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Addition of Nucleophiles to 6-Vinylpurines

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6-Vinylpurines readily participate in nucleophilic addition reactions. Treatment with sodium salts of alcohols and thiols, as well as stabilised carbanions, results in clean conversion into a variety of functionalized purine derivatives. Additions performed in the presence of acid give 1 : 1 adducts together with dimeric purine products. Under acidic conditions the adduct first formed reacts further with another molecule of vinylpurine.

Purines and purine nucleosides bearing carbon substituents at C-2, C-6 or C-8 are associated with important medicinal[1] and agrochemical properties.[2] Relatively few methods exist, however, for the facile introduction of alkyl groups into these positions.[3] Recently, low stabilities of 6- and 8-vinylpurines, probably due to addition reactions,[4] have been observed. These findings indicated to us that certain alkenylpurines possess electron-deficient properties which can be explored in nucleophilic additions giving a variety of substituted alkylpurines, analogous to reactions described for 2- and 4-vinylpyridines.[5] Our hypothesis was strengthened by some newly reported examples of 6-vinylguanosine functionalization.[6] Recently, we demonstrated that 6-vinylpurines readily participate in Lewis acid catalysed Diels–Alder cycloadditions,[7] and we herein report our results from a study of nucleophilic addition reactions.

The 6-vinylpurines **2** and **6** were prepared by Pd-catalysed cross-coupling of the corresponding 6-halopurines **1** and **5** with organometallic reagents (Scheme 1). Both coupling with vinylic organotin[3c] and organozinc[7] reagents can easily be employed in the synthesis of the 9-benzylated isomer **2**. The *N*-7 alkylated compound **5** also participates in Stille couplings to give the vinylpurine **6**. However, the alkenyl substituent in this isomer appeared to be more activated towards nucleophilic attack than that of the corresponding 9-benzyl isomer **2**. When the crude product was treated with potassium fluoride in methanol, in order to convert the co-product Bu_3SnCl into the corresponding tin fluoride, formation of the methoxy adduct **7a** was observed after a short time (Table 1, entry 5). Work-up employing MeOH was tolerated well in the synthesis of the purine **2**, but even this vinyl compound could be converted into the corresponding methoxy adduct **3a** after prolonged exposure to KF and MeOH (Table 1, entry 4). We previously noted substantial differences in reactivity between 7- and 9-alkylated 6-halopurines in Pd-catalysed coupling reactions,[3c,3d,8] and these results indicated that the positional identity of the *N*-alkyl group also influences the electronic properties of the vinyl substituent.

The results from treatment of the vinylpurines **2** and **6** with methanol and benzenethiol under various reactions conditions (Scheme 1) are summarised in Table 1.

When the vinylpurine **2** was stirred in pure methanol, hardly any reaction took place at all. After a reaction time of 6 weeks, the **2**:**3a** ratio was ca. 13:1, as judged by the ^{1}H NMR spectrum of the crude product. On the other hand, ca. 30% of the methoxy adduct **7a** was formed when the 7-benzylated vinylpurine **6** was subjected to the same set of reaction conditions. The reactivities towards benzenethiol (PhSH) were, not unexpectedly, found to be considerably higher. The vinylpurines **2** and **6** were consumed after ca. 4 h to give the adducts **3b** and **7b** together with small amounts of the dimers **4b** and **8b** (Table 1, entries 6 and 7). The structures of these by-products were determined by HETCOR, COSY and COLOC NMR spectroscopy. Camphor-10-sulfonic acid (CSA) has recently been reported to catalyse adduct formation on 6-vinylguanosines.[6a] When MeOH or PhSH were reacted with the alkenes **2** and **6** in the presence of CSA, we found, however, that the formation of the dimers **4** and **8** was much more profound (Table 1, entries 1, 8 and 9). Furthermore, most of the starting material decomposed when MeOH addition to compound **6** was attempted under these reaction

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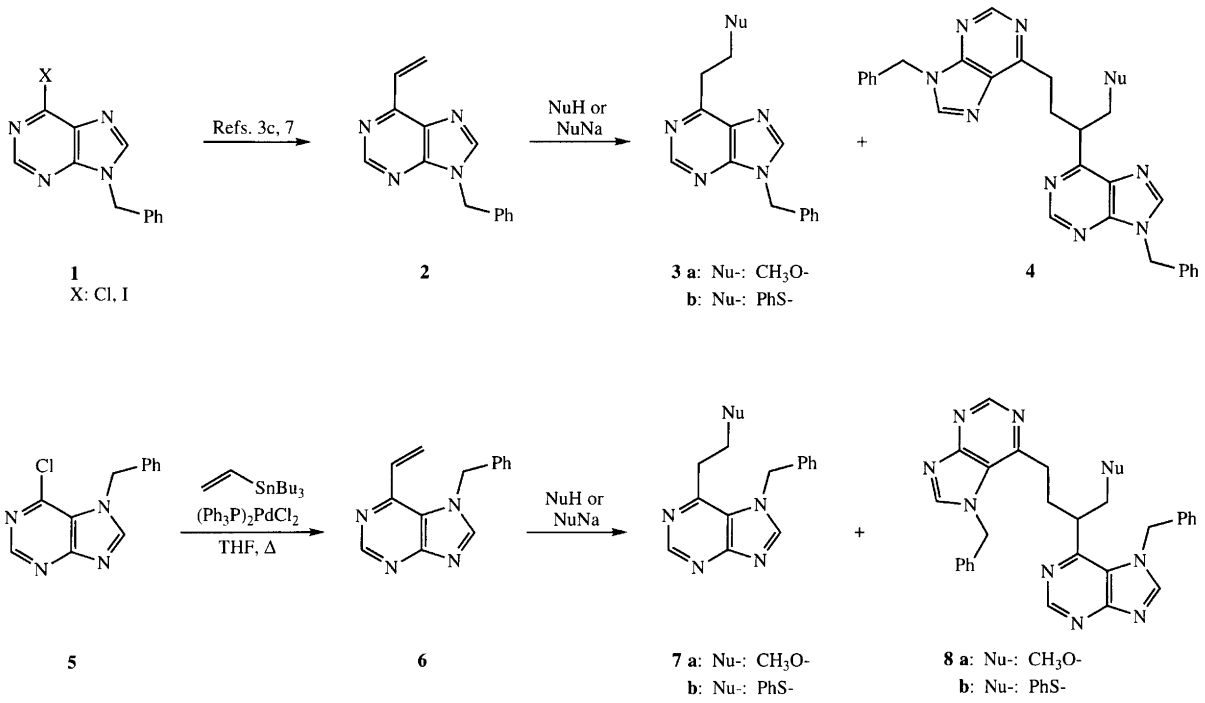


Scheme 1.

Table 1. Addition of alcohols and thiols.

Entry	Vinylpurine	NuH or NuNa	Co-reagent	Solvent	Time	**2**:**3**:**4**[a] or **6**:**7**:**8**[a]	Yield (%) **3** or **7**[b]	Yield (%) **4** or **8**[b,c]
1	**2**	MeOH	CSA	CH_2Cl_2	24 h	—[d]:2:1	40, **3a**	21, **4a**
2	**2**	MeONa	—	DCE	42 h	Only **3a**	87, **3a**	—
3	**6**	MeONa	—	DCE	1 h	—[e]	81, **7a**	7, **8a**
4	**2**	MeOH	KF	MeOH	4 wk	Only **3a**	85, **3a**	—
5	**6**	MeOH	KF	MeOH	40 h	—[e]	31, **7a**	—
6	**2**	PhSH	—	DCE	4 h	—[d]:10:1	75, **3b**	5, **4b**
7	**6**	PhSH	—	DCE	4 h	—[d]:9:1	71, **7b**	16, **8b**
8	**2**	PhSH	CSA	DCE	2 h	—[d]:2:1	32, **3b**	37, **4b**
9	**6**	PhSH	CSA	DCE	3 h	—[e,f]	36, **7b**	31, **8b**
10	**2**	PhSNa	—	DCE	24 h	Only **3b**	76, **3b**	—
11	**6**	PhSNa	—	DCE	3 h	—[d]:16:1	83, **7b**	12, **8b**

[a] From the ^{1}H NMR spectra of the crude products. [b] Yields of isolated products. [c] Based on the amount of the purine **2** or **6** used. [d] Not detectable in the ^{1}H NMR spectrum. [e] Not determined. [f] A complex mixture was formed.

conditions. On the other hand, reactions of compounds **2** and **6** with MeONa or PhSNa gave the 1:1 adducts **3** and **7** in high yields (Table 1, entries 2, 3, 10 and 11) and in the additions to the *N*-9 alkylated purine **2**, no by-product **4** could be detected.

