MODIFIED TRICYCLIC ANALOGUES OF ACYCLOVIR. A DIRECT ALKYNYLATION IN THE FUSED RING

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Two types of new 7-alkynylated tricyclic analogues (3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-ones) of acyclovir differing by the presence of N-5 substituent, a temporary 2-(4-nitrophenyl)ethyl or a permanent 3-hydroxypropyl were obtained by a Sonogashira coupling. 7-Alk-1-ynyl-5-(3-acetoxypropyl) compounds (**19a**–**19d**, **21a**–**21c**) were efficiently prepared from 7-iodo, 7-iodo-6-methyl precursors **12** and **11**, respectively, and deprotected while the products with unsubstituted N-5 were unstable (e.g. **17**). Iodide **12** was generally less reactive than **11** and underwent a preferable reduction (48%) to deiodinated **8** when coupled with ethynyltrimethylsilane.

Keywords: Acyclovir; Alkynes; Fused purines; Acyclic nucleosides; Sonogashira reaction; Mitsunobu alkylation; NH protecting groups; Reductive deiodination.

The guanine moiety of the potent antiherpetic drug acyclovir 9-[(2-hydroxyethoxy)methyl]guanine, ACV, may be transformed into tricyclic 3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one system via an alkylation–condensation reaction with suitable α-bromoketones or masked α-bromoaldehydes. 6- and 7-Substituted derivatives of TACV (for the systematic name 3-[(2-hydroxyethoxy)methyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one, the abbreviation TACV is used throughout this paper) generated in this way show some advantageous physical properties (solubility, fluorescence) in respect to ACV [1]. The site of substitution (positions 6, 7 or both) and the nature of the substituent (alkyl, aralkyl, aryl) in the fused ring modulate the biological activity of the compounds[1,2]. For example, lipophilic 6-[(4-methoxy)phenyl]- and 7-methyl-6-phenyl-TACV have matched parental ACV in antiviral activity and selectivity. Moreover, these fluorescent antivirals showed cytostatic activity and a pronounced bystander effect in HSV thymidine kinase gene-transduced tumor cell lines[3]. This makes them unique to be applied as markers and agents in the combined gene/chemotherapy of cancer. Surprisingly, replacing 7-methyl group with phenyl provides strongly

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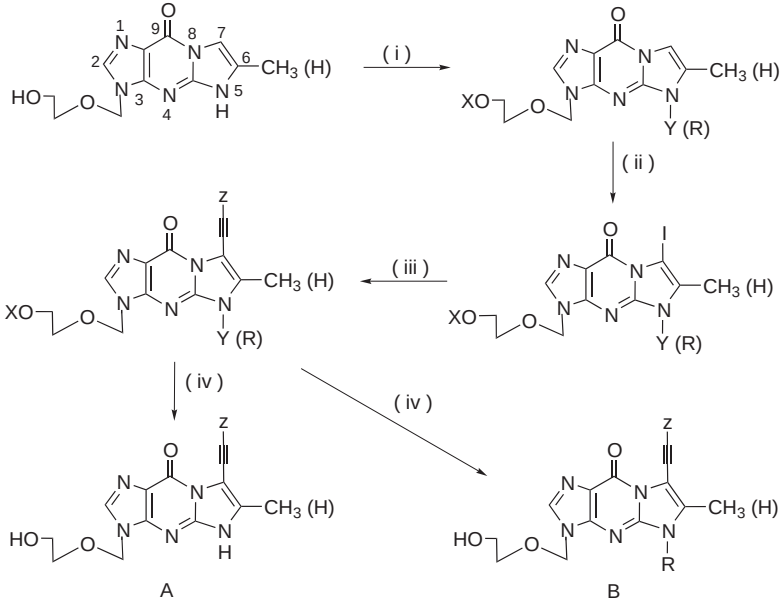
fluorescent 6,7-diphenyl-TACV non selective and highly cytotoxic. Yet, *O*-silylated 6-methyl-7-trityl-TACV shows selective cytotoxicity against human tumor cells[4]. These results were found encouraging to study how less sterically demanding substituents in the 7 position of TACV might shape its biological activity.

Alkynyl substituents seemed to be attractive because of their known property to impact to purine nucleosides a remarkable cytostatic, antiviral or other biological activity[5]. The choice of applicable alkynes was limited to acetylene and terminal alkynes with aromatic residues or capable of forming more than one hydrogen bond. On the other hand, it seemed desirable to evaluate the role of a N-5 substituent suitable for hydrogen bonding. Therefore, two types of target compounds were designed (Scheme 1, structures A, B), and the study of their synthesis presented here was focused on direct modification of the preformed tricyclic system in the 7 position.



(i) Protection, (ii) iodination, (iii) Sonogashira reaction, (iv) deprotection

SCHEME 1

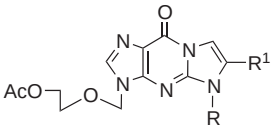
It has been reported that the N-5 unsubstituted fused ring of TACV could be oxidatively cleaved upon treatment with NBS/H_2O or I_2/MeOH [6]. For that reason, placing a substituent on N-5 of the TACV system was necessary and the synthesis was planned to be performed in four steps: (i) N-5 protection, (ii) iodination in position 7, (iii) Sonogashira coupling[7] with an alkyne, (iv) deprotection. A preliminary coupling of *N*-5-benzylated 7-iodo-6-methyl-TACV with ethynyltrimethylsilane has been achieved in a good yield[8].

RESULTS AND DISCUSSION

There are only a few protecting groups for heterocyclic NH which do not change the electronic effects of nitrogen atom and can be cleaved under mild conditions[9]. Those cleavable by a base-induced β-elimination, e.g. 2-(4-nitrophenyl)ethyl (NPE)[10], seemed to be most suitable to protect the N-5 position of TACV. Introduction of the NPE group in the N-5 position of TACV could be achieved in two ways. The acid hydrogen of N-5 could be easily abstracted, e.g. by sodium hydride, and thus the formed nucleophilic centre would readily react with alkylating agents. Unfortunately, the previously reported reaction with 2-(4-nitrophenyl)ethyl iodide is not regioselective: both 5-NPE- and 7-NPE products have been formed[8]. Another approach – alkylation under Mitsunobu conditions – has been found superior to the above-mentioned reaction; however, the ambident nucleophilic reactivity displayed by anionic TACV [11] has become troublesome again and two products have been formed[8].

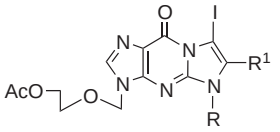
When a betaine is generated[10] from triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in the presence of *O*-acylated compound **1a** (Scheme 2) and 2-(4-nitrophenyl)ethanol (NPEOH), it affords an anion of **1a**. This particular compound as a C-nucleophile may attack first the residual DIAD and then, being already 7-substituted, shows N-nucleophilic reactivity affording the undesired byproduct **2a**, 7-substituted (with a hydrazinedicarboxylic diester moiety) 5-[2-(4-nitrophenyl)ethyl]-6-methyl-TACV (Scheme 2).

The structure of **2a** was easily established using spectral data: the absence of 7-H signal in ^{1}H NMR spectrum as well as the presence of multiplets δ 4.83 and 1.69 ascribed to isopropoxy groups and a singlet of exchangeable proton of δ 8.45. Thus, to prevent the formation of **2a**, in favor of the desired 5-[2-(4-nitrophenyl)ethyl]-6-methyl-TACV (**2b**), the betaine should be obviously preformed prior to addition of substrate **1a** and alcohol. It has been shown previously that the final result of the Mitsunobu reaction may depend on the order of addition of reactants[12]. After careful investigation,



2, 4, 7, 8

(iv)

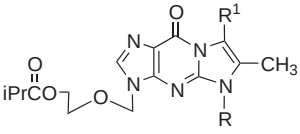


9, 10, 11, 12

1, R = H, $R^1 = CH_3$ ⇄ (i)
2, R = NPE, $R^1 = CH_3$
3, R = H, $R^1 = H$ ⇄ (i)
4, R = NPE, $R^1 = H$
5, R = $(CH_2)_3OH$, $R^1 = CH_3$
6, R = $(CH_2)_3OH$, $R^1 = H$
7, R = $(CH_2)_3OAc$, $R^1 = CH_3$
8, R = $(CH_2)_3OAc$, $R^1 = H$

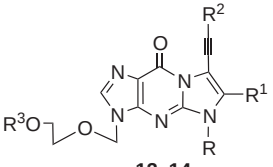
9, R = NPE $R^1 = CH_3$
10, R = NPE $R^1 = H$
11, R = $(CH_2)_3OAc$ $R^1 = CH_3$
12, R = $(CH_2)_3OAc$ $R^1 = H$

1, **3** (ii) → **5**, **6** (iii) → **7**, **8**



9, **10**

(v)

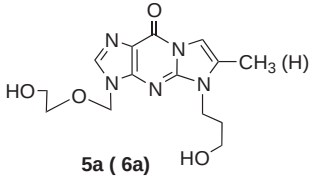


13, **14**

1a, R = H, $R^1 = H$
2a, R = NPE
R^1 = N(COOiPr)NH(COOiPr)
2b, R = NPE, $R^1 = H$

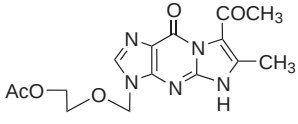
13, R = NPE, $R^1 = CH_3$, R^2 = TMS, R^3 = Ac
14, R = NPE, $R^1 = H$, $R^2 = CH_2NHCOCF_3$, R^3 = Ac
15, R = NPE, $R^1 = CH_3$, $R^2 = H$, R^3 = Ac
16, R = NPE, $R^1 = CH_3$, $R^2 = H$, $R^3 = H$
17, R = H, $R^1 = CH_3$, R^2 = TMS, R^3 = Ac

5, **6** (vi) → **5a**, **6a**



5a (6a)

13 (vii) → **16**
13 (viii) → **17**



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Reagents: (i) PPh_3, DIAD or DEAD, THF, DMF, 4-$O_2NC_6H_4CH_2CH_2OH$; (ii) PPh_3, DEAD, THF, DMF, propane-1,3-diol; (iii) Ac_2O, Py; (iv) CF_3CO_2Ag, I_2, CH_2Cl_2; (v) $[Pd(PPh_3)_4]$, CuI, Et_3N, DMF, alkyne: TMS-acetylene or 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide; (vi) NH_3/MeOH; (vii) MeOH, dioxane, DMSO, aq. NH_3: 1:2:0.2:2; (viii) DBU/Py

SCHEME 2

the following optimal reaction conditions were fixed to obtain 6-Me-5-NPE-TACV (**2**) as a sole product in an excellent yield (92–94%): the betaine had to be generated first with 5% excess of PPh_3 to DIAD (in THF) and treated with a solution of substrate **1** (in DMF) followed by NPEOH (in THF). The insoluble **2** precipitated from the reaction mixture.

