The Determinative Influence of the O^6-(Diphenylcarbamoyl) Group on the Exocyclic Nitrogen Benzylation in 2-Amino-6-oxopurine Derivatives

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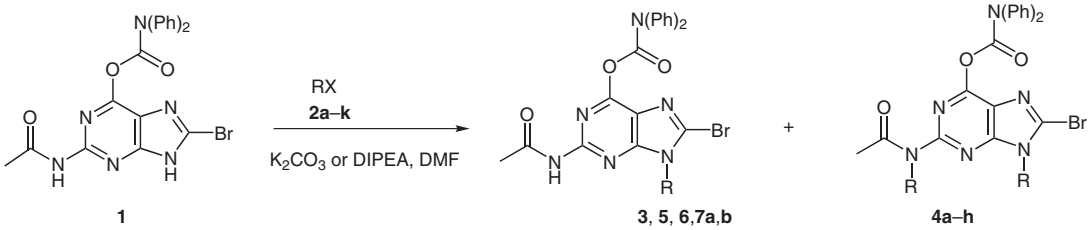
Abstract: A series of novel 2-(benzylamino)-6-oxopurine derivatives has been synthesized by arylalkylation of the corresponding 2-(acetylamino)-6-(diphenylcarbamoyloxy)purines. The decisive role of the temporary O^6-(diphenylcarbamoyl) protection on the benzylation of the exocyclic amino group in 2-(acetylamino)-6-oxopurines has been demonstrated.

Key words: nucleobases, benzylation, protecting groups, substituent effects, synthesis

Derivatives of 2-amino-1,9-dihydro-6*H*-purin-6-one (guanine) containing an arylalkyl residue in the molecule represent a promising group of organic compounds due to their potential biological applications.[1] So far the greatest effort of chemists working in the field of nucleobase modification has been devoted to the preparation and elaboration of the derivatives of 2-amino-6-(benzyloxy)purine, which was developed to inactivate *O*^{6}-alkylguanine-DNA alkyltransferase (AGT) and to increase the antitumor activity of chemotherapeutic alkylating agents.[1a] 2-Amino-6-oxopurines arylalkylated at other sites in the purine ring and, in particular, those with more than one arylalkyl residue in the molecule have not been systematically studied, in part due to problems connected with their synthesis.

In continuation of our long-term research on polyfunctional purine nucleobases, we were interested in the synthesis of 2-amino-6-oxopurine derivatives containing an arylalkyl group at the ring nitrogen and another at the exocyclic oxo or amino group. Initially, we looked for an efficient method for the synthesis of 2-amino-9-benzyl-8-bromo-1,9-dihydro-6*H*-purin-6-one that would serve as a useful intermediate for further introduction of the second arylalkyl group. As our previous attempts to synthesize the target compound from 2-(acetylamino)-8-bromo-1,9-dihydro-6*H*-purin-6-one and benzyl bromide resulted in the formation of N-benzylated regioisomers,[2] we decided to improve the process by using as a substrate 2-(acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-1*H*-purine (**1**) synthesized by us earlier.[3] The choice was motivated by the well-established fact that constraining 2-amino-6-oxopurine from its dominant 6-lactam structure to its lactim (enolate) form by a suitable protecting group at O^6 has a beneficial effect on the regioselectivity of alkylation.[4] In this paper we present the results of the arylalkylation of purine derivative **1** and various substituted analogues.

In a model reaction, compound **1** was treated with benzyl bromide (**2a**) under standard conditions, i.e. potassium carbonate/*N*,*N*-dimethylformamide system at room temperature using a slight excess of bromide **2a** (1.1 equiv). Two reaction products were isolated and identified, the expected 2-(acetylamino)-9-benzyl-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (**3**) (48%) and 2-[acetyl(benzyl)amino]-9-benzyl-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (**4a**) (36%) (Scheme 1, Table 1). Increasing the amount of benzylating reagent **2a** up to 2.4 equivalents and elevating the reaction temperature (70 °C) gave the dibenzylated compound **4a** in 58% yield. Therefore, the tendency of the starting purine **1** to form the dibenzylated product was evident even when carrying out the reaction with almost an equivalent amount of the benzylating agent. As the formation of a similar product was not observed during the benzylation of 2-(acetylamino)-8-bromo-1,9-dihydro-6*H*-purin-6-one,[5] it was possible to conclude that the presence of the diphenylcarbamoyloxy group at position 6 of the purine ring promoted the benzylation at the cycle nitrogen and also at the exocyclic amino group.



1 **3**, **5**, **6**,**7a**,**b** **4a–h**

Scheme 1

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Table 1 N-Benzylation and N-Benzyloxymethylation of 2-(Acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-1*H*-purine (**1**)

Entry	Substrate			Product			
		R	X		Yield (%)		Yield (%)
1	**2a**	Bn	Br	**3**	29	**4a**	58
2	**2b**	2-$FC_6H_4CH_2$	Br	–	–	**4b**	65
3	**2c**	3-$ClC_6H_4CH_2$	Cl	–	–	**4c**	41
4	**2d**	3,4-$Cl_2C_6H_3CH_2$	Cl	–	–	**4d**	60
5	**2e**	2-$BrC_6H_4CH_2$	Br	–	–	**4e**	78
6	**2f**	3-$BrC_6H_4CH_2$	Cl	–	–	**4f**	73
7	**2g**	3-$O_2NC_6H_4CH_2$	Br	–	–	**4g**	70
8	**2h**	4-$MeO_2CC_6H_4CH_2$	Br	–	–	**4h**	71
9	**2i**	$PhCH_2OCH_2$	Cl	**5**	76	–	–
10	**2j**	$PhC(=O)CH_2$	Br	**6**	75	–	–
11	**2k**	EtO_2CCH_2	Br	**7a**	68[a]	–	–

[a] Alongside the 7-EtO_2CCH_2-isomer **7b** (11%).