Formation of the dimers **4** and **8** might be rationalised by the following sequence. First, addition of the nucleophile to the starting material **2** or **6** gives the 1:1 adduct **3** or **7**, and the adduct reacts further with another molecule of **2** or **6**, i.e., the carbon atom attached to the purine 6-position in **3** or **7** attacks the vinyl group in **2** or **6**. When equimolar amounts of compounds **2** and **3b** in DCE was reacted in the presence of CSA, the dimer **4b** could be isolated in 42% yield after 3 days. On the other hand, when only compound **3b** was treated with CSA in DCE, **4b** was not observed in the ^{1}H NMR spectrum of the evaporated reaction mixture. These results demonstrate that the dimer is formed by addition of alkylpurine at vinylpurine; consequently a mechanism involving a substitution of the PhS-group is excluded. Furthermore, this observation indicates that the addition of PhSH to the vinylpurine is irreversible under acidic conditions. The addition of **3b** to **2** resembles acid-catalysed condensation of α- or γ-methyl(di)azines with aldehydes,[9] a reaction previously reported for 6-methylpurine.[10]

Our observations from the treatment of vinylpurines **2** and **6** with MeOH or KF–MeOH (*vide supra*) show that the 7-alkylated isomer **6** is more activated towards nucleophilic attack than is isomer **2**. However, the results described above demonstrate that either isomer can easily be converted into adducts under mild reaction conditions.

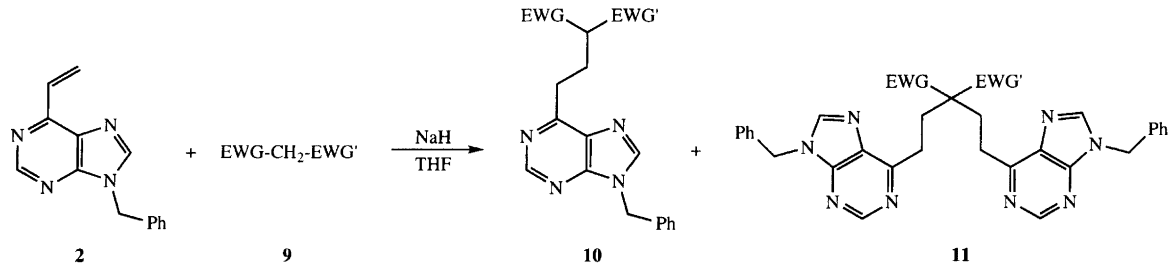
The tendency to form dimeric products is somewhat higher for the *N*-7 benzylated compound **6**.

Additions of carbon nucleophiles to the vinylpurine **2** were also examined. Diethyl malonate and related nucleophiles **9** reacted with **2** in the presence of sodium hydride (NaH) to give the adducts **10** (Scheme 2, Table 2).

When Michael additions of compounds **9** are performed in the presence of a full equivalent base, the final anion may subsequently act as a Michael donor,[11] and various amounts of the compounds **11** were indeed formed, when a slight excess of NaH was employed (Table 2, entries 1, 5 and 14). Only **9d** gave the 1:1 adduct **10d** exclusively in the presence of 1.2 equiv. NaH (Table 2, entry 16). The formation of the 1:2 adduct **11a** was more predominant when the diethyl malonate addition was carried out in acetonitrile relative to tetrahydrofuran (Table 2, entries 2 and 3), indicating that the vinylpurine **2** is a Michael acceptor of moderate reactivity, and that relatively poor solvation of the anionic nucleophiles is beneficial for a reasonable reaction rate and selectivity.[12] Reducing the amount of base, improved the **10**–**11** ratio. When 0.5–0.6 equiv. NaH were employed, little or no 1:2 adduct could be observed in the additions of the *C*-nucleophiles **9a** and **9c** (Table 2, entries 3, 4 and 15) and the 1:1 adducts **10a** and **10c** were isolated in high yields. A reduction of the amount of base below ca. 0.5 equiv. did not result in significant improvements in yields and product distribution, but the reaction time was generally increased. The nature of the base employed appeared to have little influence on the outcome of these reactions (*vide infra*).

In the reactions of the β-cyano ester **9b**, the formation of the 1:2 adduct was more profound compared with the reactions with **9a**, **9c** and **9d**, probably due to the relatively small steric requirements of the Michael donor **9b**.[13] Here the product distribution was attested to only a limited extent by the amount of base employed (Table 2, entries 5, 6 and 8). The reaction was also performed with various amounts of a different base, 1,1,3,3-tetramethylguanidine (TMG). As shown in Table 1 (entries 6–9), no significant differences between NaH and TMG could be observed, and these findings did not encourage further screening of bases. The results from the reactions of diethyl malonate **9a** suggested that relatively low solvent polarity might be beneficial for high 1:1 adduct selectivity, but changing the solvent from THF to diethyl ether or benzene (Table 2, entries 12 and 13) did not have the desired effect. On the other hand, when a large excess **9b** or higher reaction temperature were employed, the 1:1 adduct selectivity was improved (Table 2, entries 10 and 11).

The reactivity of the malonate adduct **10a** differs



2 **9** **10** **11**

Scheme 2.

Table 2. Addition of stabilised carbanions.

Entry	EWGCH$_2$EWG', **9**	Base, Equiv.	Solvent	*T*/°C	Time	Yield (%) **10**[a]	Yield (%) **11**[a]
1	$(EtO_2C)_2CH_2$, **9a**	NaH, 1.2	THF	RT	2 h	59, **10a**	32, **11a**
2	$(EtO_2C)_2CH_2$, **9a**	NaH, 0.6	MeCN	RT	5 h	75, **10a**	17, **11a**
3	$(EtO_2C)_2CH_2$, **9a**	NaH, 0.6	THF	RT	6 h	85, **10a**	2, **11a**
4	$(EtO_2C)_2CH_2$, **9a**	NaH, 0.5	THF	RT	5 h	83, **10a**	—[b]
5	MeO_2CCH_2CN, **9b**	NaH, 1.2	THF	RT	8 h	24, **10b**	71, **11b**
6	MeO_2CCH_2CN, **9b**	NaH, 0.5	THF	RT	22 h	32, **10b**	60, **11b**
7	MeO_2CCH_2CN, **9b**	TMG, 0.5	THF	RT	28 h	34, **10b**	62, **11b**
8	MeO_2CCH_2CN, **9b**	NaH, 0.2	THF	RT	42 h	38, **10b**	59, **11b**
9	MeO_2CCH_2CN, **9b**	TMG, 0.1	THF	RT	44 h	34, **10b**	51, **11b**
10[c]	MeO_2CCH_2CN, **9b**	NaH, 0.5	THF	RT	18 h	68, **10b**	25, **11b**
11	MeO_2CCH_2CN, **9b**	NaH, 0.5	THF	Δ	1.5 h	51, **10b**	38, **11b**
12	MeO_2CCH_2CN, **9b**	NaH, 0.5	Ether	RT	8 days	21, **10b**	79, **11b**
13[d]	MeO_2CCH_2CN, **9b**	NaH, 1.0	Benzene	RT	4 days	11, **10b**	4, **11b**
14[e]	EtO_2CCH_2COMe, **9c**	NaH, 1.2	THF	RT	48 h	66, **10c**	9, **11c**
15	EtO_2CCH_2COMe, **9c**	NaH, 0.6	THF	RT	72 h	83, **10c**	2, **11c**
16[f]	$(MeCO)_2CH_2$, **9d**	NaH, 1.2	THF	50	48 h	68, **10d**	—[b]

[a] Yields of isolated products. [b] Not detectable. [c] 5.0 equiv. of **9b** were used. [d] 76% Vinylpurine was recovered. [e] 12% Vinylpurine was recovered. [f] 17% Vinylpurine was recovered.

considerably from that of the alcohol and thiol adducts **3a** and **3b**. In the presence of base, the adduct **10a** readily reacted with the vinylpurine **2** giving compound **11a** in 68% yields, but **10a** was almost unreactive towards the alkene **2** in acidic media. When **10a** was reacted with compound **2** in the presence of CSA, only 4% of the adduct **12** (Fig. 1) was isolated and 68% of **10a** could be recovered. Under these conditions the benzenethiol adduct **3b** readily reacts with compound **2** (*vide supra*).