When applied to a more polar substrate **3**, the reaction led to a single product, 5-NPE-TACV (**4**), as expected. Inconveniently, **4** was quite a soluble compound and had to be isolated by chromatography; it lowered the yield to 84%. The 5-NPE derivatives **2** and **4** were fully characterized by ^1H, ^{13}C NMR, UV and elemental analyses. These results encouraged to apply the established procedure to *O*-acetylated tricycles **1** and **3** with propane-1,3-diol to reach the second synthetic goal, namely alkynylated TACV derivatives with 3-hydroxypropyl as permanent substituent of N-5 (Scheme 1, B). Expected 5-(3-hydroxypropyl) compounds **5** and **6** were obtained in high yields (87 and 89%) as well.

In order to improve their solubility and to avoid side reactions, both **5** and **6** were acetylated to give fully protected acetates **7** and **8**, respectively. Subsequent iodination of tricyclic **2**, **4**, **7** and **8** used the method described for 5,6-dimethyl-7-iodo-3-(2,3,5-*O*-triacetyl-β-D-ribofuranosyl)-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one[13] and provided the required iodides **9**–**12** in much better yields (64–81%) than that (51%) of the original compound. In accordance with the already reported findings[8], the reactions of 6-unsubstituted compounds **4** and **8** were fully regioselective, besides, both **4** and **8** were more reactive toward the electrophilic I^+ than their 6-methyl counterparts **2**, **7**. It is worthy to note that 7-iodo-6-methyl derivatives **9** and **11** were less stable during purification than the respective 6-unsubstituted 7-iodotricycles **10**, **12**. The difference had probably an impact on the course of coupling reactions investigated later on.

Mild conditions[14] of the Sonogashira reaction seemed to be appropriate for coupling of 5-NPE-7-iodo compounds with alkynes bearing protecting groups: **9** with ethynyltrimethylsilane and **10** with 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide. Both couplings gave satisfactory yields: 6-methyl-7-[(trimethylsilyl)ethynyl]-5-NPE-TACV (**13**; 76%) and 7-[3-(trifluoroacetamido)-prop-1-yn-1-yl]-5-NPE-TACV (**14**; 70%). Due to the observed complexation of the alkynylated products **13**, **14** with Cu^{2+} cations, it was necessary to remove metal ions before routine purification. The presence of protecting groups of **13**, **14** was beneficial and obviously simplified the work-up procedure making the extraction with aqueous solution of disodium EDTA possible. On the other hand, deprotection of the just obtained alkynylated products required careful investigation.

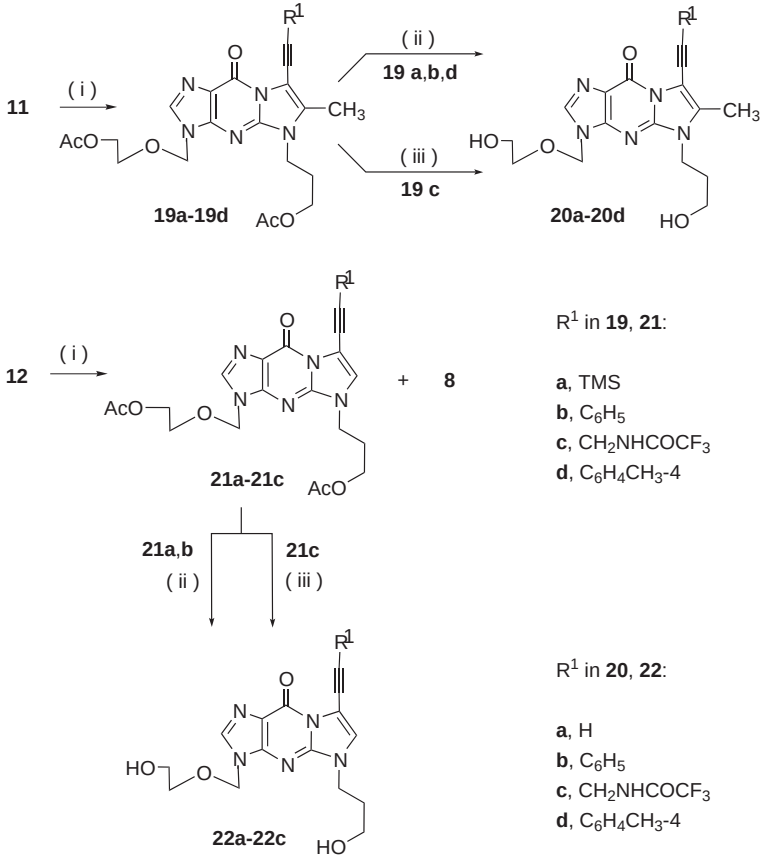
It could be assumed that the base-labile protecting groups of **13**, **14** might be removed stepwise and the deblocking performed in two ways. Preliminary experiments showed that the elimination of NPE group even from poorly soluble substrate **2** did not pose difficulty when effected with DBU in DMF at 60 °C (70% recovery of **1**). The first method, cleavage of TMS and acetyl groups of **13** by the treatment with methanolic or aqueous ammonia, resulted in a rapid desilylation and quantitative precipitation of *O*-acetyl-7-ethynyl-6-methyl-5-NPE intermediate **15**. Poor solubility of acetate **15** rendered impossible to eliminate NPE group next either in pyridine or in DMF. The mixture of methanol, dioxane, DMSO and aqueous ammonia in a peculiar ratio 10:20:2:0.2 (v/v) prevented precipitation of **15** and the other intermediate **16** (84%) bearing only the NPE protecting group was subjected to the action of DBU in different solvents. The experiments indicated that the liberated product underwent immediately further transformations, which ended up with many unidentified products. The other approach, limited to well soluble substrates, eliminates the 5-NPE group of **13** selectively with DBU in pyridine. The yield of this particular reaction was not reproducible: 29–75% of highly reactive product **17** could be obtained depending on the chosen method of purification. The reactivity of **17** was proved in an NMR experiment in a deuterated DMSO solution of purified sample of **17**. In two days, in the presence of merely 2.6 equivalents of water 7-alkynyl derivative **17** was transformed into its hydration product, 7-acetyl derivative **18**. The reaction could be catalyzed by traces of silica gel present in a sample of **17** after PLC purification. The structure of **18** was established unambiguously by ^{1}H and ^{13}C 1D and HETCOR NMR spectra. Simultaneous deprotection of less hindered compound **14** with an excess of DBU in pyridine resulted in a complex mixture of 4-nitrostyrene and many inseparable products more polar than **14**.

Therefore, a general conclusion may be drawn here that the absence of any substituent at N-5 position of 7-alkynylated TACV dramatically increases susceptibility of conjugated triple, double C6–C7 bonds to electrophilic addition. In contrast, 7-alkynylated 5-substituted TACV, e.g. **13**, **14**, proved to be resistant in a slightly acidic medium, e.g. a silica gel support. Nevertheless, an efficient method to obtain stable 7-alkynylated 5-substituted TACV derivatives (Scheme 1, B) was established.

Several unhindered alkynes were chosen to couple with 5-(3-acetoxypropyl)-7-iodo compounds **11** and **12** (Scheme 3). The simplest, ethynyltrimethylsilane, reacted readily with 6-methyl compound **11** to afford 7-[(trimethylsilyl)ethynyl] compound **19a** in 77% yield. Coupling of the same alkyne with more stable tricyclic **12** resulted in a mixture of precursor

8 (48%) a major product, and an alkynylated product **21a**. The latter was merely a minor product isolated in 40% yield. Distribution of the products and calculated yields reminded of those obtained in preliminary experiments[8]. To improve the yield of **21a**, the reaction was performed in THF [15] in the presence of smaller amounts of catalysts or an alkyne, but the yields were even less satisfactory (51% of **8**, 25% of **21a**).

The results of further couplings of iodides **11** and **12** with more acid alkynes (Scheme 3) suggested the intrinsically low reactivity of tricyclic **12** in oxidative addition of Pd catalytic species, which is the reason for undesired double course of its coupling reaction.



(i) alkyne, $[Pd(PPh_3)_4]$, CuI, Et_3N, DMF; (ii) NH_3/MeOH; (iii) MeONa/MeOH

SCHEME 3

Reductive deiodination of **12** which accompanied couplings consumed as much as 10–15% of the substrate. Nevertheless, the alkynylated products **21b**, **21c** were obtained in satisfactory yields, 68 and 70%, and the corresponding 6-methyl derivatives **19b**–**19d** in good yields (77–87%).

