Solid-phase synthesis of 7-substituted 3*H*-imidazo[2,1-*i*]purines

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A method for solid-supported synthesis of *N*,*N*-disubstituted (3*H*-imidazo[2,1-*i*]purin-7-yl)methyl amines has been developed. The key features of this library synthesis are: (i) immobilization of commercially available N^6-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyadenosine 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) by phosphitylation to a hydroxyl-functionalized support, (ii) quantitative conversion of the deprotected adenine base to 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde with bromomalonaldehyde in DMF in the presence of formic acid and 2,6-lutidine, (iii) reductive amination of the formyl group followed by *N*-alkylation or *N*-acylation, and (iv) release from the support by acidolytic cleavage of the *N*-glycosidic bond. Steps (ii) and (iii) have been optimized in some detail by using (adenin-9-yl)acetic acid anchored to a Phe–Wang resin as a model compound.

Introduction

Purine-based compounds display an exceptionally wide spectrum of biological activities. As summarized by Legraverend and Grierson[1] in their recent review, numerous purine-based compounds are currently in medical use against viral infections, cancer, systemic mastocytosis and organ rejection, and an increasing number of purine derivatives have been reported to show potential as inhibitors of kinases,[2] phosphodiesterases,[3] chaperone Hsp90[4] and sulfotransferases,[5] as inducers of interferon[6] and effectors of cell dedifferentiation,[7] as agonists[8] and antagonists[9] of adenosine receptors, as antagonists of corticotropin-releasing factor,[10] and as anti-mycobacterium agents.[11] Numerous targeted combinatorial libraries of substituted purines have been prepared to improve the efficiency and reduce the toxicity of the drug candidates. However, in surprisingly few cases has solid-phase chemistry been utilized, but the libraries have been obtained by conventional solution phase transformations. Only libraries of 2,6-disubstituted,[12] 2,6,9-trisubstituted[13] purines and 2,6,8-trisubstituted purine nucleosides[14] have been prepared by solid-phase parallel synthesis. The present study is aimed at adding a solid-supported synthesis of 7-substituted 3*H*-imidazo[2,1-*i*]purines to this repertoire. The idea of using 3*H*-imidazo[2,1-*i*]purine as a scaffold of a combinatorial library is based on the observations of others,[15] according to which pyrrolo-, imidazo- and triazolo-purinones, *i.e.* tricyclic extensions of xanthine nucleus, exhibit high affinity to adenosine receptors. 3*H*-imidazo[2,1-*i*]purines have previously been obtained in solution by a reaction of 9-substituted adenine with α-halocarbonyl compounds,[16] epoxycarbonyl compounds,[17] 2-chloroketene diethyl acetal[18] and 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline.[19] In the present study, the reaction of adenine with bromomalonaldehyde was successfully optimized to result in a quantitative conversion of a support-bound adenine to 7-formyl-3*H*-imidazo[2,1-*i*]purine that served as a starting material for the subsequent transformations.

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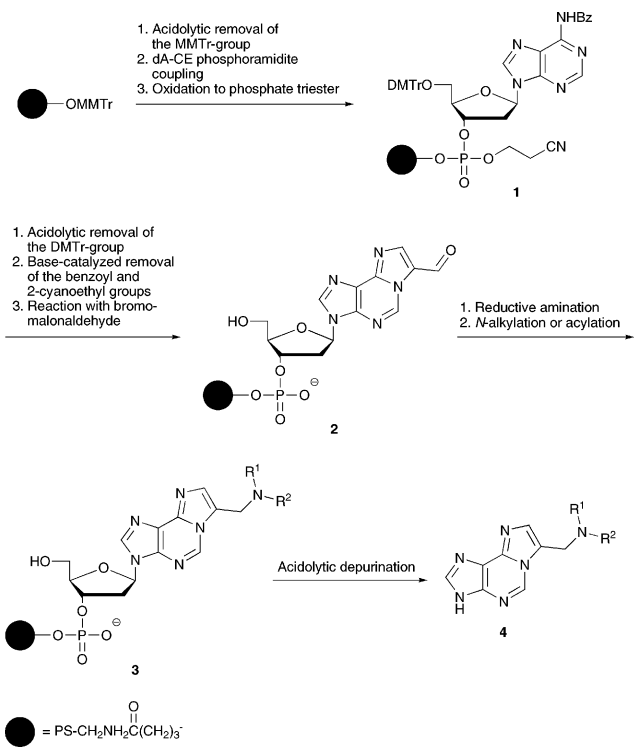
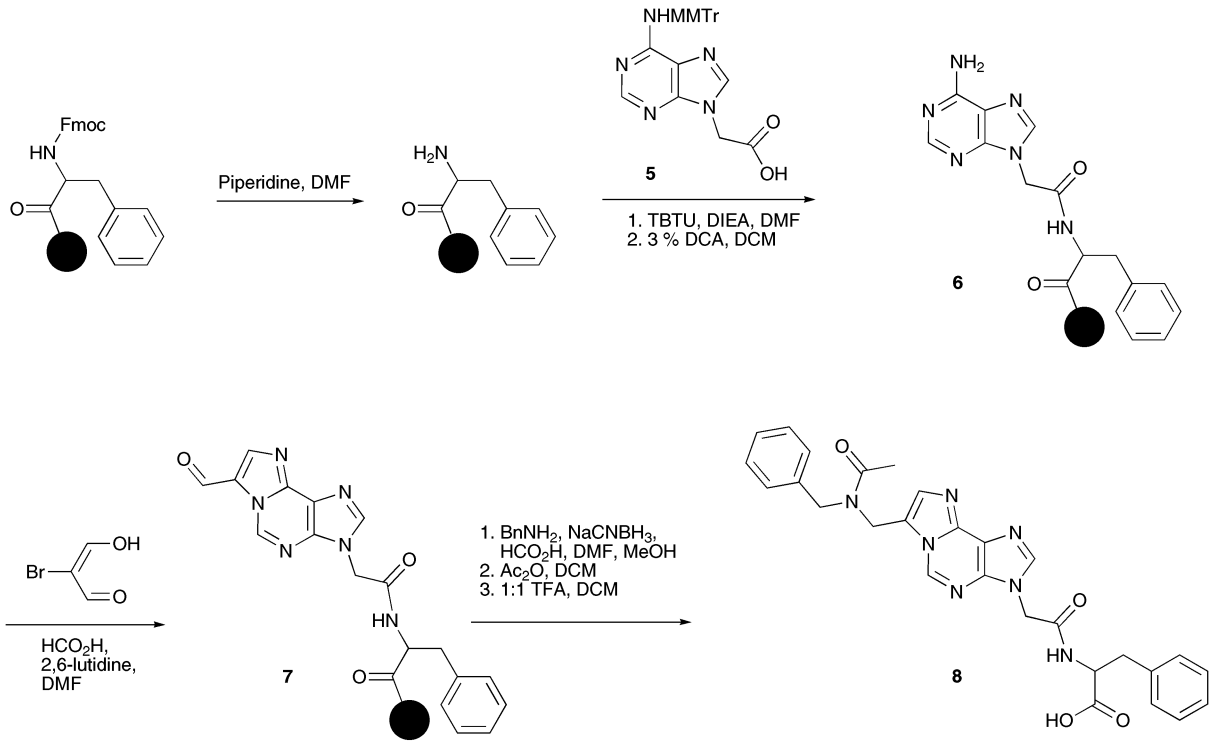
Results and discussion

The solid-supported synthesis applied to the preparation of 7-substituted 3*H*-imidazo[2,1-*i*]purines is outlined in Scheme 1. The key steps of this library synthesis are quantitative conversion of adenine base to 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde and reductive amination of this product. These steps were first studied in some detail by using (adenin-9-yl)acetic acid anchored to a Phe–Wang resin as a model compound.



