound* **51** as a white solid (60 mg, 98 %), R_f 0.13 (10 % MeOH/EtOAc), m.p. 212 - 218 °C (Found: M^+ + 1, 381.0553, $C_{15}H_{18}N_4O_3{}^{79}Br$ requires *M*, 381.0557); ν_{max}/cm^{-1} 3386, 2926, 1655, 1610, 1593, 1428, 1377, 1273, 1252, 1227, 1194, 1098, 1073, 1021, 969, 893, 846 and 724; δ_H (500 MHz, $CDCl_3$) 1.94 (2 H, br. s, NH_2), 2.19 (3 H, s, 3′-CH_3), 3.14 (6 H, s, 2 × NCH_3), 3.70 (2 H, s, 5-CH_2), 5.67 (2 H, s, OCH_2), 6.03 (1 H, s, 4′- H) and 6.92 (1 H, s, 6-H); δ_C (125 MHz, $CDCl_3$) 11.4, 37.7, 42.1, 63.7, 93.4, 104.1, 123.0, 130.6, 134.3, 143.0, 147.5, 159.7, 161.5 and 168.4; *m/z* (ES+) 383 (M^+ + 1, 100%), 381 (M^+ + 1, 96), 366 (85) and 364 (80).

1′-{6-[7-Bromo-2-dimethylamino-4-(3-methylisoxazol-5-ylmethoxy)benz[*d*]oxazol-5-ylmethylamino]-9*H*-purin-9-yl}-2′,3′-*O*-isopropylidene-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (64)

Triethylamine (44 μL, 0.315 mmol) and purine **4** (56 mg, 0.157 mmol) were added to the amine **51** (60 mg, 0.157 mmol) in ethanol (2.5 mL) and the reaction mixture was heated under reflux for 18 h. After concentration under reduced pressure, chromatography of the residue (EtOAc to 10% MeOH/EtOAc) gave the *title compound* **64** as a transparent solid (100 mg, 91%), R*f* 0.17 (EtOAc), m.p. 105 – 110 °C (Found: M^+ + 1, 698.1662. $C_{29}H_{33}N_9O_7{}^{79}Br$ requires *M*, 698.1681); ν_{max}/cm^{-1} 3288, 3082, 2928, 2805, 2358, 1653, 1612, 1535, 1476, 1429, 1406, 1377, 1328, 1273, 1211, 1156, 1088, 981, 899, 869, 850, 796 and 726; δ_H (400 MHz, $CDCl_3$) 1.30 and 1.55 (each 3 H, s, CH_3), 2.18 (3 H, s, 3′′′-CH_3), 2.55 (3 H, d, *J* 5.0 Hz, NHC*H*$_3$), 3.14 (6 H, s, 2 × NCH_3), 4.64 (1 H, s, 4′-H), 4.74 (2 H, br. s, 5′′-CH_2), 5.26 (2 H, m, 2′-H and 3′-H), 5.70 (2 H, d, *J* 1.0 Hz, 5′′′-CH_2), 5.95 (1 H, d, *J* 2.0 Hz, 1′-H), 6.05 (1 H, s, 4′′′-H), 6.35 (1 H, br. s, 6-NH), 7.05 (1 H, s, 6′′-H), 7.27 (1 H, br. s, N*H*CH_3), 7.68 (1 H, s, 2-H) and 8.27 (1 H, br. s, 8-H); δ_C (100 MHz, $CDCl_3$) 11.4, 14.2, 21.1, 25.1, 25.6, 27.1, 37.7, 60.4, 63.8, 82.5, 83.7, 85.7, 92.1, 93.5, 104.2, 114.5, 123.6, 134.3, 139.2, 143.3, 148.0, 153.2, 154.8, 159.7, 161.5, 168.2 and 169.5; *m/z* (ES+) 700 (M^+ + 1, 100%) and 698 (M^+ + 1, 93).

1′-{6-[7-Bromo-2-dimethylamino-4-(3-methylisoxazol-5-ylmethoxy)benz[*d*]oxazol-5-ylmethylamino]-9*H*-purin-9-yl}-1′-deoxy-*N*-methyl-β-D-ribofuranuronamide (50).