Finally the *N*-7 alkylated vinylpurine **6** was treated with diethyl malonate **9a** in the presence of NaH. No symmetrical dimer, such as compound **11a**, was formed. Instead, 7% of compound **14** (Fig. 1) was isolated together with 55% of the 1:1 adduct **13** (Fig. 1). Again the nucleophilicity of the carbon atom situated at the purine 6-position is increased when the purine is alkylated at *N*-7. Under identical conditions, the 9-benzylated isomer **10a** does not form the dimer **12** (*vide supra*).

The results described herein demonstrate that 6-vinylpurines act as Michael acceptors when treated with nucleophilic reagents. 6-Vinylpurines may therefore be attractive intermediates in syntheses of a variety of 6-alkylpurine derivatives. Even though the vinylpurines participate in acid-catalysed additions, reactions with anionic nucleophiles are cleaner and synthetically more useful. This study also demonstrates that the position of the *N*-substituent on *N*-alkylated 6-vinylpurines influences the reactivity of the vinyl group as well as the reactivity of the α-carbon in the alkylpurine addition product. With the alkyl group situated at *N*-7, the ethenyl group is somewhat more prone to nucleophilic attack and the α-carbon in the adduct is substantially more nucleophilic, compared with the *N*-9 alkylated isomers.

Experimental

The ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500, at 300 MHz with a Bruker Avance DPX 300 or at 200 MHz with a Bruker Avance DPX 200 MHz instrument. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the above mentioned spectrometers. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m/z* (% rel. int.). Methane was used for chemical ionisation. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). THF and diethyl ether were distilled from sodium–benzophenone. Dichloroethane, dichloromethane and acetonitrile were distilled from CaH_2. Benzene was dried over sodium wire. Methanol was distilled from magnesium and iodine and stored over molecular sieves. Benzenethiol was distilled at reduced pressure and stored over molecular sieves. A ca. 60% oily dispersion of sodium hydride was washed with hexane (×3) and dried *in vacuo* prior to use. All other reagents were commercially available and used as received.

Starting materials available by literature procedures. 9-Benzyl-6-ethenyl-9*H*-purine (**2**),[3c,7] 7-benzyl-6-chloro-7*H*-purine (**5**).[3c]

*7-Benzyl-6-ethenyl-7*H*-purine* (**6**). A mixture of 7-benzyl-6-chloro-7*H*-purine **5** (245 mg, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and ethenyl(tributyl)tin (410 µl, 1.40 mmol) in dry THF (5 ml) was refluxed under N_2 for 3.5 h and evaporated *in vacuo*. The residue was dissolved in acetonitrile (50 ml), washed with hexane (4 × 100 ml) and evaporated. The crude product was purified by flash chromatography eluting with EtOAc–acetone (1:1); yield 212 mg (90%) colourless crystals. M.p. 141–143 °C. ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 5.61 (s, 2 H, CH_2N), 5.63 (dd, J_{cis} 10.6 Hz, J_{gem} 1.9 Hz, 1 H, =CH_2), 6.65 (dd, J_{trans} 16.7 Hz, J_{gem} 1.9 Hz, 1 H, =CH_2), 7.00 (dd, J_{trans} 16.7 Hz, J_{cis} 10.6 Hz, 1 H, =CH), 7.1 (m, 2 H, Ph), 7.3–7.4 (m, 3 H, Ph), 8.24 (s, 1 H, H-8), 8.96 (s, 1 H, H-2). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 51.6 (CH_2), 122.5 (C-5), 124.8 (CH_2=), 126.6 (CH=), 128.6, 129.1 and 130.0 (CH in Ph), 135.4 (C in Ph), 147.5 (C-6), 149.7 (C-8), 153.2 (C-2), 162.8 (C-4). MS (EI): 237 (11), 236 (72, M^+), 235 (38), 221 (6), 208 (6), 92 (6), 91 (100), 65 (14). HRMS: Found 236.1059, calc. for $C_{14}H_{12}N_4$: 236.1062.

*Addition of methanol to 9-benzyl-6-ethenyl-9*H*-purine* (**2**) *in the presence of camphor-10-sulfonic acid.* 9-Benzyl-6-ethenyl-9*H*-purine **2** (93 mg, 0.39 mmol) and camphor-10-sulfonic acid (91 mg, 0.39 mmol) were dissolved in dry dichloromethane (4 ml) and the mixture was stirred for 10 min at ambient temperature under N_2 before dry

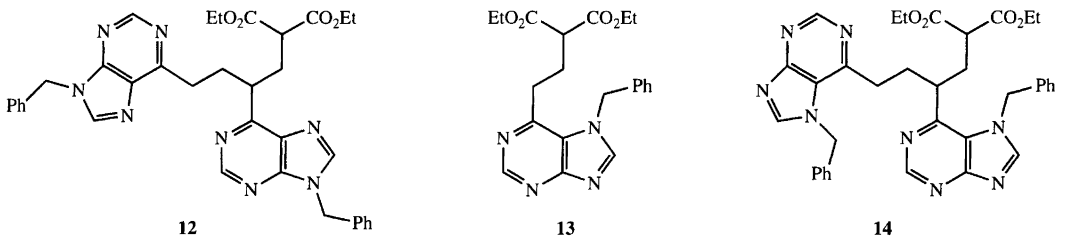


Fig. 1.

methanol (20 µl, 0.49 mmol) was added. The reaction was quenched with triethylamine (70 µl, 0.50 mmol) after 24 h, the mixture was evaporated *in vacuo*, and the products were isolated by flash chromatography on silica gel. 9-Benzyl-6-(2-methoxyethyl)-9*H*-purine **3a** was eluted with EtOAc–acetone (1:1) and 2,4-di(9-benzyl-6-purinyl)-1-methoxybutane **4a** was eluted with EtOAc–acetone–MeOH (10:10:1).

3a. Yield 42 mg (40%) colourless powdery crystals. M.p. 57–58 °C (pentane). Anal.: C, H. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.35 (s, 3 H, CH_3), 3.50 (t, *J* 6.6 Hz, 2 H, CH_2), 4.00 (t, *J* 6.6 Hz, 2 H, CH_2O), 5.42 (s, 2 H, CH_2N), 7.3 (m, 5 H, Ph), 8.04 (s, 1 H, H-8), 8.94 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 33.2 (CH_2), 46.9 (CH_2N), 58.3 (CH_3), 70.2 (CH_2O), 127.6, 128.2 and 128.8 (CH in Ph), 132.7 (C-5), 134.9 (C in Ph), 143.5 (C-8), 150.6 (C-4), 152.2 (C-2), 159.5 (C-6). MS (EI): 268 (2, M^+), 253 (53), 235 (9), 147 (9), 91 (100), 65 (12), 45 (10).