The results discussed here remained in line with the observations presented by others[16]. Tretyakov et al. while conducting a Sonogashira reaction of 4-iodopyrazoles with alkynes bearing electron-releasing substituents have noticed a reductive deiodination of substrates instead of coupling, accompanied by a homocoupling of alkynes. After careful investigation, the authors have concluded that the mechanism of deiodination may be represented as an interaction of alkynylbis(triphenylphosphine)palladium(II) hydride with a derivative of 4-iodopyrazole resulting in the formation of alkynylbis(triphenylphosphine)palladium(II) iodide and a pyrazole derivative. Consecutive reductive elimination of alkynyl iodide from the palladium complex would allow to: (i) enter a new catalytic cycle by [(Pd(0)-$(PPh_3)_2$)], (ii) remove alkynyl iodide by the Cadiot–Chodkiewicz reaction.

All alkynylated tricycles, **19a**–**19d**, **21a**–**21c**, were deprotected to afford final products **20a**–**20d**, **22a**–**22c** either upon treatment with methanolic ammonia (**20a**, **20b**, **20d**, **22a**, **22b**) or by sodium methoxide in catalytic amount[17] in methanol (**20c**, **22c**). The latter method allowed to preserve trifluoroacetamide functionality in good yields (80, 86%)

CONCLUSIONS

The synthesis of two types of 7-alkynylated tricyclic analogues of acyclovir differing by the presence of the N-5 substituent was investigated. The products with unsubstituted N-5 appeared to be exceptionally unstable due to their high susceptibility to electrophilic addition, which was exemplified by hydration of 6-methyl-7-[(trimethylsilyl)ethynyl] derivative **17** to 7-acetyl derivative **18** under conditions far from those routinely used[18]. Therefore, the first part of the synthetic project was not accomplished. Inasmuch as the presence of a permanent N-5 substituent sufficiently decreased reactivity of the triple bond of alkynylated TACV, the second part of the synthesis could be successfully performed. Surprisingly, the standard conditions applied to iodination and subsequent alkynylation of 6-methyl and 6-unsubstituted compounds indicated substantial differences in their reactivity. In particular, coupling reactions with ethynyltrimethylsilane performed on both substrates resulted in main products of a different kind. A standard procedure of the Mitsunobu alkylation was adapted to overcome the troublesome ambident reactivity of anionic TACV and to obtain in this way

N-5-alkylated products exclusively. At present, this can be denoted as a very efficient and the most versatile approach to N-5-alkylated tricyclic analogues of acyclovir.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP II capillary melting point apparatus and are uncorrected. UV spectra (λ, in nm) were recorded on a Perkin–Elmer Lambda EZ201 spectrophotometer. LR and HR mass spectra were measured on an AMD-604 mass spectrometer using LSI (glycerol or 3-nitrobenzyl alcohol as matrices) or on a ZQ Waters Micromass spectrometer using ES ionization technique (LR spectra). Elemental analyses were performed by Microanalytical Laboratories of the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Unity 300 Varian spectrometer operating at 299.95, 75.43 and 282.25 MHz, respectively. Tetramethylsilane was used as the internal standard (^{1}H and ^{13}C NMR), trifluoroacetic acid (^{19}F NMR) was used as the external standard. Chemical shifts (δ-scale) are reported in ppm, coupling constants (*J*) in Hz. Thin-layer chromatography (TLC) and preparative layer chromatography (PLC) were performed on Merck precoated 60 F_{254} or silanized 60 F_{254} silica gel plates. Short-column chromatography was carried out on Merck silica gel 60H (40–63 or 15–40 μm). Dichloromethane was distilled from P_2O_5 and immediately used in iodination experiments. Dimethylformamide dried over P_2O_5, was distilled in vacuo and stored over molecular sieves. Anhydrous pyridine was prepared by refluxing over P_2O_5, distillation, treatment with CaH_2, distillation and storage over molecular sieves. Anhydrous tetrahydrofuran was prepared immediately before Mitsunobu reactions by refluxing with sodium/benzophenone and distillation. The other solvents were dried and purified in the usual manner. All Mitsunobu and coupling reactions were performed under argon. 2,2,2-Trifluoro-*N*-(prop-2-ynyl)acetamide was prepared according to Trybulski at al.[19] 3-[(2-Acetoxyethoxy)methyl]-6-methyl-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**1**) was prepared as described previously[20].

3-{[2-(Isobutyryloxy)ethoxy]methyl}-6-methyl-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**1a**) was prepared in reaction with isobutyryl chloride according to[20] (0.820 g, 82%), m.p. 191 °C. ^{1}H NMR (DMSO-d_6): 0.99 d, *J* = 7.2, 6 H (2 × CH_3); 2.26 d, *J*(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 2.42 sep, *J* = 7.2, 1 H (CH); 3.70 m, 2 H (CH_2O); 4.09 m, 2 H (CH_2O); 5.49 s, 2 H (OCH_2N); 7.37 d, *J*(H-7,6-CH_3) = 1.2, 1 H (H-7); 8.02 s, 1 H (H-2); 12.42 brs, 1 H (NH).

Acetylation of 3-[(2-hydroxyethoxy)methyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one[21] was performed according to[20] to yield 2.64 g (91%) of *3-[(2-acetoxyethoxy)methyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one* (**3**), m.p. 235 °C. ^{1}H NMR (DMSO-d_6): 1.94 s, 3 H (CH_3); 3.71 m, 2 H (CH_2O); 4.06 m, 2 H (CH_2OAc); 5.50 s, 2 H (OCH_2N); 7.46 d, *J*(H-6,H-7) = 2.7, 1 H (H-6); 7.63 d, *J*(H-7,H-6) = 2.7, 1 H (H-7); 8.06 s, 1 H (H-2); 12.55 brs, 1 H (NH).

N-5 Alkylation of **1a** under Standard Mitsunobu Conditions

Dimethylformamide (2 ml) was injected into an Ar-purged flask containing **1a** (0.066 g, 0.2 mmol). To the vigorously stirred solution, triphenylphosphine (0.105 g, 0.4 mmol) was added. Next, a solution of diisopropyl azodicarboxylate (0.081 g, 0.4 mmol) in anhydrous dioxane (2 ml) was added dropwise during 4 h. The reaction mixture was stirred at room temperature overnight. The starting material was consumed and two products were formed.

Solvents were removed in vacuo and the products were isolated on a silica gel (15 g) column with a gradient of methanol (0–5%) in CH_2Cl_2.

The first eluted product: *diisopropyl 2-({3-[(2-isobutyryloxy)ethoxy]methyl}-6-methyl-5-[2-(4-nitrophenyl)ethyl]-9-oxo-3,9-dihydro-5H-imidazo[1,2-a]purin-7-yl)hydrazine-1,2-dicarboxylate* (**2a**) was obtained as a foam (24 mg, 17%). UV (MeOH), λ_{max}: 231, 276. ^{1}H NMR (DMSO-d_6): 0.98 d, J = 7.2, 6 H (2 × CH_3); 1.69 m, 12 H (4 × CH_3); 2.13 s, 1 H (6-CH_3); 2.41 sep, J = 7.2, 1 H (CH); 3.25 m, 2 H (CH_2); 3.78 m, 2 H (CH_2O); 4.14 m, 2 H (CH_2O); 4.37 m, 2 H (NCH_2); 4.83 m, 2 H (2 × OCH); 5.53 s, 2 H (OCH_2N); 7.42 d, J = 8.7 (H-arom.); 8.08 m, 3 H (H-arom., H-2); 8.45 s, 1 H exchangeable (NH).

The second eluted product: *3-{[(2-isobutyryloxy)ethoxy]methyl}-6-methyl-5-[2-(4-nitrophenyl)-ethyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one* (**2b**) was obtained as yellow crystals (69 mg, 71%), m.p. 181–182 °C (CH_2Cl_2/EtOH 3:1). UV (MeOH), λ_{max}: 230, 283. ^{1}H NMR (DMSO-d_6): 0.99 d, J = 7.2, 6 H (2 × CH_3); 2.12 d, J(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 2.41 sep, J = 7.2, 1 H (CH); 3.25 t, J = 6.9, 3 H (CH_2); 3.78 m, 2 H (CH_2O); 4.14 m, 2 H (CH_2O); 4.34 t, J = 6.9, 3 H (NCH_2); 7.42 d, J(H-7,6-CH_3) = 1.2, 1 H (H-7); 7.46 d, J = 8.7, 2 H (H-arom.); 8.05 s, 1 H (H-2); 8.12 d, J = 8.7, 2 H (H-arom.).

N-5 Alkylation of TACV Derivatives under Mitsunobu Conditions by Employing Preformed Betaine. General Procedure

Method A. Alkylation with 2-(4-Nitrophenyl)ethanol

Freshly distilled THF (4 ml) was injected to an Ar-purged flask containing PPh_3 (0.550 g, 2.10 mmol). A solution was stirred vigorously under Ar at 0 °C and diisopropyl azodicarboxylate (0.404 g, 2.0 mmol) was added dropwise through a septum during 10 min. A suspension of the precipitated betaine was stirred at 0 °C for 20 min, then a solution of a substrate (1 mmol) in DMF (10 ml) was added dropwise. A clear solution was obtained. In 10 min, the reaction mixture was treated with a solution of 2-(4-nitrophenyl)ethanol (0.334 g, 2.0 mmol) in THF (4 ml). The stirring was continued at 0 °C for 90 min, then at room temperature overnight. The N-5 alkylated product was collected by filtration or isolated by chromatography of the reaction mixture after work-up.