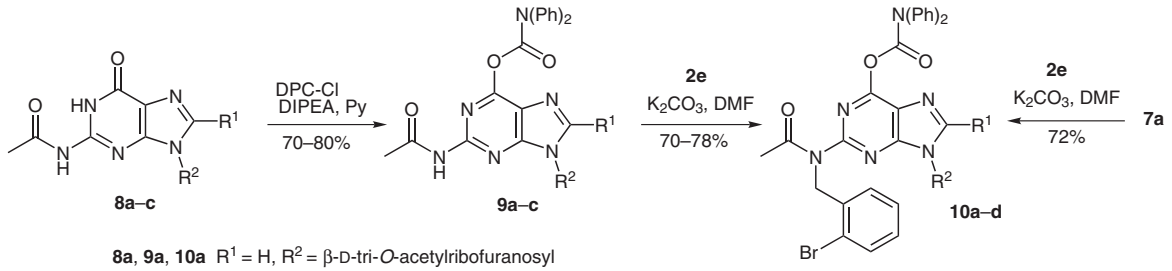
During the next step of our work we selected a series of commercially available substituted benzyl bromides and chlorides **2b**–**g** based on their varied electronic and steric properties and used them for the benzylation of purine **1**. In all experiments the main product of the reaction was the corresponding 2-[acetyl(benzyl)amino]-9-benzyl-8-bromo-6-(diphenylcarbamoyloxy)purine **4b**–**g**, sometimes present in the reaction mixture together with the mono N^9-benzylated counterpart (<10% yield) (Table 1). All benzylated products were purified by column chromatography and recrystallized from ethanol, except for bromo-substituted benzyl derivatives, **4e**,**f**, which were almost insoluble in boiling ethanol. Heating the reaction mixture to 70–75 °C helped to run the process to completion, although in some cases the elevated temperatures could be replaced by longer reaction times. A greater excess of the benzylating agent, i.e. more than 2.4 equivalents, was not advisable since it led to a messier reaction mixture hampering the product isolation. Both benzyl bromides and chlorides could be used for the synthesis of compounds **4a**–**g** although the yields of the products synthesized using chlorides **2c**,**d** were lower (Table 1, entries 3 and 4). The experiments carried out did not allow us to evaluate completely the cumulative effects of the electronic and steric properties of substituents on the benzene ring of the benzyl group on the benzylation reaction. However, it was evident that all the benzyl bromides and chlorides **2b**–**g** were suitable for the benzylation of both the endocyclic and the exocyclic nitrogen of purine **1** and they were all better than benzyl bromide (**2a**) with regard to the yield of the corresponding N^2,N^9-dibenzylated product. The most efficient benzylating reagent was 2-bromobenzyl bromide (**2e**). This fact was consistent with the previously observed general steric enhancement of arylcarbenium ion stabilization energies for *ortho*-substituents as compared to their *meta*- or *para*-substituted analogues.[6]

In such a way, by treating purine **1** with a series of benzyl halides, we succeeded in synthesizing the target dibenzylated derivatives **4a**–**g** in a straightforward way. It is generally accepted that the direct alkylation or arylalkylation of the exocyclic amino group in 2-amino-6-oxopurine derivatives often fails due to its low nucleophilicity. Therefore, special strategies must generally be used for the synthesis of 2-(alkylamino)- or 2-(arylamino)-6-oxopurines. The majority of which are uncatalyzed or palladium-catalyzed reactions of 6-(benzyloxy)-2-halopurines with the corresponding amines, the treatment of 2-amino-6-halopurines with alcohols under the Mitsunobu reaction condition, the reduction of pre-synthesized 2-(acylamino)-6-oxopurines, or via tricyclic wyosine as the protected intermediate.[5a–d] The influence of substitution at the exocyclic oxygen on the displacement at the exocyclic nitrogen in 2-amino-6-oxopurines has been observed previously, e.g. using the 6-(mesyloxy) derivative of guanosine for its N^2-methylation.[7] The formation of the N^2,O^6-dimethylated or the N^2,O^6-dibenzylated products together with the mono-O^6-substituted products observed during the methylation and benzylation of the certain 2-(acetylamino)-6-oxopurine derivatives also suggested the directive influence of the 6-methoxy and 6-benzyloxy functions on the second methyl or benzyl group attachment site.[8] We have not found literature references to the benzylation of 2-aminopurine derivatives containing the 6-(diphenylcarbamoyloxy) moiety with benzyl halides, but the alkylation of such compounds usually produces the corresponding N^9-alkylated products, sometimes contaminated with the corresponding N^7-alkylated regioisomer.[4] At the same time, the formation of a small amount (<3%) of the N^2,N^9-disubstituted product was detected

during the ribosylation of silylated 2-(acetylamino)-6-(diphenylcarbamoyloxy)purine.[9] The latter data as well as our results on the benzylation of purine **1** suggested that the product distribution in the alkylation reactions of 2-(acetylamino)-6-(diphenylcarbamoyloxy) purines should depend not only on the presence of the carbamoyloxy function at position 6 of the purine ring, but also on the structure of the alkylating agent. To test this suggestion two alternative arylalkylating agents, i.e. benzyl chloromethyl ether (**2i**) and phenacyl bromide (**2j**) were used for the treatment of purine **1**. The reaction of **2i** was carried out under the same conditions as for halides **2a**–**h**. In the case of **2j**, potassium carbonate was replaced by *N*,*N*-diisopropylethylamine for the reaction to proceed successfully. The sole product isolated in the reaction of purine **1** with derivatives **2i**, **j** was 2-(acetylamino)-9-[(benzyloxy)methyl]-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (**5**) and 2-(acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-9-(2-oxo-2-phenylethyl)-9*H*-purine (**6**), respectively (Scheme 1, Table 1). Treatment of substrate **1** with ethyl 2-bromoacetate (**2k**), which was structurally more distant from benzyl halides than **2i**,**j**, also did not afford reaction at the exocyclic amino group. Instead, a certain amount (10%) of the N^7-substituted regioisomer **7b** was isolated together with the main product, i.e. 2-(acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-9-[(ethoxycarbonyl)methyl]-9*H*-purine (**7a**) when the reaction was carried out in the presence of either potassium carbonate or *N*,*N*-diisopropylethylamine (Scheme 1, Table 1). Therefore, the results obtained support the proposition that changes in the structure of the alkylating agent influence the outcome of the alkylation of purine **1**, and that the predominant formation of N^2,N^9-disubstituted derivatives is typical only for benzyl halides.

To evaluate further the limits of the direct N^2-benzylation of 2-(acetylamino)-6-(diphenylcarbamoyloxy)purine derivatives the compatibility of the reaction with the presence of various substituents at positions 7, 8, and 9 of the purine heterocycle has been investigated. Hence, we prepared the 6-(diphenylcarbamoyloxy) derivatives of several 9- and 8-substituted 2-amino-6-oxopurines **9a**–**c** according to the standard procedure and treated these compounds, as well as **7a**, with a slight excess of 2-bromobenzyl bromide (**2e**) (Scheme 2). In all the cases, the corresponding 2-[acetyl(2-bromobenzyl)amino]-6-(diphenylcarbamoyloxy) derivatives **10a**–**d** were isolated in moderate to good yields, which demonstrated that direct benzylation at the exocyclic 2-(acetylamino) group was possible not only in purine **1**, but also in its analogues with various substituents at positions 8 and 9 of the purine ring. The number of experiments performed is insufficient to generalize the influence of the structure of the substituent on the benzylation reaction, although the favorable effect of the 8-(benzylsulfanyl) group was evident from the comparison of the yields of isolated products **10a**–**d**. At the same time, an attempt to benzylate the exocyclic amino group in 2-(acetylamino)-6-(diphenylcarbamoyloxy)-7-substituted purine was unsuccessful. We failed to synthesize the corresponding O^6-(diphenylcarbamoyl) derivative of the model compound 7-[(2-acetoxyethoxy)methyl]-2-(acetylamino)-1,9-dihydro-6*H*-purin-6-one under standard conditions, i.e., diphenylcarbamoyl chloride (DPC-Cl)/pyridine/*N*,*N*-diisopropylethylamine, but the reaction of bromide **2e** with compound **7b**, isolated in the reaction of purine **1** with 2-bromoacetate **2k**, did not afford the benzylation product.