Scheme 1

The preparation of [N^6-(4-methoxytrityl)adenin-9-yl]acetic acid (**5**) has been recently described.[20] This compound was coupled to deprotected commercially available *N*-Fmoc–Phe–Wang



Scheme 2

resin using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) in the presence of *N*,*N*-diisopropylethylamine (DIEA) as an activator (Scheme 2). Two equivalents of the acid component and three hours reaction time gave **6** in a 70% yield, according to the 4-monomethoxytrityl cation assay. A separate capping step was not introduced to protect the unreacted amino groups, since they reacted with bromomalonaldehyde[21] in the next step and were most likely converted to (2-bromo-3-oxopropenyl)amino groups.

Bromomalonaldehyde is known to react with pyrimidine and purine bases, yielding a variety of products[16d,22,23] in aqueous solutions. Adenosine and 9-methyladenine, for example, give the respective 3*H*-imidazo[2,1-*i*]purine and 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde derivatives.[22] Both have been suggested to be formed through a common intermediate, *viz.* an acyclic carbinolamine that still contains the halogen substituent. This intermediate may undergo cyclization by displacement of the halogen substituent by the adenine *N*1 atom, or hydrolytic deformylation may take place prior to the cyclization and, hence, a 7-unsubstituted ring-system is obtained. In both cases, elimination of water from the cyclic carbinolamine intermediate obtained then leads to the 3*H*-imidazo[2,1-*i*]purine ring system, bearing either a formyl group or a hydrogen atom at C7. These two derivatives are obtained in an approximately equimolar ratio when the pH is below 3.5. At higher pH, the unsubstituted derivative predominates.

On the basis of the preceding results, water was considered to be a suboptimal solvent for the fabrication of 3*H*-imidazo[2,1-*i*]purine-7-carbaldehydes. Fortunately, anhydrous DMF turned out to allow almost quantitative conversion of adenine to this product, when the reaction was carried out on a polystyrene solid support at somewhat elevated temperature (60 °C). According to a previous report,[24] the reaction of bromomalonaldehyde with 2′-deoxyadenosine gives the 7-formyl derivative in DMF at room temperature in modest 19% yield. Under similar conditions, an even lower yield may be expected on polystyrene. Elevated temperature and an appropriate buffer system, however, dramatically alter the situation. As seen from Table 1, a somewhat acidic buffer system is needed to drive the formation of 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde to completion. Triethylammonium acetate buffer[25] gave only a 14% conversion of **6** to solid-supported *N*-[(7-formylimidazo[2,1-*i*]purin-3-yl)acetyl]phenylalanine (**7**) with five equivalents of bromomalonaldehyde in 330 min (entry 1). Triethylammonium formate buffer (entries 2 and 3) was more efficient, but the yield was still lower than that obtained in the absence of any buffer constituents (entries 4–6). When triethylamine was replaced with a weaker base, *viz.* 2,6-lutidine, a good yield was obtained (entries 7–10). The reaction rate

Table 1 Effect of buffer on the solid-supported synthesis of *N*-[(7-formylimidazo[2,1-*i*]purin-3-yl)acetyl]phenylalanine (**7**) on Wang resin in DMF (see Scheme 1)

Entry	Buffer	Equiv.[a]	*t*/min	Yield
1	Acetic acid–triethylamine	10/10	330	14%
2	Formic acid–triethylamine	10/10	330	35%
3	Formic acid–triethylamine	28/10	270	39%
4	—	—	65	51%
5	—	—	180	55%
6	—	—	360	62%
7	Formic acid–2,6-lutidine	50/10	65	54%
8	Formic acid–2,6-lutidine	30/10	180	87%
6	Formic acid–2,6-lutidine	10/10	270	92%
10	Formic acid–2,6-lutidine	30/10	360	93%

[a] Compared to the amount of **6**. 5 equiv. of bromomalonaldehyde was used. $T = 60$ °C.

was rather insensitive to the ratio of the concentrations of formic acid and 2,6-lutidine. For the synthesis of **7**, indicated in Scheme 2, a 1 : 1 ratio was used.

Reductive amination of the support-bound 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde (**7**) was sluggish when acetic acid was used as a catalyst. With ten equivalents of benzylamine and sodium cyanoborohydride in DMF acidified with 4% acetic acid, 30% of the starting material remained unreacted after 24 hours. On using formic acid, the amination was complete in 5 hours. No reduction of the formyl group[26,27] to a hydroxymethyl function was detected under these conditions. This was the case even when amination with a sterically hindered amine was attempted: all the aldehyde remained unchanged after 4 hours treatment. The source of the hydride ion markedly influenced the reaction rate. Under similar reaction conditions, 6.7 equiv. of sodium cyanoborohydride (20 equiv. of hydride ions) gave 2.4 times as high yield as 8 equiv. of sodium triacetoxyborohydride (8 equiv. of hydride ions). Sodium cyanoborohydride in a mixture of MeOH and DMF was, hence, used for the syntheses. Although 10 equiv. of benzylamine and a short 30 minutes reaction time for imine formation prior to sodium cyanoborohydride addition was used, about 6% of dialkylated product was formed.

Acetylation of the solid-supported *N*-benzyl(imidazo[2,1-*i*]purin-7-yl)methylamine group was performed with acetic anhydride in dichloromethane. Acidolytic release from the support yielded *N*-{[7-(*N*-benzylacetamidomethyl)imidazo[2,1-*i*]purin-3-yl]acetyl}phenylalanine (**8**). Fig. 1 shows the HPLC trace of the crude product.

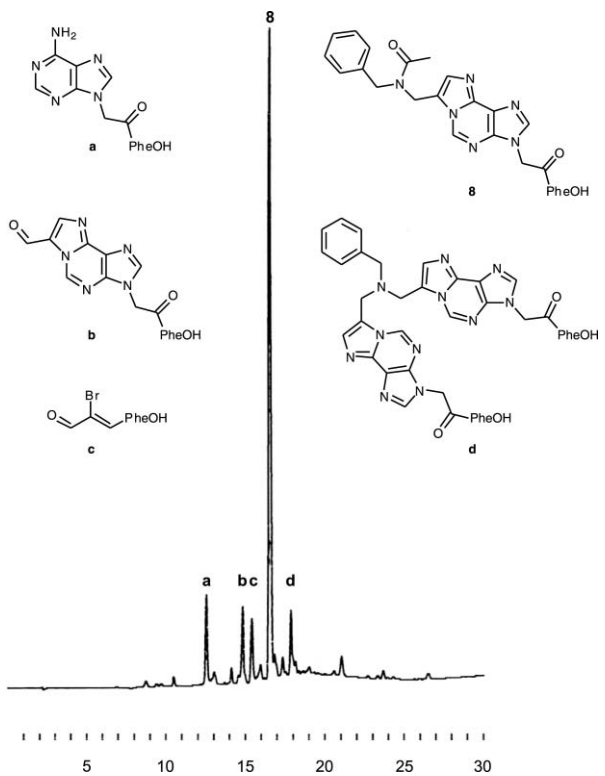


Fig. 1 HPLC trace of crude *N*-{[7-(*N*-benzylacetamidomethyl)imidazo-[2,1-*i*]purin-3-yl]acetyl}phenylalanine (**8**) (RP HPLC, 0–100% MeCN, 0.1% TFA, $\lambda = 220$ nm).