3-[(2-Acetoxyethoxy)methyl]-6-methyl-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5H-imidazo-[1,2-a]purin-9-one (**2**) was prepared from **1** by method *A*. Compound **2** was collected by filtration and washed with diethyl ether. Yellow powder (0.427 g, 94%), m.p. 156 °C (dec.) (CH_2Cl_2/EtOH 1:1). UV (MeOH), λ_{max}: 230, 283 (40 700, 26 400); poorly soluble in DMSO-d_6. ^{1}H NMR (DMSO-d_6): 1.93 s, 3 H (CH_3); 2.12 d, J(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 3.25 t, J = 6.9, 2 H (CH_2); 3.77 m, 2 H (CH_2O); 4.11 m, 2 H (CH_2OAc); 4.34 t, J = 6.9, 2 H (NCH_2); 5.52 s, 2 H (OCH_2N); 7.48–7.42 m, 3 H (H-arom., H-7); 8.04 s, 1 H (H-2); 8.10 m, 2 H (H-arom.). For $C_{21}H_{22}N_6O_6$ (454.4) calculated: 55.50% C, 4.88% H, 18.49% N; found: 55.32% C, 4.92% H, 18.30% N.

3-[(2-Acetoxyethoxy)methyl]-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**4**) was prepared from **3** by method *A*. After evaporation of solvents, **4** was isolated from the residual mixture on a silica gel column (40 g) with a gradient of ethanol (5–10%) in CH_2Cl_2. Compound **4** was obtained as a yellow powder (0.370 g, 84%), m.p. 183–185 °C (CH_2Cl_2/EtOH 2:1). UV (MeOH), λ_{max}: 228, 284 (43 000, 25 700). ^{1}H NMR (DMSO-d_6): 1.94 s, 3 H (CH_3); 3.31 t, J = 6.9, 2 H (CH_2); 3.75 m, 2 H (CH_2O); 4.11 m, 2 H (CH_2OAc); 4.42 t, J = 6.9, 2 H (NCH_2); 5.53 s, 2 H (OCH_2N); 7.49 d, J = 8.7, 2 H (H-arom.); 7.46 d, J(H-6,H-7) =

2.7, 1 H (H-6); 7.63 d, *J*(H-7,H-6) = 2.7, 1 H (H-7); 8.07 s, 1 H (H-2); 8.12 d, *J* = 8.7, 2 H (H-arom.). ^{13}C NMR (DMSO-d_6): 20.43 (CH_3); 33.83 (CH_2); 45.10 (NCH_2); 62.66 (CH_2OAc); 66.86 (CH_2O); 71.81 (OCH_2N); 106.10 (CH-7); 115.08 (C-9a); 119.40 (CH-6); 123.35, 130.07, 144.72, 146.19 (C-arom.); 139.30 (CH-2); 146.25 (C-4a); 150.18 (C-3a); 151.08 (C-9); 170.14 (C=O). For $C_{20}H_{20}N_6O_6$ (440.4) calculated: 54.54% C, 4.58% H, 19.08% N; found: 54.41% C, 4.62% H, 18.83% N.

Method B. Alkylation with Propane-1,3-diol

Method *A* was optimized by using smaller excess of reagents: diethyl azodicarboxylate (DEAD) 1.2 equiv., triphenylphosphine 1.25 equiv., propane-1,3-diol 1.35 equiv., calculated for 1 mmol of a substrate. After the reaction was complete, volatiles were removed in vacuo and the residue was chromatographed on a silica gel column (40 g) with a gradient of ethanol (5–15%) in $CHCl_3$ to give products **5** or **6**.

3-[(2-Acetoxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**5**) was prepared from **1** by method *B* as a white hygroscopic solid (0.316 g, 87%), m.p. 118–120 °C. ^{1}H NMR (DMSO-d_6): 1.90 pent, *J* = 6.6, 2 H (CH_2); 1.95 s, 3 H (CH_3); 2.35 d, *J*(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 3.42 m, 2 H (CH_2OH); 3.76 m, 2 H (CH_2O); 4.08–4.14 m, 4 H (CH_2OAc, NCH_2); 4.62 t, *J* = 4.8, 1 H exchangeable (OH); 5.52 s, 2 H (OCH_2N); 7.48 d, *J*(H-7,6-CH_3) = 1.2, 1 H (H-7); 8.05 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.41 (6-CH_3); 20.43 (CH_3); 31.04 (CH_2); 40.16 (NCH_2) overlap. with DMSO-d_5; 57.52 (CH_2OH); 62.64 (CH_2OAc); 66.88 (CH_2O); 71.84 (OCH_2N); 102.85 (CH-7); 115.21 (C-9a); 127.71 (CH-6); 139.11 (C-2); 144.92 (C-4a); 149.86 (C-3a); 150.94 (C-9); 170.21 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-hydroxypropyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**6**) was prepared from **3** by method *B* as a white, hygroscopic solid (0.310 g, 89%), m.p. 97–99 °C. ^{1}H NMR (DMSO-d_6): 1.90–2.00 m, 5 H (CH_2, CH_3); 3.42 m, 2 H (CH_2OH); 3.76 m, 2 H (CH_2O); 4.08–4.18 m, 4 H (CH_2OAc, NCH_2); 4.64 t, *J* = 5.1, 1 H exchangeable (OH); 5.53 s, 2 H (OCH_2N); 7.46 d, *J*(H-6,H-7) = 2.7, 1 H (H-6); 7.63 d, *J*(H-7,H-6) = 2.7, 1 H (H-7); 8.07 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 20.48 (CH_3); 31.35 (CH_2); 41.99 (NCH_2); 57.65 (CH_2OH); 62.67 (CH_2OAc); 66.87 (CH_2O); 71.89 (OCH_2N); 106.01 (CH-7); 115.11 (C-9a); 119.41 (CH-6); 139.30 (CH-2); 144.80 (C-4a); 150.32 (C-3a); 151.18 (C-9); 170.17 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-6-methyl-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**7**) was obtained from **5** (1.52 g, 4.18 mmol) in a reaction with acetic anhydride (1.08 g, 10.6 mmol) in pyridine (10 ml). The volatiles were evaporated in vacuo and the residue was co-evaporated with MeOH then with toluene. Finally, it was washed with diethyl ether and dried to give 1.60 g (95%) of white microcrystals, m.p. 132–133 °C. UV (MeOH), λ_{max}: 230, 286. ^{1}H NMR (DMSO-d_6): 1.91 s, 3 H (CH_3); 1.95 s, 3 H (CH_3); 2.09 pent, *J* = 6.6, 2 H (CH_2); 2.34 d, *J*(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 3.75 m, 2 H (CH_2O); overlap. 4.04 t, *J* = 6.0, 2 H (CH_2OAc); overlap. 4.10 m, 2 H (CH_2OAc); 4.15 t, *J* = 6.6, 2 H (NCH_2); 5.52 s, 2 H (OCH_2N); 7.50 d, *J*(H-7,6-CH_3) = 1.2, 1 H (H-7); 8.06 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.39 (6-CH_3); 20.38, 20.43 (CH_3); 27.21 (CH_2); 40.20 (NCH_2); 62.46, 62.60 (CH_2OAc); 66.88 (CH_2O); 71.78 (OCH_2N); 103.07 (CH-7); 115.25 (C-9a); 127.39 (C-6); 139.11 (CH-2); 145.10 (C-4a); 149.84 (C-3a); 150.88 (C-9); 170.10, 170.13 (C=O).

Compound **7** (0.215 g, 0.53 mmol) was deacetylated by treatment with methanolic ammonia (8 ml). The volatiles were removed in vacuo and the residue was crystallized from propan-2-ol to give *3-[(2-hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one* (**5a**): 0.154 g (91%) of white crystalline material, m.p. 147–148 °C.

UV (MeOH), λ_{max}: 230, 286 (29 800, 13 300). ^{1}H NMR (DMSO-d_6): 1.88 pent, *J* = 6.6, 2 H (CH_2); 2.32 d, *J*(6-CH_3,H-7) = 1.2, 3 H (6-CH_3); 3.40–3.55 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.11 t, *J* = 6.9, 2 H (NCH_2); overlap. 4.64, 4.68 2 × t, *J* = 4.8, 5.4, 2 H exchangeable (2 × OH). For $C_{14}H_{19}N_5O_4$ (321.2) calculated: 52.33% C, 5.96% H, 21.79% N; found: 52.25% C, 5.93% H, 21.67% N. Compound **5a** was synthesized earlier[22] by a less efficient method (alkylation of 6-methyl-TACV with 3-bromopropanol, DMF, K_2CO_3) and not fully characterized.

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**8**) was prepared analogously to **7** as a foam (1.54 g, 94%). UV (MeOH), λ_{max}: 227, 286. ^{1}H NMR (DMSO-d_6): 1.91 s, 3 H (CH_3); 1.95 s, 3 H (CH_3); 2.14 pent, *J* = 6.6, 2 H (CH_2O); 3.75 m, 2 H (CH_2O); 4.03 t, *J* = 6.6, 2 H (CH_2OAc); 4.10 m, 2 H (CH_2OAc); 4.19 t, *J* = 6.6, 2 H (NCH_2); 5.53 s, 2 H (OCH_2N); 7.46 d, *J*(H-6,H-7) = 2.7, 1 H (H-6); 7.63 d, *J*(H-7,H-6) = 2.7, 1 H (H-7); 8.08 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 20.47, 20.70 (CH_3); 27.41 (CH_2); 41.93 (NCH_2); 61.30, 62.67 (CH_2OAc); 66.88 (CH_2O); 71.87 (OCH_2N); 106.21 (CH-7); 115.13 (C-9a); 119.35 (CH-6); 139.35 (CH-2); 144 94 (C-4a); 150.32 (C-3a); 151.18 (C-9); 170.18, 170.20 (C=O).