Finally, it was interesting to find out whether some other functionality at the 2-amino-6-oxopurine oxygen could perform the role of the diphenylcarbamoyl group with regard to the benzylation of the exocyclic nitrogen. A reasonable choice seemed to be the tosyloxy moiety, due to its convenient introduction and subsequent removal. Therefore, a model compound, 9-[(2-acetoxyethoxy)methyl]-2-(acetylamino)-8-bromo-6-(tosyloxy)-9*H*-purine (**11**) was synthesized[3] and reacted with bromide **2e** under the same conditions as in the case of purines **1**, **9a**–**c**. 9-[(2-Acetoxyethoxy)methyl]-2-[acetyl(2-bromobenzyl)-amino]-8-bromo-1,9-dihydro-6*H*-purin-6-one (**12**) was isolated as the product in 37% yield (Scheme 3). It indicated that apart from benzylation at the exocyclic nitrogen, a partial or complete loss of tosyl function at the exocyclic oxygen occurred during either the benzylation reaction or the product isolation process. This side reaction decreased the solubility of **12** and made its purification more difficult. Therefore, tosyl derivative **11** was not completely suitable for the synthesis of N^2-benzylated purine derivatives due to the facile loss of the tosyl moiety. In contrast, the O^6-(diphenylcarbamoyl) group was not



8a, **9a**, **10a** R^1 = H, R^2 = β-D-tri-*O*-acetylribofuranosyl

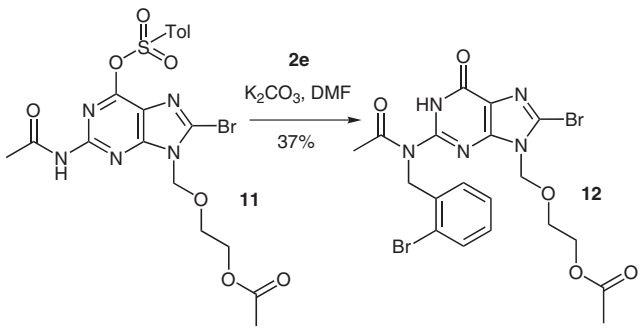
8b, **9b**, **10b** R^1 = H, R^2 = $CH_2OCH_2CH_2OAc$

8c, **9c**, **10c** R^1 = SCH_2Ph, R^2 = $CH_2OCH_2CH_2OAc$

10d R^1 = Br, R^2 = CH_2COOEt

Scheme 2

only fairly stable under the conditions of the arylalkylation reaction, but it could also be easily removed together with the N^2-acetyl group in the resulting 2-[acetyl(benzyl)amino]-6-(diphenylcarbamoyloxy)purines by their treatment with saturated ammonia in ethanol solution. This was demonstrated by deprotection of several selected arylalkylated products **4f**, **5**, **10b–d** to give 2-(benzylamino)-1,9-dihydro-6*H*-purine-6-one derivatives **13a–e** (Scheme 4, Table 2). The acetoxy function in compound **13c** and the ester group in compound **13e** were stable under the deprotection conditions used, but they could be easily removed by some other well-established procedures, if necessary.



Scheme 3

Scheme 4

The ^{1}H NMR spectra were the main method to support the structures of the arylalkylated 2-amino-6-oxopurine derivatives. The presence and the number of benzyl groups in the molecule were indicated by the NCH_2 group protons singlet at δ = 5.40 for the benzyl functionality attached to the endocyclic nitrogen and at δ = 5.15 for the benzyl group at the exocyclic nitrogen. The attachment of a benzyl fragment at the exocyclic 2-(acetylamino) group caused a notable downfield shift of the $COCH_3$ function protons singlet. Such a shift was characteristic also for 9-[(2-acetoxyethoxy)methyl]-2-[acetyl(benzyl)amino]-6-benzyloxy-9*H*-purine and its 8-bromo counterpart synthesized previously.[8] However, a similar shift was not observed in the spectrum of 2-[acetyl(2-bromobenzyl)amino]-1,9-dihydro-6*H*-purin-6-one **12**. The chemical shifts of NH group (δ =10.79 and 10.69) as well as of N^9-CH_2 and N^7-CH_2 group proton singlets at δ = 5.04 and 5.06, respectively, in the spectra of derivatives **7a**,**b** corresponded with the established pattern of proton chemical shifts in the structurally close 6-(diphenycarbamoyloxy)-2-(isobutyrylamino)-9(or -7)-[(methoxycarbonyl)methyl)purine.[4] To determine the benzylation site in product **4f**, it was deprotected to the corresponding 8-bromo-9-(3-bromobenzyl)-2-[(3-bromobenzyl)amino]-1,9-dihydro-6*H*-purin-6-one (**13a**) whose NCH_2 group proton singlet at δ = 5.37 corresponded to that in the similar N^9-substituted purines.[10] The structure of product **6** was established as 9-(2-oxo-2-phenylethyl)purine by assuming that the reaction of purine **1** with bromide **2j** follows the same direction as in the case of other arylalkylating agents used. The N^2-arylalkylated derivatives of 2-(acetylamino)-6-(diphenylcarbamoyloxy)purine were also characterized by their ^{13}C NMR spectra. The presence of excessive carbon signals in the spectrum of compound **4b** was due to their splitting caused by C–F coupling. The final proof of benzylation sites in 2-(acetylamino)-6-(diphenylcarbamoyloxy)purines was the X-ray crystal structure analysis of derivative **4d** monocrystals (Figure 1).[11] In the unit cell of compound **4d** there are two symmetrically independent molecules, which form an associate by means of shortened intermolecular contacts. The lengths of these contacts are: C15···O12′ = 2.910(13) Å; N1···H10′ = 2.59(7) Å; N1′···H10 = 2.61(7) Å. The last two contacts could be described as very weak hydrogen bonds of NH···N type. As the spectroscopic properties of products **4a–c**,**e–g** were quite similar to those of **4d**, hence it was concluded that they are all benzylated at the same sites of the purine ring. The X-ray crystallographic analysis supported unambiguously also the structure of 2-[acetyl(2-bromobenzyl)amino]-1,9-dihydro-6*H*-purin-6-one **12** (Figure 2).[11] The purity of all the compounds synthesized, except for low melting products **10a**,**b**, were confirmed by elemental analysis. The elemental content of derivative **10b** was supported by the analysis of its deprotected form **13c**.