The conditions described above were then applied to the synthesis of a library of substituted (imidazo[2,1-*i*]purin-7-yl)methylamines, as outlined in Scheme 1. This approach makes use of the facile acid-catalyzed depurination of purine 2′-deoxyribonucleosides as a release method from the solid-support. The method is mild; the products can be cleaved from the support with 5% trifluoroacetic acid in dichloromethane in one hour, *i.e.* under conditions that *t*-butyl ester protections largely tolerate. The *N*-glycosidic bond nevertheless withstands the formic acid treatments involved in generation of the additional imidazole ring and subsequent reductive amination of the formyl group.

Aminomethylpolystyrene was first acylated with (4-methoxytrityloxy)butyric acid in DMF using diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) as activators. The trityl protection was then removed and a N^6-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyadenosine 3′-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite) building block was coupled to the exposed hydroxy functions by 4,5-dicyanoimidazole activation and oxidized to a phosphate triester (**1**) with aqueous iodine (Scheme 1). All the protecting groups were then removed, the 4,4′-dimethoxytrityl group acidolytically and the *N*-benzoyl and *O*-(2-cyanoethyl) protections by treatment with aqueous alkali. The exposed 5′-hydroxy and phosphodiester groups did not hamper the subsequent reactions. Treatment of the deprotected support-bound 2′-deoxyadenosine with bromomalonaldehyde under the conditions described in the foregoing gave the desired support-bound 3-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldeyde (**2**) in an almost quantitative yield, as seen from the HPLC traces of the acidolytically released crude product (Fig. 2).

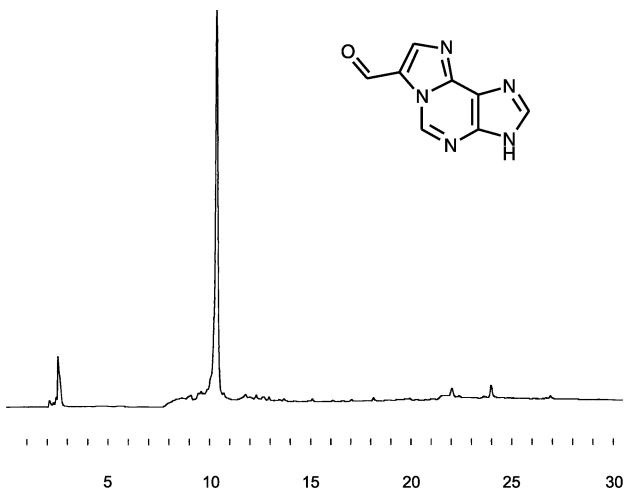
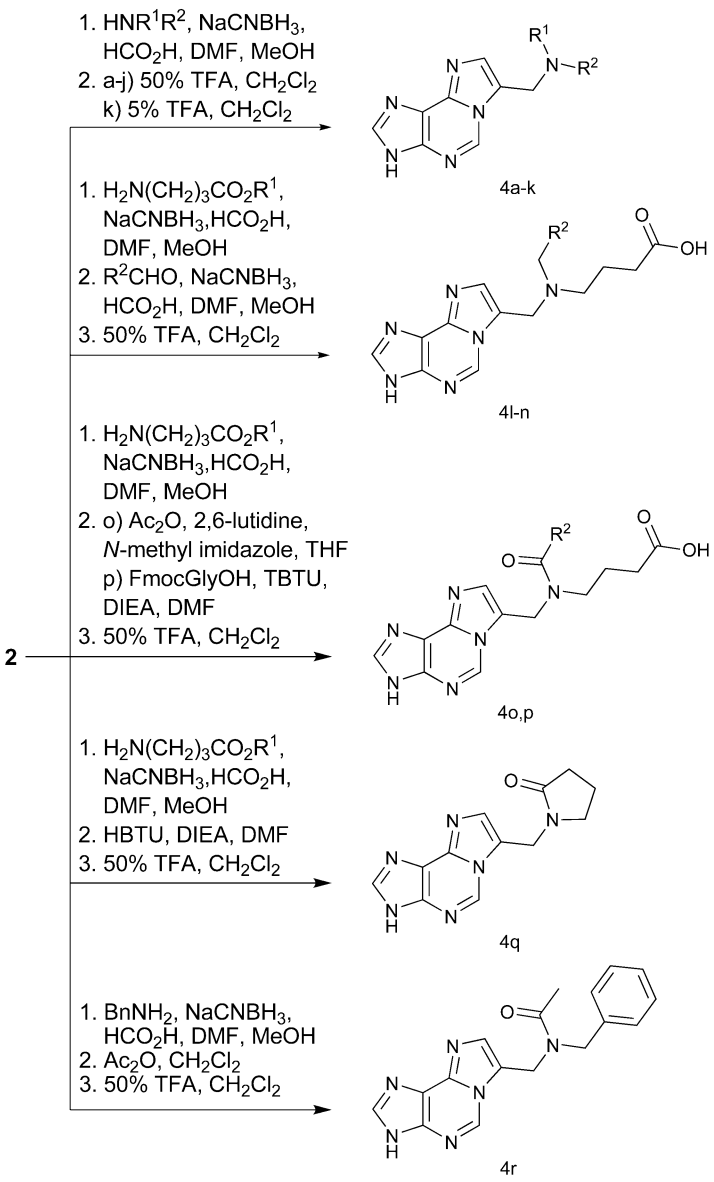


Fig. 2 HPLC trace of crude 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde cleaved from the resin (RP HPLC, 0–100% MeCN, 0.1% TFA, $\lambda = 220$ nm).

Reductive amination of **2** was attempted with a set of ten amines under the conditions optimized with **7** (Scheme 3). It was observed that after the one hour imine formation and subsequent four hours reduction step, aniline (entry **4a**) had reacted quantitatively, unhindered primary amines (entries **4b–d**) had produced 84–92% product, while sterically hindered primary amines, *t*-butylamine and tris(hydroxymethyl)aminomethane (entries **4e**,**f**), gave only a 35% yield. Among secondary amines, diethylamine and diisopropylamine (entries **4g**,**h**) did not react. By contrast,



Entry	R^1	R^2	Yield (%)[a,b]
4a	H	Ph	100
4b	H	Bz	84 (4.5)
4c	H	Pr	92
4d	H	CH_2CO_2t-Bu	91 (4.2)
4e	H	*t*-Bu	36
4f	H	$C(CH_2OH)_3$	35
4g	Et	Et	0
4h	*i*-Pr	*i*-Pr	0
4i	$(CH_2)_5$		73
4j	H	$(CH_2)_3CO_2H$	88 (5.8)
4k	H	$(CH_2)_3CO_2t$-Bu	91 (3.9)
4l	H	Me	74
4m	H	CH_2OH	80
4n	H	CO_2H	80
4o	*t*-Bu	Me	91
4p	*t*-Bu	Fmoc-$NHCH_2$	60
4q	H		89
4r			79

a) calculated from RP HPLC chromatograms
b) yield of dialkylated product in parentheses

Scheme 3

piperidine (entry **4i**) reacted smoothly, giving a 73% yield. It was, hence, concluded that the method is suitable for unhindered amines but sterically more demanding amines give lower or non-existent yields. Benzylamine (entry **4b**) and *t*-butyl glycine acetate (entry **4d**) both gave, additionally, 4% of dialkylated products.