4a. Yield 21 mg (21%) colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.49 (m, 2 H, CH_2), 3.00 (m, 1 H, CH_2), 3.16 (m, 1 H, CH_2), 3.21 (s, 3 H, CH_3), 3.77 (m, 1 H, CH_2O), 3.95 (m, 2 H, CH_2O and CH), 5.32 (m, 4 H, CH_2N), 7.2–7.3 (m, 10 H, Ph), 7.74 (s, 1 H, H-8), 7.79 (s, 1 H, H-8), 8.77 (s, 1 H, H-2), 8.87 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7 (CH_2), 30.7 (CH_2), 42.5 (CH), 47.1 and 47.2 (CH_2N), 58.8 (CH_3), 75.3 (CH_2O), 127.8–129.1 (CH in Ph), 132.4 and 133.2 (C-5), 135.1 and 135.2 (C in Ph), 143.3 and 143.5 (C-8), 150.7 and 150.9 (C-4), 152.5 and 152.7 (C-2), 161.9 and 162.7 (C-6). MS (EI): 504 (2, M^+), 472 (35), 381 (16), 281 (15), 268 (11), 263 (13), 249 (21), 237 (14), 224 (18), 91 (100). HRMS: Found 504.2410, calc. for $C_{29}H_{28}N_8O$: 504.2386.

*Addition of sodium methoxide to 9-benzyl-6-ethenyl-9*H*-purine* (**2**). 9-Benzyl-6-ethenyl-9*H*-purine **2** (120 mg, 0.51 mmol) was dissolved in dry dichloroethane (5 ml) and the mixture was stirred at ambient temperature under N_2 for 10 min before a 25% solution of sodium methoxide in methanol (140 µl, 0.61 mmol) was added. The reaction was quenched with glacial acetic acid (42 µl, 0.73 mmol) after 42 h, the mixture was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with EtOAc–acetone (1:1) to give 9-benzyl-6-(2-methoxyethyl)-9*H*-purine **3a**; yield 119 mg (87%).

*Addition of sodium methoxide to 7-benzyl-6-ethenyl-7*H*-purine* (**6**). 7-Benzyl-6-ethenyl-7*H*-purine **6** (72 mg, 0.31 mmol) was reacted with a 25% solution of sodium methoxide in methanol (85 µl, 0.37 mmol) as described for 9-benzyl-6-ethenyl-9*H*-purine **2** above. The reaction was quenched after 1 h and the products were isolated by flash chromatography on silica gel eluting with acetone followed by acetone–EtOH (4:1).

7a. Yield 66 mg (81%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.14 (t, *J* 6.1 Hz, 2 H, CH_2), 3.24 (s, 3 H, CH_3), 3.74 (t, *J* 6.1 Hz, 2 H, CH_2), 5.70 (s, 2 H, CH_2), 7.0–7.1 (m, 2 H, Ph), 7.4 (m, 3 H, Ph), 8.20 (s, 1 H, H-8), 9.05 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.1 (CH_2), 50.7 (CH_2N), 58.8 (CH_3), 70.8 (CH_2O), 124.3 (C-5), 125.8, 128.0 and 128.8 (CH in Ph), 134.9 (C in Ph), 148.4 (C-8), 152.2 (C-6), 152.3 (C-2), 160.4 (C-4). MS (EI): 268 (12, M^+), 254 (6), 253 (37), 238 (5), 237 (14), 236 (9), 235 (5), 92 (7), 91 (100), 65 (11). HRMS: Found 268.1328, calc. for $C_{15}H_{16}N_2O$: 268.1324.

8a. Yield 5 mg (7%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.05 (m, 2 H), 2.43 (m, 2 H), 3.06 (s, 3 H, CH_2), 3.33 (t, *J* 8.3 Hz, 1 H, CH_2O), 3.54 (m, 2 H, CH and CH_2O), 5.23 (d, *J* 16.1 Hz, 1 H, H_A CH_2N), 5.37 (d, *J* 16.3 Hz, 1 H, H_A CH_2N), 5.58 (d, *J* 16.1 Hz, 1 H, H_B CH_2N), 5.66 (d, *J* 16.3 Hz, 1 H, H_B CH_2N), 6.5 (m, 2 H, Ph), 6.8–6.9 (m, 2 H, Ph), 7.2 (m, 6 H, Ph), 8.18 (s, 1 H, H-8), 8.19 (s, 1 H, H-8), 8.94 (s, 1 H, H-2), 9.09 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7 (CH_2), 30.5 (CH_2), 43.0 (CH), 50.8 and 51.1 (CH_2N), 59.0 (CH_3), 76.5 (CH_2O), 123.3 and 125.3 (C-5), 125.5–129.4 (CH in phenyl), 134.5 and 135.0 (C in phenyl), 149.8 (C-8), 151.8 and 152.8 (C-2), 153.5 and 155.3 (C-6), 161.5 (C-4). MS (CI): 504 (1, M^+), 472 (2), 330 (9), 268 (7), 237 (13), 211 (9), 180 (6), 149 (13), 121 (16), 91 (100). HRMS: Found 504.2386, calc. for $C_{29}H_{28}N_8O$: 504.2386.

*Addition of benzenethiol to 9-benzyl-6-ethenyl-9*H*-purine* (**2**). 9-Benzyl-6-ethenyl-9*H*-purine **2** (120 mg, 0.51 mmol) and benzenethiol (62 µl, 0.61 mmol) were dissolved in dry dichloroethane (5 ml) and the mixture was stirred at ambient temperature under N_2. After 4 h, the mixture was evaporated *in vacuo* and the products were isolated by flash chromatography on silica gel. 9-Benzyl-6-(2-phenylthioethyl)-9*H*-purine **3b** was eluted with EtOAc–hexane (2:1) and 2,4-di(9-benzyl-6-purinyl)-1-phenylthiobutane **4b** was eluted with EtOAc–EtOH (8:1).

3b. Yield 132 mg (75%) colourless powdery crystals. M.p. 90–91 °C (hexane). Anal.: C, H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.54 (s, 4 H, CH_2CH_2), 5.40 (s, 2 H, CH_2N), 7.1–7.4 (m, 10 H, Ph), 7.99 (s, 1 H, H-8), 8.91 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.5 (CH_2), 33.0 (CH_2), 47.1 (CH_2N), 125.9–129.4 (CH in Ph), 132.5 (C-5), 135.0 and 135.8 (C in Ph), 143.7 (C-8). 150.8 (C-4), 152.4 (C-2), 159.9 (C-6). MS (EI): 346 (4, M^+), 237 (100), 224 (14), 209 (3), 123 (3), 110 (17), 91 (94), 77 (5), 65 (16).

4b. Yield 7 mg (5%) colourless powdery crystals. M.p. ca. 110 °C (decomp.). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (m, 2 H, CH_2), 2.96 (m, 1 H, CH_2), 3.14 (m, 1 H, CH_2), 3.39 (dd, *J* 5.4 and 13.0 Hz, 1 H, CH_2S), 3.65 (dd, *J* 9.2 and 13.0 Hz, 1 H, CH_2S), 3.88 (m, 1 H, CH), 5.28 (m, 4 H, CH_2N), 7.0–7.3 (m, 15 H, Ph), 7.74 (s, 1 H, H-8), 7.79 (s, 1 H, H-8), 8.74 (s, 1 H, H-2), 8.82 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.6 (CH_2), 31.8 (CH_2), 38.0 (CH_2S), 42.8 (CH), 47.0 and 47.1 (CH_2N), 125.8–129.6 (CH in Ph), 132.3 and 132.9 (C-5), 135.0, 135.1 and 136.1 (C in Ph), 143.3 and 143.6 (C-8),

150.6 and 150.9 (C-4), 152.4 and 152.5 (C-2), 161.5 and 162.6 (C-6). MS (EI): 582 (1, M^+), 473 (79), 457 (2), 445 (2), 381 (12), 345 (5), 263 (9), 249 (15), 237 (21), 110 (16), 91 (100). HRMS: Found 582.2329, calc. for $C_{34}H_{30}N_8S$: 582.2314.