In conclusion, we have demonstrated that the presence of the temporary protecting O^6-(diphenylcarbamoyl) group in 2-(acetylamino)-6-oxopurine favors its benzylation at the exocyclic nitrogen. The reaction works with a variety of benzyl halides and it tolerates the presence of substitu-

Table 2 Deprotection of **4f, 5, 10b–d**

Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**4f**	Br	3-$BrC_6H_4CH_2$	3-$BrC_6H_4CH_2$	**13a**	82
2	**5**	Br	CH_2OCH_2Ph	H	**13b**	80
3	**10b**	H	$CH_2CH_2CH_2OAc$	2-$BrC_6H_4CH_2$	**13c**	75
4	**10c**	SBn	$CH_2CH_2CH_2OH$	2-$BrC_6H_4CH_2$	**13d**	79
5	**10d**	Br	CH_2CO_2Et	2-$BrC_6H_4CH_2$	**13e**	69

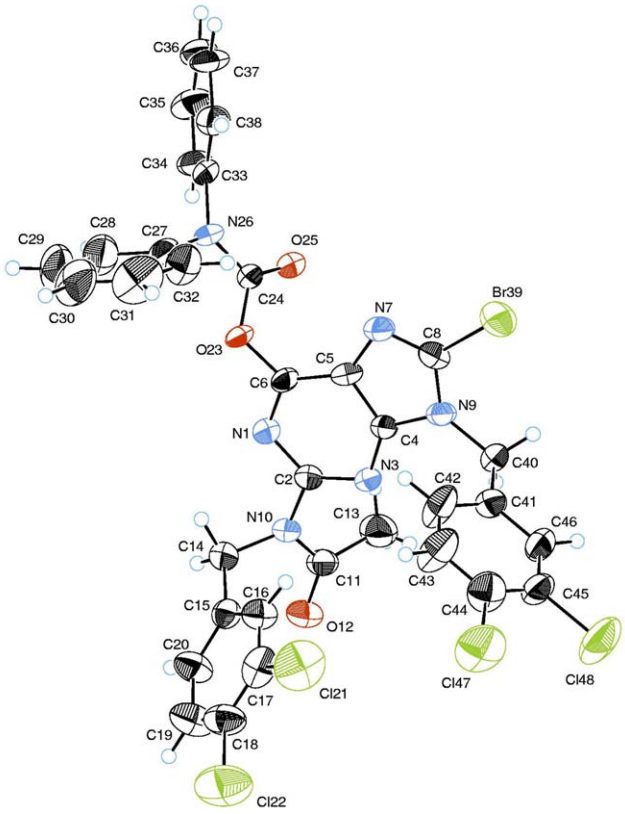


Figure 1 X-ray crystal structure of compound **4d**

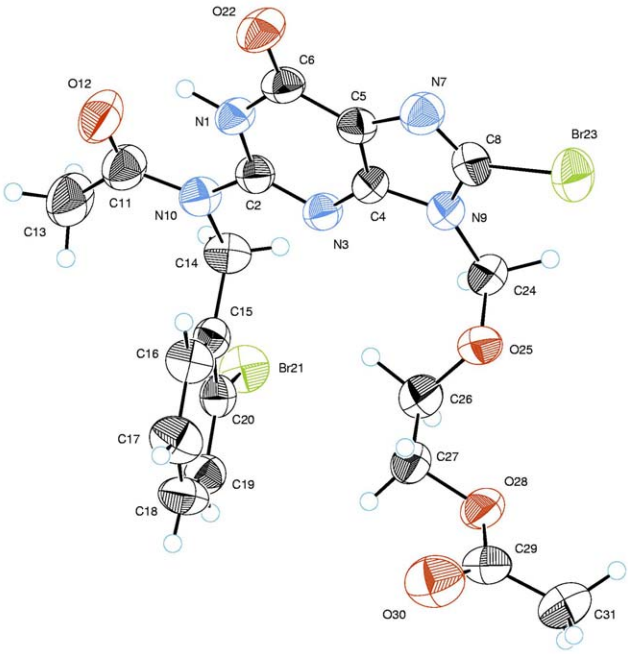


Figure 2 X-ray crystal structure of compound **12**

ents at positions 8 and 9 of the 2-(acetylamino)-6-oxopurine ring. The O^6-(diphenylcarbamoyl) group is superior to other alternative groups due to its stability under the reaction conditions, in contrast to the O^6-mesyl and O^6-tosyl functions, as well as the relative ease of its introduction and removal, in comparison with the O^6-benzyl moiety. The synthetic approach developed allowed us to synthesize a series of novel N^2-benzyl derivatives of 2-amino-6-oxopurine and it may be useful for the preparation of still more compounds of this type.

All reagents were purchased from Acros Organics and used from freshly opened containers without further purification. The reactions involving air- or moisture-sensitive reagents were carried out in anhyd solvents under anhyd argon. Merck TLC silica gel 60 F_{254} plates were used for TLC analyses and the products were visualized by UV detection. Column chromatography was carried out with Merck silica gel 60, particle size 0.040–0.063 mm. Melting points were determined on a Boetius table and are uncorrected. Elemental analyses were carried out on a Carlo Erba Elemental Analyser. NMR spectra were taken on Varian Mercury 200 and Varian Mercury 400 spectrometers with HMDS as an internal standard (δ = 0.055). X-ray crystal structure determination was performed on Bruker-Noniuss Kappa CCD automated diffractometer. Crystals of compounds **4d** and **12** were obtained by crystallization (EtOH).

N-Benzylation and N-Benzyloxymethylation of 2-(Acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-1*H*-purine (1); General Procedure

To a soln of **1** (0.234 g, 0.5 mmol) in DMF (10.0 mL) were added K_2CO_3 (0.166 g, 1.2 mmol) and the corresponding benzyl bromide **2a**,**b**,**e**,**g**,**h**, benzyl chloride **2c**,**d**,**f** or benzyl chloromethyl ether (**2i**, 1.2 mmol). The mixture was stirred at r.t. for 2 h and then heated to 70–75 °C for 4–6 h, it was then cooled to r.t., and the solvent was removed under reduced pressure. The oily residue obtained was treated with anhyd Et_2O and purified by chromatography [silica gel, $CHCl_3$ (**3**, **4a**,**b**,**f**,**g**), CH_2Cl_2–EtOH, 100:0.5 (**4d**), or CH_2Cl_2–EtOH, 100:1 (**4c**,**e**,**h**, **5**)] to afford chromatographically and spectrally pure product. An analytical sample was recrystallized (EtOH) or washed (boiling EtOH) in the case of products **4e**,**f**.