Support **2** was finally subjected to consecutive reductive amination and alkylation to obtain 4-aminobutyric acid derivatives **4l–n** and to reductive amination followed by acylation to obtain derivatives **4o–q** and *N*-benzyl-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]acetamide (**4r**). The synthesis of **4r** was performed as described for **8**, except that the reductive amination was repeated before the acylation. Reductive amination of **2** with 4-aminobutyric acid *t*-butyl ester and 4-aminobutyric acid gave, besides the expected **4j** and **4k**, 4–6% of dialkylated side products. In addition, the reaction with 4-aminobutyric acid yielded 7% of a lactamized product, obtained in all likelihood by cyanoborohydride activation.[28–30] The lactam formation was verified by HPLC by spiking with 1-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]pyrrolidin-2-one (**4q**), synthesized by 2-(1*H*-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate (HBTU)/DIEA mediated cyclization of **4j**, and by identical mass spectra of the side product and **4q**. Lactamization of **4j** was also achieved by acetic anhydride treatment. The latter method is of minor practical value, owing to concomitant formation of 21% of acetylated product **4o**.

Reductive alkylations leading to compounds **4l–n** were performed under similar conditions as the reductive aminations discussed above. For all the alkylations, three hours reaction time was sufficient when ten equivalents of aldehyde were used. Acylation of **4k** was tested with acetic anhydride (**4o**) and Fmoc protected glycine by TBTU/DIEA activation (**4p**). As expected, **4k** was fully acetylated in one hour under the conditions employed. Coupling of Fmoc glycine by using an active ester method was also completed in 1 hour. By contrast, 65% of the starting material remained unchanged after the same reaction time when a

symmetrical anhydride preformed in a 1 : 9 mixture of DMF and CH_2Cl_2 was used for the coupling in the same solvent (data not presented).

In summary, a solid-supported synthesis for *N*,*N*-disubstituted (3*H*-imidazo[2,1-*i*]purin-7-yl)methylamines has been developed. Commercially available 2′-deoxyadenosine phosphoramidite reagent immobilized by conventional phosphitylation to a hydroxy-functionalized support may be used as a traceless acid-labile linker. Alternatively, [N^6-(4-methoxytrityl)adenin-9-yl]acetic acid may be immobilized by acylation to commercially available amino acid derivatized Wang resins to obtain the *N*,*N*-disubstituted (3*H*-imidazo[2,1-*i*]purin-7-yl)methylamines as *N*3-linked amino acid (or peptide) derivatives.

Experimental

General Remarks

The chemical shifts are given in ppm downfield from internal $(CH_3)_4Si$. Appropriate 2D NMR methods, *e.g.* HMBC, HSQC and COSY, were used for peak assignment. RP HPLC analyses and separations were performed on a Hypersil HyPurity Elite C18 (150 × 4.6 mm, 5 μm) and Hypersil ODS column (250 × 10 mm, 5 μm), respectively, applying a linear gradient from 0.1% aq. TFA to MeCN in 30 min at a flow rate of 1.0 mL min^{-1} (Hypurity column) or 3.0 mL min^{-1} (ODS column). The detection wavelength was 220 nm.

Solvents and reagents were dried or tested for dryness before use. Unless otherwise indicated, analytical samples and products were cleaved from the resin by shaking in 1 : 1 TFA–DCM mixture for 1 hour. Resin was filtered by suction, rinsed successively with CH_2Cl_2 (1 mL) and MeOH (1 mL), and the solvents were removed under reduced pressure (rotary evaporation). Yields for products **4a–r** were calculated from HPLC chromatograms of filtrates. HPLC fractions containing purified products were evaporated to dryness on a centrifugal concentrator. Trityl protections were removed by washing the resin with 3% dichloroacetic acid and 3% MeOH in CH_2Cl_2 until no colour evolved when rinsed with 3% dichloroacetic acid in CH_2Cl_2. The deprotected resin was subjected to successive washings with CH_2Cl_2, CH_2Cl_2/MeOH, 10% pyridine in CH_2Cl_2, CH_2Cl_2, CH_2Cl_2–MeOH and MeOH and dried in a vacuum desiccator.

***N*-[(Adenin-9-yl)acetyl]phenylalanine–Wang resin (6).** Commercial N^{α}-Fmoc-Phe–Wang polystyrene resin (0.15 g, 1.0 mmol g^{-1}) was deprotected by 20 min treatment with 20% piperidine in DMF. The resin was washed successively with DMF, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH, and dried in vacuum. The pyridine salt of [N^6-(4-methoxytrityl)adenin-9-yl]acetic acid (163 mg, 0.30 mmol), TBTU (96.3 mg, 0.30 mmol) and DIEA (0.10 mL, 0.60 mmol) were dissolved in DMF (1.40 mL). The solution was added onto Phe–Wang resin and the reaction mixture was shaken for 3 h. The resin was subsequently washed with DMF, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. According to the 4-methoxytrityl cation assay, the loading of the resin was 70% of the theoretical value. Removal of the 4-methoxytrityl protection yielded **6**. HRMS (FAB^+) for the product cleaved from the resin: calcd for [MH^+] $C_{16}H_{17}N_6O_3$ 341.1362; found 341.1363.

Optimization of the formation of *N*-[(7-formylimidazo[2,1-*i*]-purin-3-yl)acetyl]phenylalanine on Wang resin. Resin **6** (5 mg) was preswollen in DMF (20 μL). Bromomalonaldehyde, formic or acetic acid, triethylamine or 2,6-lutidine from freshly prepared stock solutions were added in quantities indicated in Table 1 and the volume of the reaction mixture was filled up to 50 μL with DMF. The mixture was agitated at 60 °C for a chosen time, after which the resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH, and dried in a vacuum desiccator. Reaction products were cleaved from the solid support and assayed by RP HPLC as described in general remarks.

Solid supported *N*-[(7-formylimidazo[2,1-*i*]purin-3-yl)acetyl]-phenylalanine (7). Formic acid (57 μL, 1.5 mmol), 2,6-lutidine (175 μL, 1.5 mmol) and bromomalonaldehyde (113 mg, 0.75 mmol) were dissolved in 1.27 mL DMF. The solution was added onto **6** (150 mg, 0.105 mmol). The mixture was stirred at 60 °C for 4 h. The resin was washed with DMF, MeOH, DMF, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. ^{1}H NMR (500 MHz, $(CD_3)_2SO$) for the product cleaved from the resin: δ = 2.92 (dd, ^2J = 13.8 Hz, $^3J_{H\alpha,H\beta A}$ = 5.1 Hz, 1 H, $H_{\beta,Phe}A$), 3.08 (dd, ^2J = 13.8 Hz, $^3J_{H\alpha,H\beta B}$ = 8.8 Hz, 1 H, $H_{\beta,Phe}B$), 4.47 (ddd, $^3J_{H\alpha,H\beta A}$ = 5.1 Hz, $^3J_{H\alpha,H\beta B}$ = 8.8 Hz, $^3J_{H\alpha,NH}$ = 8.0 Hz, 1 H, $H_{\alpha,Phe}$), 5.01 (d, ^2J = 16.7 Hz, 1 H, $CH_{2,A}CO$), 5.14 (d, ^2J = 16.7 Hz, 1 H, $CH_{2,B}CO$), 7.19–7.29 (m, 5 H, Ar_{Phe}), 8.43 (s, 1 H, H 2′), 8.60 (s, 1 H, H 8′), 8.78 (d, $^3J_{H\alpha,NH}$ = 8.0 Hz, 1 H, NH), 9.88 (s, 1 H, H 5′), 10.01 (s, 1 H, CHO) ppm; ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ = 36.75 (CH_{2Phe}), 45.73 (CH_{2Ac}), 53.80 (CH_{Phe}), 122.08 (C9b), 124.68 (C7), 126.51 ($C4_{Phe}$), 128.24 ($C3_{Phe}$), 129.20 ($C2_{Phe}$), 136.47 (C5), 137.23 ($C1_{Phe}$), 142.01 (C3a), 144.79 (C2), 144.96 (C9a), 147.99 (C8), 165.92 (CONH), 172.49 (CO_2H), 179.12 (CHO) ppm. HRMS (EI^+) calcd for $C_{19}H_{16}N_6O_4$ 392.1233; found 392.1233.