Compound **8** was deacetylated analogously to **7** to give *3-[(2-hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one* (**6a**) as a crystalline material (0.130 g, 80%), m.p. 147–149 °C (propan-2-ol). UV (MeOH), λ_{max}: 227, 289 (30 200, 13 600). ^{1}H NMR (DMSO-d_6): 1.95 pent, *J* = 6.6, 2 H (CH_2); 3.40–3.50 m and 3.54–3.57 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.15 t, *J* = 6.9, 2 H (NCH_2); overlap. 4.65, 4.69 2 × t, *J* = 4.8, 5.7, 2 H exchangeable (2 × OH); 5.52 s, 2 H (OCH_2N); 7.46 d, *J*(H-6,H-7) = 2.7, 1 H (H-6); 7.63 d, *J*(H-7,H-6) = 2.7, 1 H (H-7); 8.06 s, 1 H (H-2). For $C_{13}H_{17}N_5O_4$ (307.3) calculated: 50.81% C, 5.58% H, 22.79% N; found: 50.69% C, 5.61% H, 22.76% N.

7-Iodination of 5-Substituted TACV Derivatives. General Procedure

CF_3CO_2Ag (0.233 g, 1.05 mmol) was added under Ar to a stirred suspension of a substrate (1 mmol) in freshly distilled dichloromethane (27 ml). In 5 min, a clear solution was obtained. Next, a solution of iodine (0.266 g, 1.05 mmol) in CH_2Cl_2 (25 ml) was transferred to the reaction mixture with argon during 15 min. Precipitation of AgI was observed and the resulting suspension was stirred for additional 3 h. AgI was then filtered off on a Celite pad and washed with CH_2Cl_2 (200 ml). The filtrate and washings were combined, transferred into a separatory funnel and washed with water followed by 5% aqueous $Na_2S_2O_3$ and water (150 ml each). The organic layer was separated, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo and the residue was carefully dried, taken up in CH_2Cl_2 and applied onto a silica gel column (80 g). The 7-iodo product was eluted either with a gradient of EtOH (1–5%) in CH_2Cl_2 or with 5% EtOH in $CHCl_3$ for **10**.

3-[(2-Acetoxyethoxy)methyl]-7-iodo-6-methyl-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5H-imidazo-[1,2-a]purin-9-one (**9**) was obtained from **2** (0.395 g, 68%) as yellow crystals, m.p. 145 °C (dec.) (CH_2Cl_2/EtOH 2:1). UV (MeOH), λ_{max}: 234, 280 (38 600, 26 000). ^{1}H NMR (DMSO-d_6): 1.94 s, 3 H (CH_3); 2.18 s, 3 H (6-CH_3); 3.20 t, *J* = 6.6, 2 H (CH_2); 3.75 m, 2 H (CH_2O); 4.11 m, 2 H (CH_2OAc); 4.37 t, *J* = 6.6, 2 H (NCH_2); 5.49 s, 2 H (NCH_2); 7.51 d, *J* = 8.7, 2 H (H-arom.); 8.02 s, 1 H (H-2); 8.14 d, *J* = 8.7, 2 H (H-arom.). ^{13}C NMR (DMSO-d_6): 10.75 (6-CH_3); 20.51 (CH_3); 33.71 (CH_2); 44.09 (NCH_2); 53.99 (C-7); 62.68 (CH_2OAc); 66.95 (CH_2O); 71.74 (OCH_2N); 115.40 (C-9a); 123.40, 130.36, 145.76, 146.33 (C-arom.); 131.64 (C-6); 139.18 (CH-2); 146.29 (C-4a); 148.49 (C-3a); 152.60 (C-9); 170.14 (C=O). For $C_{21}H_{21}IN_6O_6$ (580.3) calculated: 43.46% C, 3.65% H, 14.48% N; found: 43.46% C, 3.66% H, 14.59% N. The unreacted **2** was isolated in 15%.

3-[(2-Acetoxyethoxy)methyl]-7-iodo-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5H-imidazo[1,2-a]-purin-9-one (**10**) was prepared from **4** (0.459 g, 81%) as yellow crystals, m.p. 168 °C (dec.) (CH_2Cl_2/EtOH 2:1). UV (MeOH), λ_{max}: 232, 278 (39 900, 30 000). ^{1}H NMR (DMSO-d_6): 1.94 s, 3 H (CH_3); 3.28 t, *J* = 6.6, 2 H (CH_2); 3.73 m, 2 H (CH_2O); 4.10 m, 2 H (CH_2OAc); 4.34 t, *J* = 6.6, 2 H (NCH_2); 5.49 s, 2 H (OCH_2N); 7.61 s, 1 H (H-6); 7.50 d, *J* = 8.7, 2 H (H-arom.); 8.02 s, 1 H (H-2); 8.14 d, *J* = 8.7, 2 H (H-arom.). ^{13}C NMR (DMSO-d_6): 20.44 (CH_3); 33.66 (CH_2); 45.24 (NCH_2); 52.42 (C-7); 62.63 (CH_2OAc); 66.84 (CH_2O); 71.70 (OCH_2N); 115.21 (C-9a); 123.38, 130.05, 145.26, 146.10 (C-arom.); 126.51 (CH-6); 139.28 (CH-2); 146.26 (C-4a); 149.12 (C-3a); 152.80 (C-9); 170.14 (C=O). For $C_{20}H_{19}IN_6O_6$ (566.3) calculated: 42.42% C, 3.38% H, 14.84% N; found: 42.52% C, 3.48% H, 14.83% N.

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-7-iodo-6-methyl-3,9-dihydro-5H-imidazo-[1,2-a]purin-9-one (**11**) was prepared from **7** (0.342 g, 64%) as pale yellow microcrystals, m.p. 134–138 °C (dec.). UV (MeOH), λ_{max}: 234, 293 (29 000, 13 700). ^{1}H NMR (DMSO-d_6): 1.91 s, 3 H (CH_3); 1.95 s, 3 H (CH_3); 2.05 pent, *J* = 6.6, 2 H (CH_2); 2.34 s, 3 H (6-CH_3); 3.74 m, 2 H (CH_2O); 4.04 t, *J* = 6.6, 2 H (CH_2OAc); 4.09 m, 2 H (CH_2OAc); 4.20 t, *J* = 6.6, 2 H (NCH_2); 5.49 s, 2 H (OCH_2N); 8.02 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 10.84 (6-CH_3); 20.46, 20.49 (CH_3); 27.18 (CH_2); 40.58 (NCH_2); 54.03 (C-7); 61.57, 62.64 (CH_2OAc); 66.94 (CH_2O); 71.74 (OCH_2N); 115.32 (C-9a); 131.73 (C-6); 139.12 (CH-2); 145.89 (C-4a); 148.53 (C-3a); 152.54 (C-9); 170.06, 170.13 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-7-iodo-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**12**) was prepared from **8** (0.414 g, 80%) as a foam. UV (MeOH), λ_{max}: 231, 281, 293 (26 700, 13 200, 13 400). ^{1}H NMR (DMSO-d_6): 1.91 s, 3 H (CH_3); 1.96 s, 3 H (CH_3); 2.12 pent, *J* = 6.6, 2 H (CH_2); 3.73 m, 2 H (CH_2O); 4.02 t, *J* = 6.6, 2 H (CH_2OAc); 4.08–4.14 m, 4 H (CH_2OAc, NCH_2); 5.49 s, 2 H (OCH_2N); 7.69 s, 1 H (H-6); 8.03 s, 1 H (H-8). ^{13}C NMR (DMSO-d_6): 20.50 (2 × CH_3); 27.22 (CH_2); 42.22 (NCH_2); 52.39 (C-7); 61.38, 62.64 (CH_2OAc); 66.87 (CH_2O); 71.76 (OCH_2N); 115.25 (C-9a); 126.72 (CH-6); 139.31 (CH-2); 145.48 (C-4a); 149.27 (C-3a); 152.91 (C-9); 170.14, 170.19 (C=O).

3-[(2-Acetoxyethoxy)methyl]-6-methyl-5-[2-(4-nitrophenyl)ethyl]-
7-[(trimethylsilyl)ethynyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**13**)

A suspension of **9** (0.237 g, 0.4 mmol) in DMF (14 ml) was heated until clear solution was obtained. It was cooled to room temperature and purged with argon for 15 min. Then catalysts [$Pd(PPh_3)_4$] (46 mg, 0.04 mmol) and CuI (15 mg, 0.08 mmol) were added, followed by triethylamine (81 mg, 0.8 mmol) and ethynyltrimethylsilane (118 mg, 1.2 mmol). The reaction mixture was stirred for 20 h. The volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (40 ml) and extracted with 5% aqueous disodium EDTA (2 × 40 ml). The organic layer was washed with water (2 × 40 ml), separated and dried over anhydrous sodium sulfate. Then, the solution was filtered, concentrated in vacuo to a small volume and applied onto a silica gel (15–40 μm) column (30 g). Compound **13** was eluted with 1% of MeOH in CH_2Cl_2, affording 0.169 g (76%) as an oil. **13** was crystallized from ethanol to give yellow crystals m.p. 142–144 °C. UV (MeOH), λ_{max}: 236, 297, sh 306 (30 000, 25 700, 23 000). ^{1}H NMR (DMSO-d_6): 0.24 s, 9 H (TMS); 1.94 s, 3 H (CH_3); 2.21 s, 3 H (6-CH_3); 3.23 t, *J* = 6.6, 2 H (CH_2); 3.76 m, 2 H (CH_2O); 4.11 m, 2 H (CH_2OAc); 4.35 t, *J* = 6.6, 2 H (NCH_2); 5.50 s, 2 H (OCH_2N); 7.51 d, *J* = 8.7, 2 H (H-arom.); 8.05 s, 1 H (H-2); 8.14 d, *J* = 8.7, 2 H (H-arom.). ^{13}C NMR (DMSO-d_6): –0.30 (TMS); 9.39 (6-CH_3); 20.73 (CH_3); 33.73 (CH_2); 43.87 (NCH_2); 62.97 (CH_2OAc); 67.24 (CH_2O); 72.12 (OCH_2N); 93.43 (-C≡); 101.56

(C-7); 103.09 (≡C-); 116.42 (C-9a); 123.67, 130.61, 144.60 146.50 (C-arom.); 135.52 (C-6); 139.56 (CH-2); 146.61 (C-4a); 149.25 (C-3a); 151.99 (C-9); 170.44 (C=O). For $C_{52}H_{62}N_{12}O_{13}Si_2$ (2 M + H_2O; 1119.3) calculated: 55.79% C, 5.59% H, 15.02% N; found: 55.86% C, 5.71% H, 14.89% N.