2-(Acetylamino)-9-benzyl-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (3)

Colorless crystals; yield: 0.081 g (29%); mp 203–205 °C.

^{1}H NMR (DMSO-d_6): δ = 2.16 (s, 3 H, CH_3), 5.37 (s, 2 H, CH_2), 7.27–7.49 (m, 15 H, ArH), 10.78 (s, 1 H, NH).

Anal. Calcd for $C_{27}H_{21}BrN_6O_3$: C, 58.18; H, 3.80; N, 15.08. Found: C, 58.33; H, 3.71; N, 14.93.

2-[Acetyl(benzyl)amino]-9-benzyl-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (4a)

Colorless crystals; yield: 0.186 g (58%); mp 182–183 °C.

^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 5.22 (s, 2 H, CH_2), 5.40 (s, 2 H, CH_2), 7.18–7.36 (m, 11 H, ArH), 7.38–7.47 (m, 9 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 25.78, 48.03, 49.38, 120.68, 127.25, 127.67, 127.92, 128.50, 128.64, 129.22, 129.86, 133.94, 135.52, 138.50, 141.83, 150.02, 153.87, 154.83, 155.93, 171.74.

Anal. Calcd for $C_{34}H_{27}BrN_6O_3$: C, 63.07; H, 4.20; N, 12.98. Found: C, 63.02; H, 4.06; N, 12.85.

2-[Acetyl(2-fluorobenzyl)amino]-8-bromo-6-(diphenylcarbamoyloxy)-9-(2-fluorobenzyl)-9*H*-purine (4b)

Colorless crystals; yield: 0.220 g (65%); mp 147–148 °C.

^{1}H NMR (DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 5.20 (s, 2 H, CH_2), 5.43 (s, 2 H, CH_2), 7.03–7.40 (m, 18 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 25.67, 42.45, 43.69, 115.38, 115.59, 115.94, 116.15, 120.73, 122.20, 122.34, 124.65, 124.68, 125.14,

125.17, 125.22, 125.37, 127.87, 128.98, 129.02, 129.12, 129.20, 129.86, 130.25, 130.28, 130.78, 130.86, 134.09, 141.83, 149.98, 153.94, 154.66, 156.00, 159.03, 159.21, 161.48, 161.64, 171.68.

Anal. Calcd for $C_{34}H_{25}BrF_2N_6O_3$: C, 59.75; H, 3.69; N, 12.30. Found: C, 59.75; H, 3.66; N, 12.25.

2-[Acetyl(4-chlorobenzyl)amino]-8-bromo-9-(4-chlorobenzyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (4c)
Colorless crystals; yield: 0.148 g (41%); mp 167–169 °C.

^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 5.40 (s, 2 H, CH_2), 7.21–7.44 (m, 18 H, ArH).

Anal. Calcd for $C_{34}H_{25}BrCl_2N_6O_3$: C, 57.00; H, 3.52; N, 11.73. Found: C, 56.89; H, 3.40; N, 11.97.

2-[Acetyl(3,4-dichlorobenzyl)amino]-8-bromo-9-(3,4-dichlorobenzyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (4d)
Colorless crystals; yield: 0.233 g (60%); mp 185–186 °C.

^{1}H NMR (DMSO-d_6): δ = 2.43 (s, 3 H, CH_3), 5.15 (s, 2 H, CH_2), 5.41 (s, 2 H, CH_2), 7.13–7.58 (m, 16 H, ArH).

Anal. Calcd for $C_{34}H_{23}BrCl_4N_6O_3$: C, 52.00; H, 2.95; N, 10.70. Found: C, 52.11; H, 2.76; N, 10.64.

2-[Acetyl(2-bromobenzyl)amino]-8-bromo-9-(2-bromobenzyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (4e)
Colorless crystals; yield: 0.310 g (78%); mp 200–202 °C.

^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 5.15 (s, 2 H, CH_2), 5.43 (s, 2 H, CH_2), 6.77–6.82 (m, 1 H, ArH), 7.05–7.70 (m, 17 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 25.79, 48.32, 50.11, 120.63, 122.14, 122.28, 127.83, 128.11, 128.65, 128.87, 129.12, 129.88, 130.39, 132.83, 133.32, 134.15, 134.28, 136.98, 141.81, 149.91, 154.12, 154.58, 156.10, 171.83.

Anal. Calcd for $C_{34}H_{25}Br_3N_6O_3$: C, 50.71; H, 3.13; N, 10.44. Found: C, 50.68; H, 3.01; N, 10.30.

2-[Acetyl(3-bromobenzyl)amino]-8-bromo-9-(3-bromobenzyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (4f)
Colorless crystals; yield: 0.292 g (73%); mp 170–172 °C.

^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 5.42 (s, 2 H, CH_2), 7.16–7.55 (m, 18 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 25.80, 47.27, 49.08, 120.81, 122.08, 122.39, 126.68, 126.84, 129.89, 130.22, 130.37, 130.74, 130.85, 131.43, 133.94, 138.21, 141.50, 141.82, 149.99, 153.90, 154.73, 156.04, 171.88.

Anal. Calcd for $C_{34}H_{25}Br_3N_6O_3$: C, 50.71; H, 3.13; N, 10.44. Found: C, 50.76; H, 2.90; N, 10.41.

2-[Acetyl(3-nitrobenzyl)amino]-8-bromo-6-(diphenylcarbamoyloxy)-9-(3-nitrobenzyl)-9*H*-purine (4g)
Colorless crystals; yield: 0.257 g (70%); mp >85 °C (dec.).

^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 5.40 (s, 2 H, CH_2), 7.21–7.44 (m, 18 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 25.87, 47.19, 49.13, 120.95, 122.30, 122.38, 122.88, 123.43, 127.84, 129.87, 130.17, 130.83, 133.96, 134.33, 137.65, 141.08, 141.83, 148.18, 148.31, 149.95, 153.88, 154.67, 156.12, 171.97.

Anal. Calcd for $C_{34}H_{25}BrN_8O_7$: C, 55.37; H, 3.42; N, 15.19. Found: C, 55.37; H, 3.31; N, 15.21.

2-{Acetyl[4-(methoxycarbonyl)benzyl]amino}-8-bromo-6-(diphenylcarbamoyloxy)-9-[4-(methoxycarbonyl)benzyl]-9*H*-purine (4h)
Colorless crystals; yield: 0.272 g (71%); mp 188–191 °C.