*Addition of benzenethiol to 7-benzyl-6-ethenyl-7*H*-purine* (**6**). 7-Benzyl-6-ethenyl-7*H*-purine **6** (129 mg, 0.55 mmol) was reacted with benzenethiol as described for 9-benzyl-6-ethenyl-9*H*-purine **2** above. The products were isolated by flash chromatography on silica gel. 7-Benzyl-6-(2-phenylthioethyl)-7*H*-purine **7b** was eluted with EtOAc–acetone (1:1) and 2,4-di(7-benzyl-6-purinyl)-1-phenylthiobutane **8b** was eluted with EtOAc–acetone–EtOH (3:3:1).

7b. Yield 135 mg (71%) colourless powdery crystals. M.p. 81–83 °C. Anal.: C, H. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 3.13 (m, 2 H, CH_2), 3.25 (m, 2 H, CH_2), 5.40 (s, 2 H, CH_2N), 6.88 (m, 2 H, Ph), 7.2–7.3 (m, 8 H, Ph), 8.19 (s, 1 H, H-8), 8.94 (s, 1 H, H-2). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 31.7 (CH_2), 34.2 (CH_2), 51.3 (CH_2N), 124.3 (C-5), 126.4, 126.6, 128.8, 129.4, 129.5 and 129.6 (CH in Ph), 135.6 and 136.0 (C in Ph), 149.3 (C-8), 153.0 (C-6), 153.2 (C-2), 161.7 (C-4). MS (EI): 346 (4, M^+), 313 (2), 265 (5), 237 (29), 224 (7), 186 (11), 171 (6), 110 (19), 91 (100), 77 (14).

8b. Yield 25 mg (16%) colourless oil. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 1.57 (m, 1 H, CH_2), 1.98 (m, 1 H, CH_2), 2.06 (m, 1 H, CH_2), 3.16 (d, *J* 7.2 Hz, 2 H, CH_2S), 3.35 (m, 1 H, CH), 5.07 (d, *J* 16.7 Hz, 1 H, H_A CH_2N), 5.09 (d, *J* 16.5 Hz, 1 H, H_A CH_2N), 5.23 (d, *J* 16.5 Hz, 1 H, H_B CH_2N), 5.29 (d, *J* 16.7 Hz, 1 H, H_B CH_2N), 6.40 (m, 2 H, Ph), 6.50 (m, 2 H, Ph), 7.0–7.2 (m, 11 H, Ph), 8.04 (s, 1 H, H-8), 8.06 (s, 1 H, H-8), 8.76 (s, 1 H, H-2), 8.94 (s, 1 H, H-2). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 31.1 (CH_2), 33.0 (CH_2), 38.9 (CH_2S), 42.9 (CH), 50.9 and 51.1 (CH_2N), 123.7 and 125.2 (C-5), 125.8–129.5 (CH in Ph), 135.2, 135.6 and 136.0 (C in Ph), 149.1 and 150.0 (C-8), 153.1 and 153.5 (C-2), 154.2 and 156.0 (C-6), 161.5 and 162.1 (C-4). MS (EI): 582 (0.2, M^+), 473 (11), 381 (2), 345 (3), 263 (8), 249 (7), 237 (20), 208 (3), 110 (18), 91 (100). HRMS: Found 582.2297, calc. for $C_{34}H_{30}N_8S$: 582.2314.

*Addition of benzenethiol to 9-benzyl-6-ethenyl-9*H*-purine* (**2**) *in the presence of camphor-10-sulfonic acid.* 9-Benzyl-6-ethenyl-9*H*-purine **2** (119 mg, 0.50 mmol) and camphor-10-sulfonic acid (119 mg, 0.51 mmol) were dissolved in dry dichloroethane (5 ml) and the mixture was stirred at ambient temperature under N_2 for 10 min before benzenethiol (65 µl, 0.64 mmol) was added. After 2 h, the reaction was quenched with triethylamine (85 µl, 0.61 mmol), the mixture was evaporated *in vacuo*, and the products were isolated by flash chromatography on silica gel. 9-Benzyl-6-(2-phenylthioethyl)-9*H*-purine **3b** 56 mg (32%) was eluted with EtOAc–hexane (2:1) and 2,4-di(9-benzyl-6-purinyl)-1-phenylthiobutane **4b** 55 mg (37%) was eluted with EtOAc–EtOH (8:1).

*Addition of benzenethiol to 7-benzyl-6-ethenyl-7*H*-purine* (**6**) *in the presence of camphor-10-sulfonic acid.* 7-Benzyl-6-ethenyl-7*H*-purine **6** (101 mg, 0.43 mmol) was reacted with benzenethiol in the presence of CSA as described for 9-benzyl-6-ethenyl-9*H*-purine 2 above. The products were isolated by flash chromatography on silica gel. 7-Benzyl-6-(2-phenylthioethyl)-7*H*-purine **7b** (53 mg, 36%) was eluted with EtOAc–EtOH (8:1) and 2,4-di(7-benzyl-6-purinyl)-1-phenylthiobutane **8b** (39 mg, 31%) was eluted with EtOAc–acetone–EtOH (3:3:1).

*Addition of sodium benzenethiolate to 9-benzyl-6-ethenyl-9*H*-purine* (**2**). Sodium hydride (16 mg, 0.67 mmol) was added to a solution of benzenethiol (62 µl, 0.61 mmol) in dry DCE (2 ml) at ambient temperature under N_2. After 10 min, a solution of 9-benzyl-6-ethenyl-9*H*-purine **2** (130 mg, 0.55 mmol) in dry dichloroethane (4 ml) was added and the resulting mixture was stirred for 24 h before glacial acetic acid (40 µl, 0.69 mmol) was added. The mixture was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (2:1) to give 9-benzyl-6-(2-phenylthioethyl)-9*H*-purine **3b**; yield 144 mg (76%).

*Addition of sodium benzenethiolate to 7-benzyl-6-ethenyl-7*H*-purine* (**6**). 7-Benzyl-6-ethenyl-7*H*-purine **6** (90 mg, 0.38 mmol) was reacted with sodium benzenethiolate as described for 9-benzyl-6-ethenyl-9*H*-purine **2** above. The products were isolated by flash chromatography on silica gel. 7-Benzyl-6-(2-phenylthioethyl)-7*H*-purine **7b** (109 mg, 83%) was eluted with EtOAc–EtOH (8:1) and 2,4-di(7-benzyl-6-purinyl)-1-phenylthiobutane **8b** (13 mg, 12%) was eluted with EtOAc–acetone–EtOH (3:3:1).

Synthesis of 2,4-di(9-benzyl-6-purinyl)-1-phenylthiobutane (**4b**) *from 9-benzyl-6-(2-phenylthioethyl)-9*H*-purine* (**3b**). A mixture of 9-benzyl-6-ethenyl-9*H*-purine **2** (25 mg, 0.106 mmol), 9-benzyl-6-(2-phenylthioethyl)-9*H*-purine **3b** (36 mg, 0.104 mmol) and CSA (29 mg, 0.125 mmol) in dry DCE (2 ml) was stirred for 3 days at ambient temperature under N_2. Triethylamine (20 µl, 0.143 mmol) was added, the mixture was evaporated, and the product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (2:1) followed by EtOAc–EtOH (8:1); yield 13 mg, (42%).

*General procedure for the reactions between 9-benzyl-6-ethenyl-9*H*-purine* (**2**) *and compounds* (**9**). Compound **9** (0.83 mmol) was added to a stirred suspension of sodium hydride (20 mg, 0.83 mmol) in dry THF (2 ml) at ambient temperature under N_2. After 10 min, a solution of the 9-benzyl-6-ethenyl-9*H*-purine **2** (163 mg, 0.69 mmol) in THF (5 ml) was added and the resulting mixture stirred at the temperature and for the time given below. The reaction was quenched with glacial acetic acid (50 µl, 0.87 mmol), the mixture was evaporated *in vacuo*, and

the crude product was purified by flash chromatography on silica gel.