***N*-{[7-(*N*-benzylacetamidomethyl)imidazo[2,1-*i*]purin-3-yl]-acetyl}phenylalanine (8).** Benzylamine (35.2 μL, 323 μmol) and formic acid (20 μl) dissolved in DMF (215 μL) were added on resin **7** (46 mg, 32.3 μmol). After 30 min shaking, 85% $NaCNBH_3$ (19.1 mg, 258 μmol) in a mixture of DMF (200 μL) and MeOH (30 μL) was added and the reaction mixture was shaken for additional 5 h. The support was washed with DMF, 10% MeOH in DMF, H_2O, MeOH, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH and dried in vacuum desiccator. The resin was shaken in 20% acetic anhydride in CH_2Cl_2 (1 mL) for 1 h and washed with CH_2Cl_2, 10% Py in CH_2Cl_2, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. Release from the resin and HPLC purification of the product, as described above, gave **8** (7.2 mg, 42%, overall yield 29%). The product exhibited NMR signals as two conformers in 4 : 1 ratio. Only the major conformer is assigned here. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 2.12 (s, 3 H, CH_3CO), 2.94 (dd, ^2J = 13.8 Hz, $^3J_{H\alpha,H\beta A}$ = 8.8 Hz, 1 H, $H_{\beta,Phe}A$), 3.08 (dd, ^2J = 13.8 Hz, $^3J_{H\alpha,H\beta B}$ = 4.9 Hz, 1 H, $H_{\beta,Phe}B$), 4.48 (ddd, $^3J_{H\alpha,H\beta B}$ = 4.9 Hz, $^3J_{H\alpha,H\beta A}$ = 8.8 Hz, $^3J_{H\alpha,NH}$ = 7.9 Hz, 1 H, $H_{\alpha,Phe}$), 4.59 (s, 2 H, $CH_{2,Bn}$), 4.99 (d, ^2J = 15.8 Hz, 1 H, $CH_{2,A}Im$), 5.03 (d, ^2J = 15.8 Hz, 1 H, $CH_{2,B}Im$), 5.10 (d, ^2J = 16.8 Hz, 1 H, $CH_{2,A}CO$), 5.16 (d, ^2J = 16.8 Hz, 1 H, $CH_{2,B}CO$), 7.12–7.33 (m, 10 H, Ar_{Phe}, Ar_{Bn}), 7.92 (s, 1 H, H8), 8.50 (s, 1 H, H2), 8.87 (d, $^3J_{H\alpha,NH}$ = 7.9 Hz, 1 H, NH), 9.40 (s, 1 H, H5), 12.88 (s, 1 H, CO_2H) ppm; ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ = 22.52 ($CH_{3,Ac}$), 36.79 (CH_{2Phe}), 37.70 (CH_2Im), 45.78 (CH_2Pur), 50.49 ($CH_{2,Bn}$), 53.83 (CH_{Phe}), 119.07 (C9b), 122.12 (C7), 125.37 (C8), 126.42 ($C2_{Bn}$), 126.58 ($C4_{Phe}$), 127.33 ($C4_{Bn}$), 128.31 ($C3_{Phe}$), 128.74 ($C3_{Bn}$), 129.23

($C2_{Phe}$), 135.95 (C5), 136.93 ($C1_{Bn}$), 137.21 ($C1_{Phe}$), 138.50 (C9a), 142.00 (C3a), 145.23 (C2), 165.92 ($CONH_{Phe}$), 171.47 ($CONH_{Bn}$), 172.48 (CO_2H) ppm. HRMS (FAB^+) calcd for $[MH^+]$ $C_{28}H_{28}N_7O_4$ 526.2203; found 526.2201.

4-(4-Methoxytrityloxy)butyramidomethyl polystyrene. Sodium (4-methoxytrityloxy)butyrate (0.941 g, 2.5 mmol), diisopropylcarbodiimide (0.392 mL, 2.5 mmol) and 1-hydroxybenzotriazole hydrate (0.384 g, 2.5 mmol) were dissolved in DMF (21 mL) and added on a preswollen aminomethyl polystyrene resin (2.5 g, 0.5 mmol g^{-1}). After 5 h of shaking, the resin was washed successively with DMF, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. According to the monomethoxytrityl cation assay, the loading of the resin was 0.40 mmol g^{-1}.

Solid-supported 3-(3′-*O*-phosphono-2′-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[2,1-*i*]purine-7-carbaldehyde (2). 4,5-Dicyanoimidazole (0.738 g, 6.25 mmol) and N^6-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyadenosine 3′-(2-cyanoethyl-*N*,*N*-diisopropylphosphoramidite (5.36 g, 6.25 mmol) were dissolved in THF (25 mL). The solution was added onto detritylated and preswollen 4-(4-methoxytrityloxy)butyramidomethyl polystyrene. The mixture was shaken for 1 h, washed with THF and subjected to 20 min oxidation with 0.1 mol L^{-1} iodine in pyridine containing 2% water. The resin was rinsed with pyridine, 5% water in pyridine, pyridine, CH_2Cl_2, CH_2Cl_2–MeOH and MeOH and dried. According to the dimethoxytrityl cation assay, the loading of the resin was 0.360 mmol g^{-1}. The DMTr protection was removed as described earlier. The base labile N^6-benzoyl and O^P-(2-cyanoethyl) protections were removed by refluxing the resin for 4 h in THF (36 mL) containing 1 mol L^{-1} aqueous NaOH (4 mL). The resin was rinsed with THF, water, THF–water, THF, CH_2Cl_2 and MeOH, after which it was dried, giving solid-supported 2′-deoxyadenosine 3′-phosphate (**1**).

Formic acid (2.83 mL, 75 mmol), 2,6-lutidine (2.91 mL, 25 mmol) and bromomalonaldehyde (1.89 g, 12.5 mmol) were dissolved in 19.3 mL DMF. The solution was added onto preswollen **1**. The mixture was stirred at 60 °C for 3.5 h. The resin was washed with DMF, CH_2Cl_2, pyridine, 10% MeOH in CH_2Cl_2 and MeOH. According HPLC analysis of a cleaved sample, conversion of the starting material to the solid-supported 3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde had not taken place quantitatively and, hence, the reaction was repeated using halved amounts of reagents. ^1H NMR (500 MHz, D_2O) for 7-formyl-3*H*-imidazo[2,1-*i*]purine released from the support: $\delta = 8.45$ (s, 1 H, H2), 8.52 (s, 1 H, H8), 9.93 (s, 1 H, CHO), 10.01 (s, 1 H, H5). HRMS (EI^+) calcd for $C_8H_5N_5O$ 187.0494; found 187.0499.