^{1}H NMR (DMSO-d_6): δ = 2.44 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 5.23 (s, 2 H, CH_2), 5.45 (s, 2 H, CH_2), 7.26–7.40 (m, 14 H, ArH), 7.75–7.86 (m, 4 H, ArH).

Anal. Calcd for $C_{38}H_{31}BrN_6O_7$: C, 59.77; H, 4.09; N, 11.01. Found: C, 59.65; H, 3.98; N, 10.94.

2-(Acetylamino)-9-[(benzyloxy)methyl]-8-bromo-6-(diphenylcarbamoyloxy)-9*H*-purine (5)
Colorless crystals; yield: 0.223 g (76%); mp 91–93 °C.

^{1}H NMR (DMSO-d_6): δ = 2.21 (s, 3 H, CH_3), 4.64 (s, 2 H, CH_2), 5.61 (s, 2 H, CH_2), 7.23–7.38 (m, 7 H, ArH), 7.40–7.54 (m, 8 H, ArH), 10.84 (s, 1 H, NH).

Anal. Calcd for $C_{28}H_{23}BrN_6O_4$: C, 57.25; H, 3.95; N, 14.31. Found: C, 57.10; H, 3.86; N, 14.19.

2-(Acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-9-(2-oxo-2-phenylethyl)-9*H*-purine (6)
To a soln of **1** (0.130 g, 0.28 mmol) in DMF (7.0 mL) were added DIPEA (0.080 g, 0.11 mL, 0.62 mmol) and **2j** (0.123 g, 0.62 mmol). The mixture was stirred at r.t. for 48 h. The solvent was removed under reduced pressure and the residue was taken up in $CHCl_3$ (40 mL). The soln was washed with 5% aq $NaHCO_3$ (8 mL), H_2O (2 × 8 mL), and brine (10 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residue was purified twice by chromatography [silica gel, $CHCl_3$ (first run) and CH_2Cl_2–EtOH, 100:1 (second run)]. Recrystallization (EtOH) afforded **6** as colorless crystals; yield: 0.122 g (75%); mp 186–188 °C.

^{1}H NMR (DMSO-d_6): δ = 2.11 (s, 3 H, CH_3), 5.89 (s, 2 H, CH_2), 7.29–7.82 (m, 13 H, ArH), 8.14–8.19 (m, 2 H, ArH), 10.74 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 24.97, 50.97, 120.36, 127.80, 128.87, 129.65, 129.90, 133.74, 133.98, 135.25, 141.94, 150.30, 152.83, 154.17, 156.38, 169.21.

Anal. Calcd for $C_{28}H_{21}BrN_6O_4$: C, 57.45; H, 3.62; N, 14.36. Found: C, 57.40; H, 3.57; N, 13.99.

2-(Acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-9-[(ethoxycarbonyl)methyl]-9*H*-purine (7a) and 2-(Acetylamino)-8-bromo-6-(diphenylcarbamoyloxy)-7-[(ethoxycarbonyl)methyl]-7*H*-purine (7b)
To a soln of **1** (0.420 g, 0.9 mmol) in DMF (10.0 mL) were added DIPEA (0.232 g, 0.30 mL, 1.8 mmol) and **2k** (0.300 g, 0.20 mL, 1.8 mmol). The mixture was stirred at r.t. for 24 h. The solvent was evaporated under reduced pressure. The residue was purified by chromatography (silica gel, $CHCl_3$) to afford chromatographically and spectrally pure **7a** and **7b**. Products were recrystallized (EtOH).

9-Substituted-isomer 7a
Colorless crystals; yield: 0.339 g (68%); mp 183–186 °C.

^{1}H NMR (DMSO-d_6): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 4.21 (q, *J* = 7.1 Hz, 2 H, CH_2), 5.04 (s, 2 H, CH_2), 7.27–7.55 (m, 10 H, ArH), 10.79 (s, 1 H, NH).

Anal. Calcd for $C_{24}H_{21}BrN_6O_5$: C, 52.09; H, 3.83; N, 15.19. Found: C, 52.07; H, 3.69; N, 14.82.

7-Substituted-isomer 7b
Colorless crystals; yield: 0.055 g (11%); mp 152–154 °C.

^{1}H NMR (DMSO-d_6): δ = 1.12 (t, J = 7.1 Hz, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 4.05 (q, J = 7.1 Hz, 2 H, CH_2), 5.06 (s, 2 H, CH_2), 7.25–7.52 (m, 10 H, ArH), 10.69 (s, 1 H, NH).

Anal. Calcd for $C_{24}H_{21}BrN_6O_5$: C, 52.09; H, 3.83; N, 15.19. Found: C, 52.06; H, 3.65; N, 14.99.

2-(Acetylamino)-6-(diphenylcarbamoyloxy)-9*H*-purine Derivatives 9a–c; General Procedure

To a suspension of **8a–c** (0.5 mmol) in pyridine (7.0 mL) were added DIPEA (0.280 g, 0.38 mL, 2.2 mmol) and DPC-Cl (0.232 g, 1.0 mmol). The mixture was stirred at r.t. for 4 h. H_2O (0.5 mL) was added and the mixture was stirred for another 20 min. Volatiles were removed under reduce pressure and the oily residue obtained was co-evaporated several times with EtOH to remove traces of pyridine and then taken up in CH_2Cl_2 (50 mL). The soln was washed with 5% aq $NaHCO_3$ (10 mL), H_2O (2 × 10 mL), and brine (10 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, CH_2Cl_2–EtOH, 100:1.5) and recrystallized (EtOH).

2-(Acetylamino)-6-(diphenylcarbamoyloxy)-9-(β-D-tri-*O*-acetylribofuranosyl)-9*H*-purine (9a)

Light-yellow crystals; yield: 0.214 g (66%); mp 41 °C

^{1}H NMR (DMSO-d_6): δ = 1.96 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 4.28–4.44 (m, 3 H, H4′, H5′), 5.74–5.80 (m, 1 H, H3′), 5.89–5.94 (m, 1 H, H2′), 6.24 (d, J = 4.6 Hz, 1 H, H1′), 7.30–7.50 (m, 10 H, ArH), 8.60 (s, 1 H, H8), 10.83 (s, 1 H, NH).

Anal. Calcd for $C_{31}H_{30}N_6O_{10}$: C, 57.58; H, 4.68; N, 13.00. Found: C, 57.32; H, 4.56; N, 4.79.

9-[(2-Acetoxyethoxy)methyl]-2-(acetylamino)-6-(diphenylcarbamoyloxy)-9*H*-purine (9b)

Light-yellow crystals; yield: 0.194 g (77%); mp 130–132 °C.