*9-Benzyl-6-[3,3-bis(ethoxycarbonyl)propyl]-9*H*-purine* (**10a**) *and diethyl 1,5-bis(9-benzyl-6-purinyl)pentane-3,3-dicarboxylate* (**11a**). A mixture of sodium hydride, diethyl malonate **9a** and 9-benzyl-6-ethenyl-9*H*-purine **2** was stirred at ambient temperature for 2 h and worked up as described above. EtOAc–hexane (3:1), followed by EtOAc–acetone (1:1) were used for flash chromatography.

10a. 162 mg (59%) colourless oil. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.18 (t, *J* 7.6 Hz, 6 H, CH_3), 2.46 (q, *J* 7.6 Hz, 2 H, H-2′), 3.22 (t, *J* 7.7 Hz, 2 H, H-1′), 3.45 (t, *J* 7.4 Hz, 1 H, H-3′), 4.11 (m, 4 H, CH_2CH_3), 5.36 (s, 2 H, CH_2N), 7.2–7.3 (m, 5 H, Ph), 7.93 (s, 1 H, H-8), 8.84 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0 (CH_3), 26.6 (C-2′), 30.3 (C-1′), 47.2 (CH_2N), 51.4 (C-3′), 61.4 (CH_2CH_3), 127.8, 128.5 and 129.1 (CH in Ph), 132.5 (C in Ph), 135.1 (C-5), 143.7 (C-8), 150.8 (C-4), 152.5 (C-2), 169.1 (CO). MS (EI): 396 (10, M^+), 351 (21), 323 (10), 305 (9), 277 (4), 237 (100), 224 (71), 159 (3), 91 (85), 65 (6).

11a. 70 mg (32%) colourless oil. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.27 (t, *J* 7.1 Hz, 6 H, CH_3), 2.67 (m, 4 H, H-2′, H-4′), 3.30 (m, 4 H, H-1′, H-5′), 4.22 (q, *J* 7.1 Hz, 4 H, CH_2CH_3), 5.43 (s, 4 H, CH_2N), 7.3–7.4 (m, 5 H, Ph), 7.99 (s, 2 H, H-8), 8.90 (s, 2 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (CH_3), 27.9 (C-1′), 30.8 (C-2′), 47.1 (CH_2N), 57.1 (C-3′), 61.3 (CH_2CH_3), 127.7, 128.4 and 129.0 (CH in Ph), 132.3 (C-5), 135.1 (C in Ph), 143.6 (C-8), 150.7 (C-4), 152.4 (C-2), 161.5 (C-6), 171.0 (CO). MS (EI): 632 (5, M^+), 587 (8), 559 (5), 513 (4), 445 (5), 422 (5), 289 (19), 237 (44), 224 (100), 91 (94).

*9-Benzyl-6-(3-cyano-3-methoxycarbonylpropyl)-9*H*-purine* (**10b**) *and methyl 3-cyano-1,5-bis(9-benzyl-6-purinyl)-pentane-3-carboxylate* (**11b**). A mixture of sodium hydride (18 mg, 0.75 mmol), methyl cyanoacetate **9b** (67 µl, 0.76 mmol) and 9-benzyl-6-ethenyl-9*H*-purine **2** (150 mg, 0.64 mmol) was stirred at ambient temperature for 8 h and worked up as described above. EtOAc followed by EtOAc–EtOH (8:1) were used for flash chromatography.

10b. 52 mg (24%) colourless oil. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (m, 1 H, H-2′), 2.69 (m, 1 H, H-2′), 3.45 (m, 2 H, H-1′), 3.81 (s, 3 H, CH_3), 3.93 (dd, 1 H, *J* 8.4 and 6.2 Hz, H-3′), 5.45 (m, 2 H, CH_2N), 7.3–7.4 (m, 5 H, Ph), 8.04 (s, 1 H, H-8), 8.91 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.2 (C-2′), 29.2 (C-1′), 36.7 (C-3′), 47.2 (CH_2N), 53.4 (CH_3), 116.2 (CN), 127.8, 128.6 and 129.1 (CH in Ph), 132.4 (C-5), 135.0 (C in Ph), 144.0 (C-8), 150.9 (C-4), 152.5 (C-2), 159.2 (C-6), 166.3 (CO). MS (EI): 335 (7, M^+), 304 (10), 276 (12), 237 (39), 224 (100), 91 (94), 65 (11).

11b. 129 mg (71%) colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.70 (m, 4 H, H-2′, H-4′), 3.35 (m, 2 H, H-1′, H-5′), 3.54 (m, 2 H, H-1′, H-5′), 3.82 (s, 3 H, CH_3), 5.44 (m, 4 H, CH_2N), 7.3–7.4 (m, 10 H, Ph), 8.04 (s, 2 H, H-8), 8.90 (s, 2 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.5 (C-1′), 34.3 (C-2′), 47.0 (CH_2N), 48.8 (C-3′), 53.4 (CH_3), 118.2 (CN), 127.6, 128.3, 128.9 (CH in Ph), 132.2 (C-5), 135.0 (C in Ph), 143.8 (C-8), 150.7 (C-4), 152.2 (C-2), 159.2 (C-6), 168.7 (CO). MS (EI): 571 (1, M^+), 540 (1), 512 (7), 480 (1), 445 (2), 335 (11), 237 (70), 224 (54), 91 (100). HRMS: Found 571.2449, calc. for $C_{32}H_{29}N_9O_2$: 571.2444.

*6-(3-Acetyl-3-ethoxycarbonylpropyl)-9-benzyl-9*H*-purine* (**10c**) *and ethyl 3-acetyl-1,5-bis(9-benzyl-6-purinyl)pentane-3-carboxylate* (**11c**). A mixture of sodium hydride (18 mg, 0.75 mmol), ethyl acetoacetate **9c** (100 µl, 0.79 mmol), and 9-benzyl-6-ethenyl-9*H*-purine **2** (148 mg, 0.63 mmol) was stirred at ambient temperature for 48 h and worked up as described above. EtOAc followed by EtOAc–acetone (4:1) were used for flash chromatography.

10c. 148 mg (66%) colourless oil. (Found: C. 65.03; H, 5.86. Calc. for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.25 (t, *J* 7.1 Hz, 3 H, CH_3CH_2), 2.27 (s, 3 H, CH_3), 2.49 (m, 2 H, H-2′), 3.24 (t, *J* 7.5 Hz, 2 H, H-1′), 3.64 (t, *J* 7.3 Hz, 1 H, H-3′), 4.18 (q, *J* 7.1 Hz, 2 H, CH_3CH_2), 5.45 (m, 2 H, CH_2N), 7.3–7.4 (m, 5 H, Ph), 8.05 (s, 1 H, H-8), 8.91 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9 (CH_3CH_2), 25.7 (C-2′), 28.9 (CH_3), 30.1 (C-1′), 47.1 (CH_2N), 58.3 (C-3′), 61.2 (CH_3CH_2), 127.7, 128.4 and 128.9 (CH in Ph), 132.4 (C-5), 135.0 (C in Ph), 143.7 (C-8), 150.7 (C-4), 152.3 (C-2), 160.7 (C-6), 169.2 (CO_2Et), 202.6 (COMe). MS (EI): 366 (6, M^+), 321 (14), 303 (2), 277 (7), 249 (3), 237 (70), 224 (84), 159 (3), 91 (100), 65 (8). HRMS: Found 366.1706, calc. for $C_{20}H_{22}N_4O_3$: 366.1692.