3-[(2-Acetoxyethoxy)methyl]-5-[2-(4-nitrophenyl)ethyl]-7-[3-(trifluoroacetamido)prop-1-yn-1-yl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**14**)

A suspension of **10** (112 mg, 0.2 mmol) in DMF (10 ml) was heated until a clear solution was obtained. It was cooled to room temperature and purged with Ar for 15 min. Catalysts $[Pd(PPh_3)_4]$ (23 mg, 0.02 mmol) and CuI (7.5 mg, 0.04 mmol) were added, followed by triethylamine (40 mg, 0.4 mmol) and 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide (91 mg, 0.6 mmol). The reaction mixture was stirred for 18 h. The volatiles were removed in vacuo and the residue was dissolved in CH_2Cl_2 (30 ml) and extracted with 5% aqueous disodium EDTA (2 × 30 ml). Then the organic layer was washed with water (2 × 30 ml), separated and dried over anhydrous sodium sulfate. It was filtered, reduced to dryness and the residue, dissolved in toluene/EtOH 7:1, was applied onto a silica gel column (20 g). The product was eluted with the same solvent system. It afforded 83 mg of **14** as a powder (70%). Deiodinated compound **4** (8 mg, ≈10%) was isolated with a more polar (6:1) eluent. **14** was crystallized (EtOH/ethyl acetate 1:1) to give yellow crystals, m.p. 152 °C (dec.). UV (MeOH), λ_{max}: 232, 295 (28 600, 25 400). ^{1}H NMR (DMSO-d_6): 1.99 s, 3 H (CH_3); 3.30 t, *J* = 6.6, 2 H (CH_2); 3.73 m, 2 H (CH_2O); 4.10 m, 2 H (CH_2OAc); 4.31 d, *J* = 5.7, 2 H (CH_2); overlap. 4.36 t, *J* = 6.6, 2 H (NCH_2); 5.49 s, 2 H (OCH_2N); 7.49 d, *J* = 8.7, 2 H (H-arom.); 7.87 s, 1 H (H-6); 8.05 s, 1 H (H-2); 8.13 d, *J* = 8.7, 2 H (H-arom.); 10.14 t, *J* = 5.7, 1 H (NH). ^{13}C NMR (DMSO-d_6): 20.44 (CH_3); 29.62 (CH_2NH); 33.54 (CH_2); 45.30 (NCH_2); 62.64 (CH_2OAc); 66.88 (CH_2O); 71.83 (OCH_2N); 71.13 (-C≡); 90.67 (≡C-); 103.13 (C-7); 123.40, 130.06, 144.60, 145.98 (C-arom.); 115.71 q, *J*(C,F) = 288 (CF_3); 125.65 (CH-6); 139.41 (CH-2); 146.28 (C-4a); 149.42 (C-3a); 152.04 (C-9); 156.07 q, *J*(C,F) = 36 (C=O); 170.14 (C=O). For $C_{25}H_{22}F_3N_7O_7$ (589.5) calculated: 50.94% C, 3.76% H, 16.63% N; found: 50.59% C, 3.66% H, 16.59% N.

Desilylation of **13** to 3-[(2-Acetoxyethoxy)methyl]-7-ethynyl-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**15**)

A suspension of **13** (70 mg, 0.12 mmol) in dioxane (3 ml) and 25% aqueous ammonia (3 ml) dissolved to a clear solution on stirring (5 min) but it became heterogeneous in 1 h. The precipitated product was collected by filtration, washed with methanol, and dried to give 53 mg (93%) of **15** (dec. above 170 °C). UV (MeOH), λ_{max}: 233, 290. ^{1}H NMR (DMSO-d_6): 1.94 s, 3 H (CH_3); 2.19 s, 3 H (6-CH_3); 3.24 t, *J* = 6.6, 2 H (CH_2); 3.77 m, 2 H (CH_2O); 4.11 m, 2 H (CH_2OAc); 4.35 t, *J* = 6.6, 2 H (NCH_2); 4.72 s, 1 H (C≡CH); 5.51 s, 2 H (OCH_2N); 7.50 d, *J* = 8.7, 2 H (H-arom.); 8.05 s, 1 H (H-2); 8.14 d, *J* = 8.7, 2 H (H-arom.).

One-Pot Desilylation and Deacetylation of **13** to 7-Ethynyl-3-[(2-hydroxyethoxy)methyl]-5-[2-(4-nitrophenyl)ethyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**16**)

Compound **13** was dissolved in a mixture of methanol (19 ml), dioxane (38 ml) and DMSO (3.8 ml). The solution was treated with 25% aqueous ammonia (38 ml) and set aside at ambient temperature for 5 h. Only a single product was formed. Ammonia was evaporated in vacuo and the solution was concentrated to a small volume. The precipitated product was

collected by filtration, washed with cold water, and dried to give 110 mg (84%) of **16**, m.p. 171–174 °C (dec.). UV (MeOH), λ_{max}: 233, 290. ^{1}H NMR (DMSO-d_6): 2.20 s, 3 H (6-CH_3); 3.24 t, J = 6.6, 2 H (CH_2); 3.48–3.59 m, 4 H (CH_2O, CH_2OH); 4.35 t, J = 6.6, 2 H (NCH_2); 4.67 t, J = 6.0, 1 H exchangeable (OH); overlap. 4.68 s, 1 H (C≡CH); 5.50 s, 2 H (OCH_2N); 7.50 d, J = 8.7, 2 H (H-arom.); 8.03 s, 1 H (H-2); 8.14 d, J = 8.7, 2 H (H-arom.).

Deprotection of Compound **16**

1. Dried samples of **16** (5 mg, 0.012 mmol each) in Ar-purged flasks were dissolved in pyridine/DMSO (2:1, 300 µl), (3:1, 200 µl), pyridine/DMF (2:1, 200 µl), (3:1, 250 µl) were treated with DBU (10 equiv., 18 mg) and kept under Ar at ambient temperature for 10 h. The reactions were quenched with 99.9% acetic acid (10 equiv.) at 0 °C, then the solutions were evaporated in vacuo and checked by TLC in $CHCl_3$/MeOH 4:1, the same system containing 0.5% Et_3N and in acetone/water 7:3 or acetonitrile (RP plates). TLC revealed the absence of **16** and the presence of 4-nitrostyrene as a predominant component of the mixture which contained many unidentified products.

2. Compound **16** (5 mg, 0.012 mmol) dissolved in DMF (200 µl) was treated with DBU (3 equiv., 4.5 mg). The reaction was kept under Ar at 20 °C for 2 days. According to TLC, the progress was very slow and the reaction led to many unidentified products.

Elimination of 5-[2-(4-Nitrophenyl)ethyl] Group from Compound **2**

A solution of **2** (11 mg, 0.024 mmol) in 0.14 M solution of DBU in DMF (0.51 ml, 3 equiv. DBU) was heated at 60 °C under Ar for 4 h. The reaction mixture was cooled to 0 °C and 99.9% acetic acid (6 equiv.) was added. Traces of unreacted **2** remained in the solution which was evaporated in vacuo to an oily residue. Compound **1** was isolated by PLC with $CHCl_3$/MeOH 4:1 in 5 mg yield (70%).

3-[(2-Acetoxyethoxy)methyl]- 6-methyl-7-[(trimethylsilyl)ethynyl]-3,9-dihydro-5*H*-imidazo[1,2-*a*]purine-9-one (**17**)

1. To a stirred solution of **13** (0.190 g, 0.35 mmol) in anhydrous pyridine (3 ml) under Ar, 7 equiv. of DBU (0.380 g, 2.44 mmol) were added. The reaction was conducted at 20 °C for 16 h. TLC ($CHCl_3$/MeOH 95:5) revealed the presence of 4-nitrostyrene and a single product, while all the starting material was consumed. The reaction mixture was cooled to 0 °C and treated with 99.9% acetic acid (14 equiv., 4.9 mmol, 0.294 g). The solution was diluted with CH_2Cl_2 (40 ml) and washed with 10% aqueous acetic acid (30 ml) and then with water (40 ml). The organic layer was separated, evaporated in vacuo, and co-evaporated with toluene (3 × 25 ml). The residue was extracted with hexanes and hexanes/diethyl ether 2:1 (2 × 20 ml each) to remove 4-nitrostyrene. Then, it was applied onto silica gel plates and developed twice in CH_2Cl_2/EtOH 9:1 at 4 °C. During the separation, partial decomposition of compound **17** was observed. The silica gel from UV absorbing zones was collected, the product was eluted with the same eluent and evaporated in vacuo. This yielded 40 mg (29%) of **17** as a homogeneous in TLC solid. ^{1}H NMR (DMSO-d_6): 0.24 s, 9 H (TMS); 1.94 s, 3 H (CH_3); 2.27 s, 3 H (6-CH_3); 3.69 m, 2 H (CH_2OAc); 4.06 m, 2 H (CH_2O); 5.46 s, 2 H (OCH_2N); 8.02 s, 1 H (H-2); 12.84 s, 1 H (NH). ^{13}C NMR (DMSO-d_6): –0.16 (TMS); 10.13 (6-CH_3); 20.51 (CH_3); 62.69 (CH_2OAc); 66.71 (CH_2O); 72.04 (OCH_2N); 93.52 (-C≡); 102.24 (≡C-); 101.69 (C-7); 116.12 (C-9a); 134.37 (C-6); 139.16 (CH-2); 145.05 (C-4a); 149.45 (C-3a);

151.93 (C-9); 170.19 (C=O). HR LSIMS found: 402.1598; $C_{18}H_{24}N_5O_4Si$ $[M + H]^+$ requires: 402.1597.