^{1}H NMR (DMSO-d_6): δ = 1.89 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 3.74–3.79 (m, 2 H, CH_2), 4.05–4.09 (m, 2 H, CH_2), 5.60 (s, 2 H, CH_2), 7.25–7.50 (m, 10 H, ArH), 8.59 (s, 1 H, H8), 10.75 (s, 1 H, NH).

Anal. Calcd for $C_{25}H_{24}N_6O_6$: C, 59.52; H, 4.80; N, 16.66. Found: C, 59.52; H, 4.67; N, 16.70.

9-[(2-Acetoxyethoxy)methyl]-2-(acetylamino)-8-(benzylsulfanyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (9c)

Colorless crystals; yield: 0.263 g (84%); mp 137–138 °C

^{1}H NMR (DMSO-d_6): δ = 1.87 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.63–3.73 (m, 2 H, CH_2), 3.98–4.06 (m, 2 H, CH_2), 4.66 (s, 2 H, CH_2), 5.45 (s, 2 H, CH_2), 7.18–7.36 (m, 5 H, ArH), 7.37–7.57 (m, 10 H, ArH), 10.69 (s, 1 H, NH).

Anal. Calcd for $C_{32}H_{30}N_6O_6S$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.11; H, 4.73; N, 13.33.

N^2-Benzylation of 2-(Acetylamino)-6-(diphenylcarbamoyloxy)-9*H*-purine Derivatives 7a, 9a–c; General Procedure

The reactions were carried out according to the general procedure applied for the synthesis of **3**, **4a–h**, **5** using **7a**, **9a–c** (0.3 mmol), K_2CO_3 (0.083 g, 0.6 mmol), and bromide **2e** (0.112 g, 0.45 mmol) in DMF (8.0 mL).

2-[Acetyl(2-bromobenzyl)amino]-6-(diphenylcarbamoyloxy)-9-(β-D-tri-*O*-acetylribofuranosyl)-9*H*-purine (10a)

Colorless oil; yield: 0.167 g (68%).

^{1}H NMR (DMSO-d_6): δ = 1.86 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3, overlapped with DMSO), 4.04–4.13 (m, 1 H, H5′), 4.23–4.38 (m, 2 H, H4′, H5′), 5.19 (s, 2 H, CH_2), 5.44 (t, J = 5.8 Hz, 1 H, H3′), 5.91–5.97 (m, 1 H, H2′), 6.26 (d, J = 4.8 Hz, 1 H, H1′), 7.11–7.41 (m, 13 H, ArH), 7.60 (d, J = 8.0 Hz, 1 H, ArH), 8.69 (s, 1 H, H8).

9-[(2-Acetoxyethoxy)methyl]-2-[acetyl(2-bromobenzyl)amino]-6-(diphenylcarbamoyloxy)-9*H*-purine (10b)

Light-yellow oil; yield: 0.140 g (70%).

^{1}H NMR (DMSO-d_6): δ = 1.84 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 3.61–3.65 (m, 2 H, CH_2), 3.95–4.00 (m, 2 H, CH_2), 5.21 (s, 2 H, CH_2), 5.60 (s, 2 H, CH_2), 7.12–7.40 (m, 13 H, ArH), 7.61 (d, J = 7.8 Hz, 1 H, ArH), 8.64 (s, 1 H, CH).

9-[(2-Acetoxyethoxy)methyl]-2-[acetyl(2-bromobenzyl)amino]-8-(benzylsulfanyl)-6-(diphenylcarbamoyloxy)-9*H*-purine (10c)

Colorless crystals; yield: 0.187 g (78%); mp 54 °C.

^{1}H NMR (DMSO-d_6): δ = 1.83 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3, overlapped with DMSO), 3.53–3.63 (m, 2 H, CH_2), 3.92–4.01 (m, 2 H, CH_2), 4.65 (s, 2 H, CH_2), 5.19 (s, 2 H, CH_2), 5.46 (s, 2 H, CH_2), 7.08–7.65 (m, 19 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 20.88, 25.80, 35.43, 50.26, 63.03, 67.68, 72.54, 120.50, 122.20, 127.87, 127.98, 128.13, 128.88, 129.11, 129.58, 129.85, 132.83, 137.07, 137.23, 141.99, 150.33, 152.80, 153.76, 156.15, 157.38, 170.53, 171.76.

Anal. Calcd for $C_{39}H_{35}BrN_6O_6S$: C, 58.87; H, 4.43; N, 10.56. Found: C, 58.82; H, 4.33, N, 10.44.

2-[2-Acetyl(2-bromobenzyl)amino]-8-bromo-6-(diphenylcarbamoyloxy)-9-[(ethoxycarbonyl)methyl]-9*H*-purine (10d)

Colorless crystals; yield: 0.157 g (72%); mp 123–124 °C.

^{1}H NMR (DMSO-d_6): δ = 1.17 (t, J = 7.0 Hz, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 4.15 (q, J = 7.0 Hz, 2 H, CH_2), 5.09 (s, 2 H, CH_2), 5.19 (s, 2 H, CH_2), 7.08–7.46 (m, 13 H, ArH), 7.58–7.62 (m, 1 H, ArH).

^{13}C NMR (DMSO-d_6): δ = 14.38, 26.03, 45.67, 50.07, 62.42, 120.26, 122.29, 127.87, 128.17, 129.16, 129.87, 132.85, 134.30, 137.04, 141.78, 149.87, 154.09, 154.70, 155.8, 166.97, 171.96.

Anal. Calcd for $C_{31}H_{26}Br_2N_6O_5$·0.5 H_2O: C, 50.91; H, 3.72; N, 11.49. Found: C, 50.83; H, 3.60; N, 11.28.

9-[(2-Acetoxyethoxy)methyl]-2-[acetyl(2-bromobenzyl)amino]-8-bromo-1,9-dihydro-6*H*-purin-6-one (12)

To a soln of **11** (0.200 g, 0.37 mmol) in DMF (8.0 mL) were added K_2CO_3 (0.057 g, 0.41 mmol) and bromide **2e** (0.102 g, 0.41 mmol). The mixture was stirred at r.t. for 24 h. The solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, $CHCl_3$–EtOH, 50:1) and recrystallized (EtOH) to afford **12** as colorless crystals; yield: 0.072 g (37%); mp 168–170 °C.

^{1}H NMR (DMSO-d_6): δ = 1.92 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 3.45–3.49 (m, 2 H, CH_2), 3.90–3.94 (m, 2 H, CH_2), 5.10 (s, 2 H, CH_2), 5.39 (s, 2 H, CH_2), 7.13–7.47 (m, 3 H, ArH), 7.58 (d, J = 8.4 Hz, 1 H, ArH).