11c. 17 mg (9%) colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (t, *J* 7.1 Hz, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 2.58 (m, 4 H, CH_2), 3.16 (m, 4 H, CH_2), 4.15 (q, *J* 7.1 Hz, 2 H, CH_2), 5.37 (s, 4 H, CH_2N), 7.2–7.3 (m, 10 H, Ph), 7.96 (s, 2 H, H-8), 8.85 (s, 2 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 26.8 (CH_3), 27.4 (CH_2), 29.7 (CH_2), 47.4 (CH_2N), 61.7 (CH_2), 63.0 [$C(EWG)_2$], 127.9, 128.6 and 129.2 (CH in Ph), 132.3 (C-5), 134.9 (C in Ph), 144.2 (C-8), 151.1 (C-4), 151.8 (C-2), 161.0 (C-6), 171.6 (CO_2Et), 204.4 (COMe). MS (EI): 602 (0.3, M^+), 559 (7), 513 (2), 379 (3), 366 (5), 337 (9), 289 (10), 237 (27), 224 (79), 91 (100). HRMS: Found 602.2758, calc. for $C_{34}H_{34}N_8O_3$: 602.2754.

*9-Benzyl-6-[3,3-bis(acetyl)propyl]-9*H*-purine* (**10d**). A mixture of sodium hydride (20 mg, 0.83 mmol), acetylacetone **9d** (90 µl, 0.88 mmol), and 9-benzyl-6-ethenyl-9*H*-purine **2** (168 mg, 0.71 mmol) was stirred at 50 °C for 48 h and worked up as described above. EtOAc–acetone (4:1) was used for flash chromatography; yield 162 mg (68%) colourless oil. The product exists as a ca. 1:1 mixture of keto and enol form in $CDCl_3$ solution.

Anal.: C, H. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.21 (s, 6 H, CH_3 in keto form), 2.23 (s, 6 H, CH_3 in enol form), 2.48 (m, 2 H, H-2′ in keto form), 2.87 (m, 2 H, H-2′ in enol form), 3.19 (t, 2 H, *J* 7.4 Hz, H-1′ in keto form), 3.29 (m, 2 H, H-1′ in enol form), 3.80 (t, *J* 7.2 Hz, H-3′ in keto form), 5.45 (s, 4 H, CH_2N in keto and enol form), 7.3–7.4 (m, 10 H, Ph in keto and enol form), 8.05 (s, 2 H, H-8 in keto and enol form), 8.91 and 8.93 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.8 (CH_3 in enol form), 25.9 (C-2′ in keto form), 26.3 (C-2′ in enol form), 29.0 (CH_3 in keto form), 30.2 (C-1′ in keto form), 33.6 (C-1′ enol form), 47.1 (CH_2N), 67.6 (C-3′ in keto form), 109.2 (C-3′ in enol form), 127.7, 128.4 and 128.9 (CH in Ph), 132.2 (C-5), 134.9 (C in Ph), 143.7 (C-8), 151.8 (C-4), 152.3 and 152.4 (C-2), 160.5 and 160.7 (C-6), 191.3 and 203.8 (CO). MS (EI): 336 (4, M^+), 321 (1), 293 (26), 277 (2), 266 (4), 251 (3), 237 (55), 224 (89), 91 (100).

Synthesis of diethyl-1,5-bis(9-benzyl-6-purinyl)pentane-3,3-dicarboxylate (**11a**) *from 9-benzyl-6-[3,3-bis(ethoxycarbonyl)propyl]-9*H*-purine* (**10a**). To a solution of the 9-benzyl-6-[3,3-bis(ethoxycarbonyl)propyl]-9*H*-purine **10a** (99 mg, 0.25 mmol) in dry THF (2 ml) was added a suspension of sodium hydride (8 mg, 0.33 mmol) in dry THF (1 ml) at ambient temperature under N_2. After 10 min, a solution of 9-benzyl-6-ethenyl-9*H*-purine **2** (59 mg, 0.25 mmol) in THF (2 ml) was added and the resulting mixture stirred under N_2 for 27 h. The product **11a** was isolated as described above. Yield 108 mg (68%).

Ethyl 4,6-bis(9-benzyl-6-purinyl)-2-ethoxycarbonylhexanoate (**12**). A mixture of 9-benzyl-6-ethenyl-9*H*-purine **2** (59 mg, 0.25 mmol) and CSA (70 mg, 0.30 mmol) in dry THF was stirred at ambient temperature under N_2 before a solution of 9-benzyl-6-[3,3-bis(ethoxycarbonyl)propyl]-9*H*-purine **10a** (99 mg, 0.25 mmol) in THF (2.5 ml) was added. The resulting mixture was stirred for 27 h, quenched with triethylamine (50 µl, 0.34 mmol) and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with EtOAc–hexane (3:1), followed by EtOAc–EtOH (8:1); yield 4% (7 mg) colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.12 (t, *J* 7.2 Hz, 3 H, CH_3), 1.14 (t, *J* 7.2 Hz, 3 H, CH_3), 2.56 (m, 3 H, CH_2), 2.64 (m, 1 H, CH_2), 3.03 (m, 1 H, CH_2), 3.22 (m, 2 H, CH and CH_2), 3.73 (m, 1 H, CH), 3.98 (m, 2 H, CH_2), 4.10 (m, 2 H, CH_2), 5.38 (m, 4 H, CH_2N), 7.3–7.4 (m, 10 H, Ph), 7.84 and 7.87 (s, 1 H, H-8), 8.83 and 8.91 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 14.0 (CH_3), 30.6 (CH_2), 32.4 (CH_2), 32.7 (CH_2), 40.2 (CH), 47.2 (CH_2N), 50.1 (CH), 61.3 (CH_2), 61.3 (CH_2), 127.9–129.1 (CH in Ph), 132.3 and 133.0 (C-5), 135.1 (2×C in Ph), 143.6 and 143.8 (C-8), 150.8 and 151.1 (C-4), 152.1 and 152.7 (C-2), 161.6 and 162.9 (C-6), 169.0 and 169.1 (CO). MS (EI): 584 (3), 538 (7), 482 (1), 473 (1), 361 (27), 348 (5), 289 (8), 237 (10), 224 (12), 91 (100). HRMS: Found 632.2851, calc. for $C_{35}H_{36}N_8O_4$: 632.2860. 67 mg (68%) of compound **10a** were recovered after chromatography.

*7-Benzyl-6-[3,3-bis(ethoxycarbonyl)propyl]-7*H*-purine* (**13**) *and ethyl 4,6-bis(7-benzyl-6-purinyl)-2-ethoxycarbonylhexanoate* (**14**). Diethyl malonate **9a** (91 µl, 0.60 mmol) was added to a stirred suspension of sodium hydride (6 mg, 0.25 mmol) in dry THF (1 ml) at ambient temperature under N_2. After 10 min, a solution of 7-benzyl-6-ethenyl-7*H*-purine **6** (118 mg, 0.50 mmol) in THF (3.5 ml) was added and the resulting mixture stirred at ambient temperature for 2 h. The reaction was quenched with glacial acetic acid (18 µl, 0.31 mmol), the mixture evaporated *in vacuo*, and the products were separated by flash chromatography on silica gel eluting with EtOAc–EtOH (8:1) followed by EtOAc–acetone–EtOH (3:3:1).

13. Yield 109 mg (55%) colourless powdery crystals. M.p. 83–85 °C. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (t, *J* 7.1 Hz, 6 H, CH_3), 2.25 (m, 2 H, CH_2), 2.94 (m, 2 H, CH_2), 3.40 (t, *J* 7.1 Hz, 1 H, CH), 4.12 (m, 4 H, CH_2), 5.63 (s, 2 H, CH_2N), 7.0 (m, 2 H, Ph), 7.3 (m, 3 H, Ph), 8.20 (s, 1 H, H-8), 8.98 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 27.2 (CH_2), 31.3 (CH_2), 50.7 (CH_2N), 50.9 (CH), 61.4 (CH_2), 123.6 (C-5), 125.9, 128.4 and 129.1 (CH in Ph), 135.2 (C in Ph), 148.9 (C-8), 152.9 (C-2), 153.3 (C-6), 161.2 (C-4), 168.8 (CO). MS (EI): 396 (6, M^+), 376 (2), 351 (9), 323 (10), 305 (3), 277 (5), 249 (4), 237 (38), 224 (46), 91 (100).