Synthesis of *N*-alkyl-(3*H*-imidazo[2,1-*i*]purin-7-yl)methylamines (4a–i). An appropriate primary or secondary amine (16.7 μmol) and formic acid (2.0 μL, 52 μmol) dissolved in DMF (25 μL) were added on support **2**. After 1 h imine formation, 85% $NaCNBH_3$ (0.84 mg, 11 μmol) dissolved in DMF (20 μL) and MeOH (3 μL) were added and the reaction mixture was shaken for additional 4 h. Solid support was washed with DMF, 10% MeOH in DMF, H_2O, MeOH, DCM, 10% MeOH in DCM and MeOH.

***N*-Phenyl-(3*H*-imidazo[2,1-*i*]purin-7-yl)methylamine (4a).** Yield 100%. HRMS (EI^+) calcd for $C_{14}H_{12}N_6$ 264.1123; found 264.1121.

***N*-Benzyl-(3*H*-imidazo[2,1-*i*]purin-7-yl)methylamine (4b).** Yield 84%. HRMS (EI^+) calcd for $C_{15}H_{14}N_6$ 278.1278; found 278.1278.

***N*-Propyl-(3*H*-imidazo[2,1-*i*]purin-7-yl)methylamine (4c).** Yield 92%. HRMS (EI^+) calcd for $C_{11}H_{14}N_6$ 230.1280; found 230.1280.

***tert*-Butyl {[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]amino}acetate (4d).** 91% of *tert*-butyl protections were removed under the cleavage conditions employed. The combined yield of the *tert*-butyl ester and free acid was 90%. HRMS (ESI^+) calcd for $[MH^+]$ $C_{14}H_{19}N_6O_2$ 303.1564; found 303.1560 and for $C_{10}H_{11}N_6O_2$ 247.0938; found 247.0938.

***N*-*tert*-Butyl-(3*H*-imidazo[2,1-*i*]purin-7-yl)methylamine (4e).** Yield 36%. HRMS (EI^+) calcd for $C_{11}H_{14}N_6$ 244.1436; found 244.1439.

2-(Hydroxymethyl)-2-{[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-amino}propane-1,3-diol (4f). Yield 35%. HRMS (ESI^+) calcd for $[MH^+]$ $C_{12}H_{17}N_6O_3$ 293.1357; found 293.1352.

7-[(Piperidin-1-yl)methyl]-3*H*-imidazo[2,1-*i*]purine (4i). Yield 73%. HRMS (FAB^+) calcd for $[MH^+]$ $C_{13}H_{17}N_6$ 257.1515; found 230.1524.

***N*-[(3*H*-Imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4j).** 4-Aminobutyric acid (41.2 mg, 0.40 mmol) was suspended in a mixture of formic acid (60 μl), MeOH (90 μl), and DMF (1.35 mL). The suspension was added onto resin **2** (150 mg, 50 μmol) and the mixture was shaken 30 min before adding 85% $NaCNBH_3$ (25.1 mg, 0.34 mmol). After 5 h 30 min shaking, the resin was washed with DMF, MeOH, 10% MeOH in DMF, DCM, 10% MeOH in DCM and MeOH. Yield 88%. HRMS (ESI^+) calcd for $[MH^+]$ $C_{12}H_{15}N_6O_2$ 275.1251; found 275.1257.

***tert*-Butyl *N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoate (4k).** The synthesis was performed as described for **4j**, except that *tert*-butyl 4-aminobutanoate (79.6 mg, 0.50 mmol) was used instead of 4-aminobutyric acid. Analytical sample was cleaved from the resin by shaking in 5% TFA in DCM for 1 hour. The resin was filtered by suction and rinsed successively with CH_2Cl_2 (1 mL) and MeOH (1 mL). The filtrate was neutralized with pyridine and solvents were evaporated under reduced pressure. Yield 91%. HRMS (EI^+) calcd for $C_{16}H_{22}N_6O_2$ 330.1804; found 330.1801.

***N*-Ethyl-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4l).** Acetaldehyde (4.0 mg, 91 μmol), 85% $NaCNBH_3$ (6.7 mg, 91 μmol), formic acid (12 μl), MeOH (30 μl) and DMF (260 μl) were mixed and added onto solid-supported **4j** (30 mg, 9 μmol). The reaction mixture was shaken for 3 h and then washed with CH_2Cl_2, 10% MeOH in DMF, MeOH, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. Yield 74%. ^1H NMR (500 MHz, D_2O): $\delta =$ 1.40 (t, $^3J_{H1'',H2''} = 7.3$ Hz, 3 H, $CH_{3,Et}$), 2.07 (m, 2 H, H3), 2.50 (t, $^3J_{H2,H3} = 6.9$ Hz, 2 H, H2), 3.34 (m, 2 H, H4), 3.40 (q, $^3J_{H1'',H2''} =$ 7.3 Hz, 2 H, $CH_{2,Et}$), 4.99 (s, 2 H, CH_2Im), 8.04 (s, 1 H, H8′), 8.48 (s, 1 H, H2′), 9.31 (s, 1 H, H5′). HRMS (FAB^+) calcd for $[MH^+]$ $C_{14}H_{19}N_6O_2$ 303.1569; found 303.1564.

***N*-(2-Hydroxyethyl)-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4m).** The synthesis was performed as

described for **4l**, except that glycolaldehyde dimer (10.8 mg, 90 μmol) was used instead of acetaldehyde. Yield 80%. ^{1}H NMR (500 MHz, D_2O): $\delta = 2.11$ (m, 2 H, H3), 2.51 (t, $^3J_{H2,H3} = 6.8$ Hz, 2 H, H2), 3.40 (t, $^3J_{H3,H4} = 8.1$ Hz, 2 H, H4), 3.53 (t, $^3J_{H1'',H2''} = 5.1$ Hz, 2 H, CH_2N_{Et}), 4.04 (t, $^3J_{H1'',H2''} = 5.1$ Hz, 2 H, CH_2O_{Et}), 5.09 (s, 2 H, CH_2Im), 8.10 (s, 1 H, H8′), 8.51 (s, 1 H, H2′), 9.37 (s, 1 H, H5′). HRMS (FAB$^+$) calcd for [MH$^+$] $C_{14}H_{19}N_6O_3$ 319.1519; found 319.1507.

***N*-(Carboxymethyl)-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4n).** The synthesis was performed as described for **4l**, except that glyoxylic acid monohydrate (8.3 mg, 90 μmol) was used instead of acetaldehyde. Yield 80%. ^{1}H NMR (500 MHz, D_2O): $\delta = 2.23$ (m, 2 H, H3), 2.67 (t, $^3J_{H2,H3} = 6.8$ Hz, 2 H, H2), 3.52 (t, $^3J_{H3,H4} = 7.9$ Hz, 2 H, H4), 4.08 (s, 2 H, CH_2CO), 5.15 (s, 2 H, CH_2Im), 8.26 (s, 1 H, H8′), 8.71 (s, 1 H, H2′), 9.78 (s, 1 H, H5′). HRMS (FAB$^+$) calcd for [MH$^+$] $C_{14}H_{17}N_6O_4$ 333.1311; found 333.1322.