Anal. Calcd for $C_{19}H_{19}Br_2N_5O_5$: C, 40.96; H, 3.44; N, 12.57. Found: C, 41.22, H, 3.13, N, 12.36.

Deprotection of 2-(Acetylamino)- and 2-[Acetyl(benzyl)amino]-6-(diphenylcarbamoyloxy)-9*H*-purine derivatives 4f, 5, 10b–d; General Procedure

A soln of **4f**, **5**, **10b–d** (0.2 mmol) in EtOH saturated with NH_3 (7.0 mL) was stirred overnight at r.t. and then refluxed for 1 h. Volatiles were removed under reduced pressure. The residue was purified either by crystallization (EtOH–H_2O, **13a–c**) or by chromatography [silica gel, $CHCl_3$–EtOH, 50:3 (**13d**) or $CHCl_3$–EtOH, 20:1 (**13e**)].

8-Bromo-9-(3-bromobenzyl)-2-[(3-bromobenzyl)amino]-1,9-dihydro-6*H*-purin-6-one (13a)
Colorless crystals; yield: 0.093 g (82%); mp 269–270 °C

^{1}H NMR (DMSO-d_6): δ = 4.48 (d, J = 5.8 Hz, 2 H, CH_2), 5.14 (s, 2 H, CH_2), 7.03–7.54 (m, 8 H, ArH overlapped with m, 1 H, NH), 10.93 (s, 1 H, NH).

Anal. Calcd for $C_{19}H_{14}Br_3N_5O$: C, 40.17; H, 2.48; N, 12.33. Found: C, 40.47; H, 2.27; N, 12.34.

2-Amino-9-[(benzyloxy)methyl]-8-bromo-1,9-dihydro-6*H*-purin-6-one (13b)
Colorless crystals; yield: 0.056 g (80%); mp >300 °C (dec.)

^{1}H NMR (DMSO-d_6): δ = 4.56 (s, 2 H, CH_2), 5.37 (s, 2 H, CH_2), 6.66 (s, 2 H, NH_2), 7.24–7.37 (m, 5 H, ArH), 10.56 (br s, 1 H, NH).

Anal. Calcd for $C_{13}H_{12}BrN_5O_2$: C, 44.59; H, 3.45; N, 20.00. Found: C, 44.71; H, 3.24; N, 19.86.

9-[(2-Acetoxyethoxy)methyl]-2-[(2-bromobenzyl)amino]-1,9-dihydro-6*H*-purin-6-one (13c)
Colorless crystals; yield: 0.065 g (75%); mp 268–270 °C.

^{1}H NMR (DMSO-d_6): δ = 1.92 (s, 3 H, CH_3), 3.44–3.52 (m, 2 H, CH_2), 3.85–3.94 (m, 2 H, CH_2), 4.53 (d, J = 5.5 Hz, 2 H, CH_2), 5.32 (s, 2 H, CH_2), 7.00 (t, J = 5.5 Hz, 1 H, NH), 7.12–7.44 (m, 3 H, ArH), 7.59 (d, J = 8.4 Hz, 1 H, ArH), 7.80 (s, 1 H, H8), 10.81 (s, 1 H, NH).

Anal. Calcd for $C_{17}H_{18}BrN_5O_4$: C, 46.80; H, 4.16; N, 16.05. Found: C, 46.65, H, 4.00, N, 16.34.

8-(Benzylsulfanyl)-2-[(2-bromobenzyl)amino]-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one (13d)
Colorless crystals; yield: 0.081 g (79%); mp 189–190 °C.

^{1}H NMR (DMSO-d_6): δ = 3.32 (s, 4 H, CH_2), 4.36 (s, 2 H, CH_2), 4.52 (d, J = 5.2 Hz, 2 H, CH_2 overlapped with m, 1 H, OH), 5.19 (s, 2 H, CH_2), 7.03 (t, J = 5.2 Hz, 1 H, NH), 7.13–7.44 (m, 8 H, ArH), 7.60 (d, J = 8.2 Hz, 1 H, ArH), 10.81 (s, 1 H, NH).

Anal. Calcd for $C_{22}H_{22}BrN_5O_3S$: C, 51.17; H, 4.29; N, 15.58. Found: C, 51.22; H, 4.09; N, 13.48.

8-Bromo-2-[(2-bromobenzyl)amino]-9-[(ethoxycarbonyl)methyl]-1,9-dihydro-6*H*-purin-6-one (13e)
Colorless crystals; yield: 0.067 g (69%); mp 254–255 °C.

^{1}H NMR (DMSO-d_6): δ = 1.16 (t, J = 7.2 Hz, 3 H, CH_3), 4.12 (q, J = 7.2 Hz, 2 H, CH_2), 4.51 (d, J = 5.7 Hz, 2 H, CH_2), 4.80 (s, 2 H, CH_2), 7.03–7.40 (m, 3 H, ArH overlapped with m, 1 H, NH), 7.61 (d, J = 8.2 Hz, 1 H, ArH), 10.89 (s, 1 H, NH).

Anal. Calcd for $C_{16}H_{15}Br_2N_5O_3$: C, 39.61; H, 3.12; N, 14.44. Found: C, 39.40; H, 3.07; N, 14.68.

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(11) For compounds **4d** and **12** diffraction data were collected on a Nonius KappaCCD difractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal structures of **4d** and **12** were solved by the direct method and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. *Crystal data for* **4d**: $C_{34}H_{23}BrCl_4N_6O_3$, triclinic, a = 12.0270(6), b = 12.1093(6), c = 12.5269(7) Å, α = 73.074(2), β = 81.041(2), γ = 86.769(2)°, V = 1724.0(2) Å^3, Z = 2, μ = 1.547 mm^{-1}, D_{calc} = 1.513 g cm^{-3}, space group is $P\bar{1}$. A total of 6718 independent reflection intensities were collected at r.t. For structure refinement, 3497 reflections with $I \geq 2\sigma(I)$ were used. The final R-factor is 0.0680. *Crystal data for* **12**: $C_{19}H_{19}Br_2N_5O_5$, triclinic, a = 7.5419(4), b = 12.1920(8), c = 12.6754(10) Å, α = 105.193(2), β = 91.052(3), γ = 101.808(5) °, V = 1097.8(1) Å^3, Z = 2, μ = 3.733 mm^{-1}, D_{calc} = 1.686 g cm^{-3}, space group is $P\bar{1}$. A total of 4560 independent reflection intensities were collected at r.t. For structure refinement, 2520 reflections with $I \geq 2\sigma(I)$ were used. The final R-factor is 0.0596. For further details, see crystallographic data for **4d** and **12** deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 667860, 667861.