14. Yield 11 mg (7%) colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 (t, *J* 7.1 Hz, 3 H, CH_3), 1.23 (t, *J* 7.1 Hz, 3 H, CH_3), 1.73 (m, 1 H, CH_2), 2.00 (m, 1 H, CH_2), 2.07 (m, 1 H, CH_2), 2.30 (m, 2 H, CH_2), 2.37 (m, 1 H, CH_2), 3.28 (m, 1 H, CH), 3.41 (m, 1 H, CH), 4.01 (m, 2 H, CH_2), 4.14 (m, 2 H, CH_2), 5.10 (d, *J* 16.5 Hz, 1 H, H_A CH_2N), 5.27 (d, *J* 16.5 Hz, 1 H, H_B CH_2N), 5.49 (d, *J* 16.4 Hz, 1 H, H_A CH_2N), 5.70 (d, *J* 16.4 Hz, 1 H, H_B CH_2N), 6.47 (m, 2 H, Ph), 6.78 (m, 2 H, Ph), 7.0–7.1 (m, 3 H, Ph), 7.1–7.2 (m, 3 H, Ph), 8.10 and 8.17 (s, 1 H, H-8), 8.89 and 9.08 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 14.0 (CH_3), 30.6 (CH_2), 31.4 (CH_2), 34.1 (CH_2), 39.5 (CH), 49.0 (CH), 50.6 and 50.7 (CH_2N), 61.6 (CH_2), 61.7 (CH_2), 123.5 and 124.0 (C-5), 125.3–129.2 (CH in Ph), 134.7 and 134.8 (C in Ph), 148.8 and 149.7 (C-8), 152.8 and 153.2 (C-2), 153.8 and 156.3 (C-6), 161.4 and 161.9 (C-4), 169.1 and 169.9 (CO). MS (EI): 632 (0.2, M^+), 473 (1), 460 (1), 409 (2), 395 (5), 337 (3), 324 (4), 237 (36), 224 (24), 91 (100). HRMS: Found 632.2835, calc. for $C_{35}H_{36}N_8O_4$: 632.2860.

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References

1. See for instance: (a) Montgomery, J. A. and Hewson, K. *J. Med. Chem. 11* (1968) 49; (b) Abiru, T., Yamaguchi, T., Watanabe, Y., Kogi, K., Aihara, K. and Matsuda, A. *Eur. J. Pharmacol. 196* (1991) 69; (c) Matsuda, A., Shinozaki, M., Yamaguchi, T., Homma, H., Nomoto, R., Miyasaka, T., Watanabe, Y. and Abiru, T. *J. Med. Chem. 35* (1992) 241; (d) Jacobson, K. A., Shi, D., Gallo-Rodrigues, C., Manning, M., Jr., Müller, C., Daly, J. W., Neumeyer, J. L., Kiriasis, L. and Pfleiderer, W. *J. Med. Chem. 36* (1993) 2639 and references therein; (e) Sági, G., Ötvös, L., Ikeda, S., Andrei, G., Snoeck, R. and De Clercq, E. *J. Med. Chem. 37* (1994) 1307; (f) Estep, K. G., Josef, K. A., Bacon, E. R., Carabateas, P. M., Rumney, S., IV., Pilling, G. M., Krafte, D. S., Volberg, W. A., Dillon, K., Dugrenier, N., Briggs, G. M., Canniff, P. C., Gorczyca, W. P., Stankus, G. P. and Ezrin, A. M. *J. Med. Chem. 38* (1995) 2582.
2. (a) Dammann, L. G., Leonard, N. J., Schmitz, R. Y. and Skoog, F. *Phytochemistry 13* (1974) 329; (b) Henderson, T. R., Frihart, C., Leonard, N. L., Schmitz, R. Y. and Skoog, F. *Phytochemistry 14* (1975) 1687; (c) Koyama, S., Kumazawa, Z., Kashimura, N. and Nishida, R. *Agric. Biol. Chem. 49* (1985) 1859; (d) Nishikawa, S., Kumazawa, Z., Mizutani, H. and Kondo, H. *Agric. Biol. Chem. 49* (1985) 3353; (e) Nishikawa, S., Kumazawa, Z., Mizutani, H. and Kashimura, N. *Agric. Biol. Chem. 50* (1986) 1089.
3. See for instance: (a) Taylor, E. C. and Martin, S. F. *J. Am. Chem. Soc. 96* (1974) 8095; (b) Hirota, K., Kitade, Y., Kanbe, Y. and Maki, Y. *J. Org. Chem. 57* (1992) 5268; (c) Gundersen, L.-L., Bakkestuen, A. K., Aasen, A. J., Øverås, H. and Rise, F. *Tetrahedron 50* (1994) 9743; (d) Gundersen, L.-L., Langli, G. and Rise, F. *Tetrahedron Lett. 36* (1995) 1945; (e) Désaubry, L. and Bourguignon, J.-J. *Tetrahedron Lett. 36* (1995) 7875; (f) Andresen, G., Gundersen, L.-L., Lundmark, M., Rise, F. and Sundell, S. *Tetrahedron 51* (1995) 3655; (g) Dvoráková, H., Dvorák, D. and Holy, A. *Tetrahedron Lett. 37* (1996) 1285; (h) Andresen, G., Gundersen, L.-L. and Rise, F. *Tetrahedron 52* (1996) 12979.
4. (a) Van Aerschot, A. A., Mamos, P., Weyns, N. J., Ikeda, S., De Clercq, E. and Herdewijn, P. A. *J. Med. Chem. 36* (1993) 2938; (b) Manfredini, S., Baraldi, P. G., Bazzanini, R., Marangoni, M., Simoni, D., Balzarini, J. and De Clercq, E. *J. Med. Chem. 38* (1995) 199; (c) Langli, G., Gundersen, L.-L. and Rise, F. *Tetrahedron 52* (1996) 5625.
5. See for instance: (a) Bergmann, E. D., Ginsburg, D. and Pappo, R. *Org. React. 10* (1959) 179, and references therein; (b) Danishefsky, S., Cain, P, and Nagel, A. *J. Am. Chem. Soc. 97* (1975) 380.
6. (a) Nagatsugi, F., Uemura, K., Nakashima, S., Maeda, M. and Sasaki, S. *Tetrahedron Lett. 36* (1995) 421; (b) Czernecki, S., Hoang, A. and Valéry, J.-M. *Tetrahedron Lett. 37* (1996) 8857.
7. Øverås, A. T., Gundersen, L.-L. and Rise, F. *Tetrahedron 53* (1997) 1777.
8. Gundersen, L.-L. *Acta Chem. Scand. 50* (1996) 58.
9. (a) Albert, A. and Hampton, A. *J. Chem. Soc.* (1952) 4985; (b) Holland, A. *Chem. Ind. (London) 73* (1954) 786; (c) Jerchel, D. and Heck, H. E. *Justus Liebigs Ann. Chem. 613* (1958) 171.
10. Hampton, A. *J. Heterocycl. Chem. 11* (1974) 255.
11. Jung, M. E. In: Trost, B. M. and Flemimg, I., Eds., *Comprehensive Organic Synthesis*, Vol. 4, pp. 3–4, Pergamon, Oxford 1991.
12. Kitayama, T. *Tetrahedron 52* (1996) 6139.
13. See for instance: (a) Fedorynski, M., Wojciechowski, K., Matacz, Z. and Makosza, M. *J. Org. Chem. 43* (1978) 4682; (b) Ernst, H., Ottow, E., Recker, H. G. and Winterfeldt, E. *Chem. Ber. 114* (1981) 1907.

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