***N*-Acetyl-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4o).** Solid-supported **4k** (30 mg, 9 μmol) was flushed 1 h with freshly prepared solution of acetic anhydride (100 μl), 2,6-lutidine (100 μl), and *N*-methylimidazole (160 μl) in THF (1.64 mL). The resin was washed with THF, CH_2Cl_2, 5% AcOH in CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. The product was cleaved from the solid support and purified as **4l**. Yield 91%. ^{1}H NMR (500 MHz, D_2O): $\delta = 1.91$ (m, 2 H, H3), 2.23 (s, 3 H, CH_3CO), 2.41 (t, $^3J_{H2,H3} = 7.1$ Hz, 2 H, H2), 3.45 (t, $^3J_{H3,H4} = 7.8$ Hz, 2 H, H4), 5.11 (s, 2 H, CH_2Im), 7.89 (s, 1 H, H8′), 8.51 (s, 1 H, H2′), 9.29 (s, 1 H, H5′). HRMS (FAB$^+$) calcd for [MH$^+$] $C_{14}H_{17}N_6O_3$ 317.1362; found 317.1350.

***N*-[*N*-(Fluoren-9-ylmethoxycarbonyl)glycyl]-*N*-[(3*H*-imidazo-[2,1-*i*]purin-7-yl)methyl]-4-aminobutanoic acid (4p).** *N*-(Fluoren-9-ylmethoxycarbonyl)glycine (13.4 mg, 45 μmol), TBTU (14.4 mg, 45 μmol) and DIEA (7.8 μl, 45 μmol) were dissolved in DMF (295 μl). The mixture was shaken 1 h with solid-supported **4k** (30 mg, 9 μmol). The resin was subsequently washed with CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. The product was cleaved from the solid support and purified as **4l**. Yield 60%. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): $\delta = 1.94$ (m, 2 H, H3), 2.39 (m, 2 H, H2), 3.40 (m, 2 H, H4), 4.15 (s, 2 H, CH_2CO), 4.28 (t, $^3J_{H,H} = 7.2$ Hz, 1 H, Fmoc), 4.34 (dist. d, $^3J_{H,H} = 7.2$ Hz, 2 H, Fmoc), 5.16 (s, 2 H, CH_2Im), 7.34 (m, 2 H, Fmoc), 7.41 (m, 2 H, Fmoc), 7.72 (s, 1 H, H8′), 7.76 (m, 2 H, Fmoc), 7.86 (m, 2 H, Fmoc), 8.29 (s, 1 H, H2′), 9.22 (s, 1 H, H5′). HRMS (FAB$^+$) calcd for [MH$^+$] $C_{29}H_{28}N_7O_5$ 554.2152; found 554.2174.

1-[(3*H*-Imidazo[2,1-*i*]purin-7-yl)methyl]pyrrolidin-2-one (4q). HBTU (5.7 mg, 15 μmol) and DIEA (5.2 μL, 30 μmol) were dissolved in DMF (45 μL). The solution was added onto **4j** (4.3 mg, 3 μmol). The mixture was shaken for 1 h and then washed with DMF, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. Yield 89%. ^{1}H NMR (500 MHz, $(CDCl_3)$): $\delta = 2.03$ (m, 2 H, H2′), 2.48 (t, $^3J_{H,H} = 8.1$ Hz,2 H, H1′), 3.33 (t, $^3J_{H,H} = 7.1$ Hz, 2 H, H3′), 4.91 (s, 2 H, CH_2Im), 7.59 (s, 1 H, H8), 8.28 (s, 1 H, H2), 9.33 (s, 1 H, H5). HRMS (EI$^+$) calcd for $C_{12}H_{12}N_6O$ 256.1073; found 256.1076.

***N*-Benzyl-*N*-[(3*H*-imidazo[2,1-*i*]purin-7-yl)methyl]acetamide (4r).** Benzylamine (10.7 mg, 0.1 mmol) and formic acid (12 μL, 0.32 mmol) dissolved in DMF (275 μL) were added onto **2** (30 mg, 10 μmol). After 30 min shaking, 85% $NaCNBH_3$ (6.3 mg, 85 μmol) was added to the reaction mixture and the shaking was continued for 4 h 30 min. The resin was washed with DMF, 10% MeOH in DMF, MeOH, CH_2Cl_2, 10% MeOH in CH_2Cl_2 and MeOH. The reaction was repeated and the resin was dried in a vacuum desiccator. The resin was shaken in 20% acetic anhydride in CH_2Cl_2 (1 mL) for 1 h and washed with CH_2Cl_2, 10% Py in CH_2Cl_2, DCM, 10% MeOH in CH_2Cl_2 and MeOH. Yield 79%. ^{1}H NMR (500 MHz, 10% CD_3OD, $CDCl_3$): $\delta = 2.28$ (s, 3 H, CH_3CO), 4.54 (s, 2 H, $CH_{2,Bn}$), 5.05 (s, 2 H, CH_2Im), 7.16 (m, 2 H, $H_{Bn}2$), 7.35–7.38 (m, 3 H, $H_{Bn}3$, $H_{Bn}4$), 7.51 (s, 1 H, H8), 8.33 (s, 1 H, H2), 9.40 (s, 1 H, H5). HRMS (EI$^+$) calcd for $C_{17}H_{16}N_6O_1$ 320.1386; found 320.1389.