2. To a solution of **13** (63 mg, 0.11 mmol) in anhydrous pyridine (1 ml) DBU (7 equiv., 0.123 g, 0.8 mmol) was added and the reaction was kept under Ar at 20 °C for 20 h. TLC ($CHCl_3$/MeOH 95:5) revealed the presence of 4-nitrostyrene and a single product, while all the starting material was consumed. The mixture was cooled to 0 °C and treated with 99.9% acetic acid (14 equiv., 96 mg, 1.6 mmol). The solution was diluted with CH_2Cl_2 (10 ml) and washed with 10% AcOH and with water (10 ml each). The organic layer was separated, evaporated in vacuo and the residue was washed with toluene to remove 4-nitrostyrene. The residue was dissolved in acetonitrile and applied onto a silanized silica gel column (0.063–0.200 mm, 5 g). The product was eluted with the same solvent to give 33 mg (75%) of **17** as a pale yellow solid (darkening above 49 °C). LSIMS, *m/z* (rel.%): 402 (58) $[M + H]^+$. UV (MeOH), λ_{max}: 235, 259, 295, sh 305 (32 100, 10 800, 22 000, 19 500).

3-[(2-Acetoxyethoxy)methyl]-7-acetyl-6-methyl-3,9-dihydro-5*H*-imidazo[1,2-*a*]purin-9-one (**18**)

Compound **17** (19 mg) obtained in procedure *1* was dissolved in DMSO-d_6 and directly used in an NMR experiment. According to ^{1}H NMR spectrum, the solution contained 2.6 equiv. of H_2O. ^{13}C NMR spectra, both decoupled and coupled, were measured. The decoupled spectrum presented the signals corresponding to **17** (as described above), while the latter spectrum indicated the presence of two compounds. After two days, a single compound persisted in the examined solution. Finally, ^{1}H and ^{13}C HETCOR spectra allowed to establish the structure of compound **18**. ^{1}H NMR: 1.96 s, 3 H (OAc: CH_3); 2.29 s, 3 H (6-CH_3); 2.42 (7-Ac: CH_3); 3.72 m, 2 H (CH_2O); 4.08 m, 2 H (CH_2OAc); 5.52 s, 2 H (OCH_2N); 8.10 s, 1 H (H-2); 12.54 brs, 1 H (NH). ^{13}C NMR: 10.56 (6-CH_3); 20.52 (OAc: CH_3); 31.74 (7-Ac: CH_3); 62.70 (CH_2OAc); 66.71 (CH_2O); 72.12 (OCH_2N); 116.59 (C-9a); 119.90 (C-7); 132.90 (C-6); 139.50 (CH-2); 145.75 (C-4a); 149.69 (C-3a); 170.44 (C=O); 190.44 (7-Ac: C=O). LSIMS, *m/z* (rel.%): 348 (52) $[M + H]^+$.

Alkynylation of 7-Iodo-TACV Derivatives. General Procedure

A solution of **11** or **12** (0.5 mmol) in DMF (12 ml) was purged with Ar for 15 min. Then, the catalysts $[Pd(PPh_3)_4]$ (58 mg, 0.05 mmol) and CuI (19 mg, 0.1 mmol) were added, followed by triethylamine (101 mg, 1 mmol) and an alkyne (1.5 mmol). The reaction mixture was monitored by TLC (toluene/ethanol 7:1, ethyl acetate/ethanol 9:1) and stirred for 8–24 h. Volatiles were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (50 ml). The solution was extracted with 5% aqueous disodium EDTA (2 × 60 ml) and then washed with water (2 × 60 ml). The organic layer was separated, dried over anhydrous sodium sulfate, then filtered and the solution was evaporated in vacuo. The 7-alkynylated product was subsequently isolated from the residue by chromatography.

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-6-methyl-7-[(trimethylsilyl)ethynyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**19a**). Compound **19a** was prepared from **11** by the reaction with ethynyltrimethylsilane. It was purified on a silica gel column (30 g) with toluene/ethanol 7:1 to give a pale yellow glass (0.193 g, 77%). ^{1}H NMR (DMSO-d_6): 0.26 s, 9 H (TMS); 1.93, 1.95 2 × s, 6 H (2 × CH_3); 2.15 pent, J = 6.6, 2 H (CH_2); 2.38 s, 3 H (6-CH_3); 3.75 m, 2 H (CH_2O); 4.04 t, J = 6.6, 2 H (CH_2OAc); overlap. 4.10 m, 2 H (CH_2OAc); overlap.

4.16 t, *J* = 6.6, 2 H (NCH_2); 5.50 s, 2 H (OCH_2N); 8.05 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): –0.26 (TMS); 9.17 (6-CH_3); 20.44, 20.38 (CH_3); 26.94 (CH_2); 40.02 (NCH_2); 61.38, 62.59 (CH_2OAc); 71.84 (OCH_2N); 93.25 (-C≡); 101.35 (C-7); 102.75 (≡C-); 116.09 (C-9a); 135.42 (C-6); 139.26 (CH-2); 144.48 (C-4a); 149.07 (C-3a); 151.70 (C-9); 170.09, 170.13 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-6-methyl-7-(phenylethynyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**19b**). Compound **19b** was prepared from **11** by the reaction with phenylacetylene. It was purified on a silica gel column (30 g) with toluene/ethanol 7:1 to give an off-white solid (0.220 g, 87%), m.p. 130–134 °C. ^1H NMR (DMSO-d_6): 1.93, 1.95 2 × s, 6 H (2 × CH_3); 2.11 pent, *J* = 6.6, 2 H (CH_2); 2.47 s, 3 H (6-CH_3); 3.75 m, 2 H (CH_2O); 4.07 t, *J* = 6.6, 2 H (CH_2OAc); overlap. 4.10 m, 2 H (CH_2OAc); 4.19 t, *J* = 6.6, 2 H (NCH_2); 5.52 s, 2 H (OCH_2N); 7.42–7.49 m, 3 H (H-arom.); 7.53–7.57 m, 2 H (H-arom.); 8.07 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.32 (6-CH_3); 20.45, 20.50 (CH_3); 27.04 (CH_2); 40.33 (NCH_2); 61.51, 62.66 (CH_2OAc); 66.99 (CH_2O); 71.90 (OCH_2N); 78.40 (-C≡); 96.61 (≡C-); 101.30 (C-7); 116.20 (C-9a); 122.53, 128.57, 128.73, 130.66 (C-arom.); 134.15 (C-6); 139.35 (CH-2); 144.78 (C-4a); 149.20 (C-3a); 151.97 (C-9); 170.17, 170.20 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-6-methyl-7-[3-(trifluoroacetamido)prop-1-yn-1-yl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**19c**). Compound **19c** was prepared from **11** by the reaction with 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide. It was purified by chromatography on a silica gel column (30 g) with ethyl acetate/ethanol 9:1 to give a light brown oil (0.215 g, 77%). ^1H NMR (DMSO-d_6): 1.91, 1.95 2 × s, 6 H (2 × CH_3); 2.08 pent, *J* = 6.6, 2 H (CH_2); 2.37 s, 3 H (6-CH_3); 3.74 m, 2 H (CH_2O); 4.04 t, *J* = 6.6, 2 H (CH_2OAc); overlap. 4.09 m, 2 H (CH_2OAc); overlap. 4.15 t, *J* = 6.6, 2 H (NCH_2); 4.35 d, *J* = 5.7, 2 H (CH_2); 5.50 s, 2 H (OCH_2N); 8.05 (H-2); 10.15 t, *J* = 5.7, 1 H (NH). ^{13}C NMR (DMSO-d_6): 9.04 (6-CH_3); 20.42, 20.49 (CH_3); 26.98 (CH_2); 29.88 (CH_2NH); 40.33 (NCH_2); 61.51, 62.65 (CH_2OAc); 66.98 (CH_2O); 71.38 (-C≡); 71.89 (OCH_2N); 92.41 (≡C-); 100.66 (C-7); 115.79 q, *J*(C,F) = 289 (CF_3); 116.04 (C-9a); 134.94 (C-6); 139.29 (CH-2); 144.63 (C-4a); 149.19 (C-3a); 151.79 (C-9); 156.11 q, *J*(C,F) = 36 (C=O); 170.14, 170.19 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-6-methyl-7-[(4-methylphenyl)ethynyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**19d**). Compound **19d** was prepared from **11** by the reaction with ethynyl-4-methylbenzene. It was purified on a silica gel column (25 g) with toluene/ethanol 9:1 to give an off-white solid (0.217 g, 83%), m.p. 137–140 °C. ^1H NMR (DMSO-d_6): 1.93, 1.96 2 × s, 6 H (2 × CH_3); 2.10 pent, *J* = 6.6, 2 H (CH_2); 2.35 s, 3 H (CH_3); 2.45 s, 3 H (6-CH_3); 3.75 m, 2 H (CH_2O); 4.06 t, *J* = 6.6, 2 H (CH_2OAc); overlap. 4.10 m, 2 H (CH_2OAc); 4.19 t, *J* = 6.6, 2 H (NCH_2); 5.51 s, 2 H (OCH_2N); 7.25 d, *J* = 8.1, 2 H (H-arom.); 7.43 d, *J* = 8.1, 2 H (H-arom.); 8.06 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.31 (6-CH_3); 20.46, 20.52 (CH_3); 21.04 (CH_3); 27.05 (CH_2); 40.33 (NCH_2); 61.52, 62.68 (CH_2OAc); 67.00 (CH_2O); 71.90 (OCH_2N); 77.72 (-C≡); 96.74 (≡C-); 101.47 (C-7); 116.18 (C-9a); 119.53, 129.35, 130.62, 138.37 (C-arom.); 133.79 (C-6); 139.35 (CH-2); 144.76 (C-4a); 149.20 (C-3a); 151.99 (C-9); 170.19, 170.23 (C=O).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-7-[(trimethylsilyl)ethynyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**21a**). Compound **21a** was prepared from **12** by the reaction with ethynyltrimethylsilane. It was purified by chromatography on a silica gel column (30 g) with a gradient of EtOH (0–7%) in CH_2Cl_2 to give a yellow oil (0.195 g, 40%). ^1H NMR (DMSO-d_6): 0.25 s, 9 H (TMS); 1.92, 1.96 2 × s, 6 H (2 × CH_3); 2.12 pent, *J* = 6.6, 2 H (CH_2); 3.73 m, 2 H (CH_2O); 4.02 t, *J* = 6.6, 2 H (CH_2OAc); 4.08–4.15 m, 4 H (CH_2OAc, NCH_2); 5.51 s, 2 H (OCH_2N); 7.99 s, 1 H (H-6); 8.07 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): –0.41 (TMS); 20.40, 20.49 (CH_3); 27.05 (CH_2); 42.13 (NCH_2); 61.15, 62.60 (CH_2OAc); 66.84 (CH_2O); 71.86