A solution of the acetonide **64** (50.0 mg, 0.0716 mmol) in aqueous formic acid (80%, 0.5 mL) was stirred at rt for 16 h then concentrated under reduced pressure. Chromatography of the residue (1% MeOH/EtOAc) and recrystallisation from ethyl acetate gave the *title compound* **50** (40 mg, 85 %) as a white solid, R_f 0.37 (10% MeOH/EtOAc), m.p. 235 - 237 °C (Found: M^+ + 1, 658.1373. $C_{26}H_{29}N_9O_7{}^{79}Br$ requires *M*, 658.1368); ν_{max}/cm^{-1} 3198, 2939, 2360, 1666, 1591, 1625, 1484, 1432, 1405, 1385, 1360, 1339, 1299, 1260, 1189, 1145, 1093, 1065, 1026, 961, 894, 857, 794, 756 724 and 638; δ_H (400 MHz, DMSO-d_6) 1.96 (3 H, s, 3′′′-CH_3), 2.47 (3 H, d, *J* 4.5 Hz, NHC*H*$_3$), 2.91 (6 H, s, 2 × NCH_3), 3.91 (1 H, m, 3′-H), 4.08 (1 H, s, 4′-H), 4.33 (1 H, m, 2′-H), 4.44 (2 H, br. s, 5′′-CH_2), 5.34 (1 H, d, *J* 6.0 Hz, 2′-OH), 5.49 (2 H, s, 5′′′-CH_2), 5.52 (1 H, d, *J* 4.3 Hz, 3′-OH), 5.74 (1 H, d, *J* 7.3 Hz, 1′-H), 6.21 (1 H, s, 4′′′-H), 6.74 (1 H, s, 6′′-H), 8.03 (1 H, s, 2-H), 8.16 (1 H, br. s, 6-NH), 8.21 (1 H, s, 8-H), 8.66 (1 H, q, *J* 4.5 Hz, N*H*CH_3); δ_C (100 MHz, DMSO-d_6) 10.9, 25.3, 37.3, 60.1, 63.2, 72.1, 73.0, 84.6, 87.8, 92.8, 104.6, 120.0, 121.0, 127.4, 134.3, 140.8, 142.2, 146.5, 148.2, 152.5, 154.4, 159.6, 161.2, 167.8 and 169.8; *m/z* (ES+) 682 (M^+ + 23, 100%), 680 (M^+ + 23, 75), 660 (M^+ + 1, 49) and 658 (M^+ + 1, 58).

X-Ray crystal data

5,7-Dimethyl-2-dimethylamino-oxazolo[4,5-*b*]pyridine 4-oxide (**14**): $C_{10}H_{13}NO_2$; unit cell parameters: *a* 16.652(2), *b* 6.8992(9), *c* 18.610(3); Pbca, CCDC number 1442372.

2-Dimethylamino-7-hydroxymethyl-5-methyloxazolo[4,5-*b*]pyridine (**15**): $C_{10}H_{13}N_3O_2$; unit cell parameters: *a* 7.6207(7), *b* 12.3266(12), *c* 11.1367(11); P21, CCDC number 1442373.

7-Bromo-2-dimethylamino-5-hydroxymethyl-4-(3-methylisoxazol-5 ylmethoxy)benz[*d*]oxazole (**62**): $C_{15}H_{16}BrN_3O_4$; unit cell parameters: *a* 27.5444(14), *b* 4.0773(4), *c* 26.9996(14); Pca21, CCDC number 1442374.

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Notes and references

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1. (a) V. E. Laubach, B. A. French and M. D. Okusa, *Expert. Opin. Ther. Targets*, 2011, **15**, 103; (b) P. Fishman, S. Bar-Yehuda, B. T. Liang and K. A. Jacobson, *Drug Discov. Today*, 2012, **17**, 359; (c) V. J. McIntosh and R. D. Lasley, *J. Cardiovasc. Pharmacol. Therapeutics*, 2012, **17**, 21; (d) P. G. Baraldi, D. Preti, P. A. Borea and K. Varani, *J. Med. Chem.*, 2012, **55**, 5676; (e) A. M. Almerico, M. Tutone, L. Pantano and A. Lauria, *J. Mol. Graphics Modell.*, 2013, **42**, 60.
2. P. A. Borea, K. Varani, F. Vincenzi, P. G. Baraldi, M. A Tabrizi, S. Merghi and S. Gessi, *Pharmacol. Rev.*, 2015, **67**, 74.
3. C. Gallo-Rodriguez, X.-d. Ji, N. Melman, B. D. Siegman, L. H. Sanders, J. Orlina, B. Fischer, Q. Pu, M. E. Olah, P. J. M. van Galen, G. L. Stiles and K. A. Jacobson, *J. Med. Chem.*, 1994, **37**, 636.
4. (a) P. G. Baraldi, B. Cacciari, G. Spalluto, X.-d. Ji, M. E. Olah, G. Stiles, S. Dionisotti, C. Zocchi, E. Ongini and K. A. Jacobson, *J. Med. Chem.*, 1996, **39**, 802; (b) M. P. DeNinno, H. Masamune, L. K. Chennard, K. J. DiRico, C. Eller, J. B. Etienne, J. E. Tichner, S. P. Kennedy, D. R. Knight, J. Kong, J. J. Oleynek, W. R. Tracey and R. J. Hill, *J. Med. Chem.*, 2003, **46**, 353; (c) S. M. Devine, A. Gregg, H. Figler, K. McIntosh, V. Urmaliya, J. Linden, C. W. Pouton, P. J. White, S. E. Bottle, P. J. Scammells, *Bioorg. Med. Chem.*, 2010, **18**, 3078.
5. R. H. Davies, C. McGuigan, unpublished observations.
6. R. H. Davies, unpublished observations.
7. R. A. Olsson, S. Kusachi, R. D. Thompson, D. Ukena, W. Padgett and J. W. Daly, *J. Med. Chem.*, 1986, **29**, 1683.