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References

1 M. Legraverend and D. S. Grierson, *Bioorg. Med. Chem.*, 2006, **14**, 3987–4006.
2 (*a*) H. Daub, K. Specht and A. Ullrich, *Nat. Rev. Drug Discovery*, 2004, **3**, 1001; (*b*) F. I. Raynaud, P. M. Fischer, B. P. Nutley, P. M. Goddard, D. P. Lane and P. Workman, *Mol. Cancer Ther.*, 2004, **3**, 353; (*c*) Z. A. Knight and K. M. Shokat, *Chem. Biol.*, 2005, **12**, 621; (*d*) Y. Liu and N. S. Gray, *Nat. Chem. Biol.*, 2006, **2**, 358.
3 (*a*) P. Raboisson, C. Lugnier, C. E. Müller, J.-M. Reimund, D. Schultz, G. Pinna, A. Le Bec, H. Basaran, L. Desaubry, F. Gaudiot, M. Selouma and J.-J. Bourguignon, *Eur. J. Med. Chem.*, 2003, **38**, 199; (*b*) J. W. F. Whitehead, G. P. Lee, P. Gharagozloo, P. Hofer, A. Gehrig, P. Wintergerst, D. Smyth, W. McCoull, M. Hachicha, A. Patel and D. J. Kyle, *J. Med. Chem.*, 2005, **48**, 1237; (*c*) F. S. Menniti, W. S. Faraci and C. J. Schmidt, *Nat. Rev. Drug Discovery*, 2006, **5**, 660.
4 L. Llauger, H. He, J. Kim, J. Aguirre, N. Rosen, U. Peters, P. Davies and G. Chiosis, *J. Med. Chem.*, 2005, **48**, 2892.
5 E. Chapman, M. D. Best, S. R. Hanson and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2004, **43**, 3526.
6 A. Kurimoto, T. Ogino, S. Ichii, Y. Isobe, M. Tobe, H. Ogita, H. Takaku, H. Sajiki, K. Hirota and H. Kawakami, *Bioorg. Med. Chem.*, 2004, **12**, 1091.
7 (*a*) X. Wu, J. Walker, J. Zhang, S. Ding and P. G. Schultz, *Chem. Biol.*, 2004, **11**, 1229; (*b*) S. Chen, Q. Zhang, X. Wu, P. G. Schultz and S. Ding, *J. Am. Chem. Soc.*, 2004, **126**, 410.
8 P. G. Baraldi, F. Fruttarolo, M. A. Tabrizi, R. Romagnoli, D. Preti, A. Bovero, M. J. Pineda de Las Infantas, A. R. Moorman, K. Varani and P. A. Borea, *J. Med. Chem.*, 2004, **47**, 5535.
9 (*a*) S.-A. Poulsen and R. J. Quinn, *Bioorg. Med. Chem.*, 1998, **6**, 619; (*b*) Y. C. Kim, X. Ji, N. Melman, J. Linden and K. A. Jakobsen, *J. Med. Chem.*, 2000, **43**, 1165; (*c*) J. Hockemeyer, J. C. Burbiel and C. E. Müller, *J. Org. Chem.*, 2004, **69**, 3308; (*d*) J. Zablocki, R. Kalla, T. Perry, V. Palle, V. Varkhedkar, D. Xiao, A. Piscopio, T. Maa, A. Gimbel, J. Hao, N. Chu, K. Leung and D. Zeng, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 609.
10 J. P. Beck, A. G. Arvanitis, M. A. Curry, J. T. Rescinito, L. W. Fitzgerald, P. J. Gilligan, R. Zaczek and G. L. Trainor, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 967.
11 A. K. Pathak, V. Pathak, L. E. Seitz, W. J. Suling and R. C. Reynolds, *J. Med. Chem.*, 2004, **47**, 273.
12 (*a*) T. C. Norman, N. S. Gray, J. T. Koh and P. G. Schultz, *J. Am. Chem. Soc.*, 1996, **118**, 7430; (*b*) V. Brun, M. Legraverend and D. S. Grierson, *Tetrahedron Lett.*, 2001, **42**, 8165; (*c*) W. J. Pitts, W. Vaccaro, T. Huynh, K. Leftheris, J. Y. Roberge, J. Barbosa, J. Guo, B. Brown, A. Watson, K. Donaldson, G. C. Starling, P. A. Kiener, M. A. Poss, J. H. Dodd and J. C. Barrish, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2955; (*d*) E. Gunic, R. Amador, F. Rong, J. W. Abt, H. An, Z. Hong and J.-L. Girardet, *Nucleosides, Nucleotides Nucleic Acids*, 2004, **23**, 495; (*e*) J. Chang, C. Dong, X. Guo, W. Hu, S. Cheng, Q. Wang and R. Chen, *Bioorg. Med. Chem.*, 2005, **13**, 4760.

13 (*a*) Y.-T. Chang, N. S. Gray, G. R. Rosania, D. P. Sutherlin, S. Kwon, T. C. Norman, R. Rarohia, M. Leost, L. Meijer and P. G. Schultz, *Chem. Biol.*, 1999, **6**, 361; (*b*) S. Ding, N. S. Gray, Q. Ding and P. G. Schultz, *J. Org. Chem.*, 2001, **66**, 8273; (*c*) P. H. Dorff and R. S. Garigipati, *Tetrahedron Lett.*, 2001, **42**, 2771; (*d*) V. Brun, M. Legraverend and D. S. Grierson, *Tetrahedron*, 2002, **58**, 7911; (*e*) S. Ding, N. S. Gray, Q. Ding, X. Wu and P. G. Schultz, *J. Comb. Chem.*, 2002, **4**, 183.
14 Y.-h. Koh, M. B. Landesman, R. Amador, F. Rong, H. An, Z. Hong and J.-L. Girardet, *Nucleosides, Nucleotides Nucleic Acids*, 2004, **23**, 501.
15 (*a*) P. G. Baraldi, D. Preti, M. A. Tabrizi, F. Fruttarolo, R. Romagnoli, A. A. Zaid, A. R. Moorman, S. Merighi, K. Varani and P. A. Borea, *J. Med. Chem.*, 2005, **48**, 4697; (*b*) S. Moro, Z.-G. Gao, K. A. Jacobson and G. Spalluto, *Med. Res. Rev.*, 2006, **26**, 131.
16 (*a*) N. K. Kochetkov, V. N. Shibaev and A. A. Kost, *Tetrahedron Lett.*, 1971, **22**, 1993; (*b*) J. R. Barrio, J. A. Secrist, III and N. J. Leonard, *Biochem. Biophys. Res. Commun.*, 1972, **46**, 597; (*c*) R. B. Meyer, Jr., D. A. Shuman, R. K. Robins, J. P. Miller and L. N. Simon, *J. Med. Chem.*, 1973, **16**, 1319; (*d*) V. Nair, R. J. Offerman and G. A. Turner, *J. Org. Chem.*, 1984, **49**, 4021; (*e*) N. J. Leonard and K. A. Cruickshank, *J. Org. Chem.*, 1985, **50**, 2480; (*f*) J. Mäki, R. Sjöholm and L. Kronberg, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2923; (*g*) P. Virta, T. Holmström, T. Munter, T. Nyholm, L. Kronberg and R. Sjöholm, *Nucleosides, Nucleotides Nucleic Acids*, 2003, **22**, 85; (*h*) M. B. Doughty, K. Aboudehen, G. Anderson, K. Li, B. Moore, II and T. Poolson, *Nucleosides, Nucleotides Nucleic Acids*, 2004, **23**, 1751.
17 (*a*) V. Nair and R. J. Offerman, *J. Org. Chem.*, 1985, **50**, 5627; (*b*) R. S. Sodum and F.-L. Chung, *Cancer Res.*, 1991, **5**, 137; (*c*) V. M. Carvalho, D. Gasparutto, P. Di Mascio, M. H. Medeiros and J. Cadet, *Bioorg. Med. Chem.*, 2003, **11**, 2445.
18 B. Devadas and N. J. Leonard, *J. Am. Chem. Soc.*, 1990, **112**, 3125.
19 N. Tohme, C. Courseille, M. Demeunynck, M. F. Lhomme and J. Lhomme, *Tetrahedron Lett.*, 1985, **26**, 3799–3802.
20 L. Bialy, J. J. Diaz-Mochon, E. Specker, L. Keinicke and M. Bradley, *Tetrahedron*, 2005, **61**, 8295.
21 S. Trofimenko, *J. Org. Chem.*, 1963, **28**, 3243.
22 S. Mikkola, N. Koissi, K. Ketomäki, S. Rauvala, K. Neuvonen and H. Lönnberg, *Eur. J. Org. Chem.*, 2000, 2315.
23 A. M. Ruohola, N. Koissi, S. Andersson, I. Lepistö, K. Neuvonen, S. Mikkola and H. Lönnberg, *Org. Biomol. Chem.*, 2004, **2**, 1943.
24 F. Le Curieux, T. Munter and L. Kronberg, *Chem. Res. Toxicol.*, 1997, **10**, 1180.
25 G. F. Field and W. J. Zally, *US Pat.* 4194049, 1980.
26 R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897–2904.
27 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849–3862.
28 A. F. Abdel-Magid, B. D. Harris and C. A. Maryanoff, *Synlett*, 1994, 81–83.
29 A. Pelter and T. E. Levitt, *Tetrahedron*, 1970, **26**, 1545–1553.
30 D. B. Collum, S. C. Chen and B. Ganem, *J. Org. Chem.*, 1978, **43**, 4393–4394.