8. (a) Y. Wang, M.-C. Liu, T.-S. Lin and A. C. Sartorelli, *J. Med. Chem*., 1992, **35**, 3667; (b) E. Blanz and F. French, *Cancer Res*., 1968, **28**, 2419; (c) K. C. Agrawal, A. J. Lin, B. A. Booth, J. R. Wheaton and A. C. Sartorelli, *J. Med. Chem*., 1974, **17**, 631; (d) V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc*., 1964, **86**, 4917.
9. (a) D. Chapman and J. Hurst, *J. Chem. Soc., Perkin Trans. I*, 1980, 2398; (b) S. Furukawa, *Yakugaku Zasshi*, 1956, **76**, 900.
10. R. C. De Selms, *J. Org. Chem*., 1968, **33**, 478.
11. (a) R. Sathunuru, U. N. Rao and E. Biehl, *Arkivoc*, 2003, **15**, 124; (b) N. C. Ganguly, M. Datta, P. De and R. Chakravarty, *Synth. Commun*., 2003, **33**, 647; R. Sathunuru and E. Biehl, *Arkivoc*, 2004, **14**, 89.
12. (a) M. Katada, *Yakugagu Zasshi*, 1947, **67**, 51; (b) S. Furukawa, *Pharm. Bull*., 1955, **3**, 413.
13. C. Fontenas, E. Bejan, H. A. Haddou and G. G. A. Balavoine, *Synth. Commun*., 1995, **25**, 629.
14. P. Månsson, *Tetrahedron Lett*., 1982, **23**, 1845.
15. T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett*., 1995, **36**, 6373.
16. (a) Y. Sato, M. Yamada, S. Yoshida, T. Soneda, M. Ishikawa, T. Nizato, K. Suzuki and F. Konno, *J. Med. Chem*., 1998, **41**, 3015; (b) S. Yoshida, S. Shiokawa, K. Kawano, T. Ito, H. Marakami, H. Suzuki and Y. Sato, *J. Med. Chem*., 2005, **48**, 7075.
17. (a) K. Gunnar and J. Sandström, *Acta Chem. Scand*., 1969, **23**, 2888; (b) I. J. Turchi and M. J. S. Dewar, *Chem. Rev*., 1975, **75**, 389.
18. T. Fukuyama, M. Cheung and T. Kan, *Synlett*, 1999, 1301.
19. T. Kan and T. Fukuyama, *Chem. Commun*., 2004, 353.
20. (a) G. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc*., 1997, **119**, 9913; (b) D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, *J. Am. Chem. Soc*., 1998, **120**, 8011.
21. J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res*., 2002, **35**, 984.
22. (a) K. C. Nicolaou, A. Li and D. J. Edmonds, *Angew. Chem. Int. Edn*., 2006, **45**, 7086; (b) K. C. Nicolaou, A. Li, D. J. Edmonds, G. S. Tria and S. P. Ellery, *J. Am. Chem. Soc*., 2009, **131**, 16905.
23. (a) S. R. Crabtree, W. L. A. Chu and L. N. Mander, *Synlett*, 1990, 169; L. N. Mander and S. P. Sethi, *Tetrahedron Lett*., 1983, **24**, 5425; (c) S. R. Crabtree, L. N. Mander and S. P. Sethi, *Org. Synth*., 1991, **70**, 256.
24. J. Wang, V. Lee and H. O. Sintim, *Chem. Eur. J*., 2009, **15**, 2747.
25. J. McNulty, J. J. Nair and A. Capretta, *Tetrahedron Lett*., 2009, **50**, 4087.
26. (a) J. Liu, B. Liang, D. Shu, Y. Hu, Z. Yang and A. Lei, *Tetrahedron*, 2008, **64**, 9581; C. F. J. Barnard, *Org. Process Res. Devel*., 2008, **12**, 566.
27. (a) S. Narasimban, K. G. Prasad and S. Madhavan, *Synth. Comm*., 1995, **25**, 1689; (b) J. W. Lampe, Y.-L. Chou, R. G. Hanna, S. V. DiMeo, P. W. Erhardt, A. A. Hegedorn, III, W. R. Ingebretson and E. Cantor, *J. Med. Chem*., 1993, **36**, 1041.