(OCH_2N); 93.11 (-C≡); 101.01 (≡C-); 103.81 (C-7); 115.97 (C-9a); 126.32 (CH-6); 139.39 (CH-2); 144.70 (C-4a); 149.45 (C-3a); 152.08 (C-9); 170.11, 170.13 (C=O).

A second, more polar product **8**, was eluted with 7% EtOH in CH_2Cl_2 (94 mg, 48%).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-7-(phenylethynyl)-3,9-dihydro-5H-imidazo-[1,2-a]purin-9-one (**21b**). Compound **21b** was prepared from **12** by the reaction with phenylacetylene. It was purified on a silica gel column (25 g) with toluene/ethanol 7:1 to give an yellow oil (0.167 g, 68%). ^{1}H NMR (DMSO-d_6): 1.93, 1.96 2 × s, 6 H (2 × CH_3); 2.16 pent, J = 6.6, 2 H (CH_2); 3.75 m, 2 H (CH_2O); 4.02 t, J = 6.6, 2 H (CH_2OAc); overlap. 4.09–4.19 m, 4 H (CH_2OAc, NCH_2); 5.52 s, 2 H (OCH_2N); 7.44–7.48 m, 3 H (H-arom.); 7.53–7.56 m, 2 H (H-arom.); 8.04 s, 1 H (H-6); 8.08 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 20.49, 20.53 (CH_3); 27.13 (CH_2); 42.28 (NCH_2); 61.28, 62.68 (CH_2OAc); 66.93 (CH_2O); 71.92 (OCH_2N); 78.48 (-C≡); 94.70 (≡C-); 103.85 (C-7); 116.09 (C-9a); 122.23, 128.82, 128.85, 130.80 (C-arom.); 125.26 (CH-6); 139.53 (CH-2); 144.96 (C-4a); 149.61 (C-3a); 152.36 (C-9); 170.21 (2 × C=O).

A second, more polar product **8**, was eluted with the same solvent system (20 mg, 10%).

3-[(2-Acetoxyethoxy)methyl]-5-(3-acetoxypropyl)-7-[3-(trifluoroacetamido)prop-1-yn-1-yl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**21c**). Compound **21c** was prepared from **12** by the reaction with 2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide. It was purified by chromatography on a silica gel column (30 g) with ethyl acetate/ethanol 9:1 to give a cream powder (0.189 g, 70%), dec. above 132 °C. ^{1}H NMR (DMSO-d_6): 1.90, 1.95 2 × s, 6 H (2 × CH_3); 2.12 pent, J = 6.6, 2 H (CH_2); 3.73 m, 2 H (CH_2O); 4.02 t, J = 6.6, 2 H (CH_2OAc); 4.09 m, 2 H (CH_2OAc); overlap. 4.13 t, J = 6.6, 2 H (NCH_2); 4.33 d, J = 5.7, 2 H (CH_2); 5.50 s, 2 H (OCH_2N); 7.96 s, 1 H (H-6); 8.07 (H-2); 10.16 t, J = 5.7, 1 H (NH). ^{13}C NMR (DMSO-d_6): 20.46, 20.54 (CH_3); 27.13 (CH_2); 29.71 (CH_2NH); 42.24 (NCH_2); 61.29, 62.67 (CH_2OAc); 66.92 (CH_2O); 71.91 (OCH_2N); 71.32 (-C≡); 90.65 (≡C-); 103.23 (C-7); 115.93 q, J(C,F) = 288 (CF_3); 116.01 (C-9a); 126.04 (CH-6); 139.49 (CH-2); 144.84 (C-4a); 149.60 (C-3a); 152.18 (C-9); 156.14 q, J(C,F) = 36 (C=O); 170.19, 170.23 (C=O).

A second, more polar product **8**, was eluted with the same solvent system (29 mg, 15%).

Deprotection of Compounds **19a**, **19b**, **19d**, **21a**, **21b**. General Procedure

A suspension of 7-alkynylated compound (0.3 mmol) in MeOH saturated with NH_3 (12 ml) was stirred at room temperature overnight. According to TLC ($CHCl_3$/MeOH 6:1), it afforded a single polar product. The solution was evaporated in vacuo and the residue was chromatographed on a silica gel column (15 g) with $CHCl_3$/MeOH 6:1 as eluent.

7-Ethynyl-3-[(2-hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-3,9-dihydro-5H-imidazo-[1,2-a]purin-9-one (**20a**) homogeneous in TLC: 99 mg (86%); white microcrystals (aqueous propan-2-ol), m.p. 198 °C (dec.). UV (MeOH), λ_{max}: 234, 293 (31 200, 20 000). ESIMS, *m/z* (rel.%) ES^+: 346 (26) $[M + H]^+$, 368 (53) $[M + Na]^+$; ES^-: 380 (100) $[M + Cl]^-$. ^{1}H NMR (DMSO-d_6): 1.90 pent, J = 6.6, 2 H (CH_2); 2.40 s, 3 H (6-CH_3); 3.40–3.57 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.12 t, J = 6.6, 2 H (NCH_2); 4.64 t, J = 4.8, 1 H (OH); 4.69 t, J = 5.1, 1 H (OH); 4.73 s, 1 H (C≡CH); 5.50 s, 2 H (OCH_2N); 8.05 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.10 (6-CH_3); 30.77 (CH_2); 40.23 (NCH_2); 57.67, 59.84 (CH_2OH); 70.85 (CH_2O); 72.13 (CH_2N); 72.25 (-C≡); 88.72 (≡CH); 100.56 (C-7); 116.04 (C-9a); 135.47 (C-6); 139.32 (CH-2); 144.45 (C-4a); 149.22 (C-3a); 151.85 (C-9). For $C_{16}H_{19}N_5O_4$ (345.4) calculated: 55.65% C, 5.55% H, 20.28% N; found: 55.62% C, 5.48% H, 20.38% N.

3-[(2-Hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-7-(phenylethynyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**20b**) homogeneous in TLC: 0.131 g (93%); white microcrystals

(ethanol/$CHCl_3$ 2:1), m.p. 202 °C (dec.). UV (MeOH), λ_{max}: 237, 315, 333 (41 000, 29 200, 27 800). ESIMS, *m/z* (rel.%) ES^+: 422 (22) $[M + H]^+$, 444 (66) $[M + Na]^+$; ES^-: 456 (100) $[M + Cl]^-$. ^1H NMR (DMSO-d_6): 1.93 pent, *J* = 6.6, 2 H (CH_2); 2.48 s (6-CH_3) overlap. with DMSO-d_5; 3.41–3.58 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.15 t, *J* = 6.6, 2 H (NCH_2); overlap. 4.64, 4.69 2 × t, *J* = 4.8, 5.1, 2 H (2 × OH); 5.51 s, 2 H (OCH_2N); 7.41–7.48 m, 3 H (H-arom.); 7.53–7.57 m, 2 H (H-arom.); 8.06 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.37 (6-CH_3); 30.79 (CH_2); 40.31 (NCH_2); 57.70, 59.86 (CH_2OH); 70.89 (CH_2O); 72.17 (CH_2N); 78.57 (-C≡); 96.52 (≡C-); 101.06 (C-7); 116.23 (C-9a); 122.60, 128.54, 128.74, 130.05 (C-arom.); 134.45 (C-6); 139.38 (CH-2); 144.61 (C-4a); 149.20 (C-3a); 152.03 (C-9). For $C_{22}H_{23}N_5O_4$ (421.5) calculated: 62.70% C, 5.50% H, 16.62% N; found: 62.66% C, 5.37% H, 16.42% N.

3-[(2-Hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-7-[(4-methylphenyl)ethynyl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**20d**) homogeneous in TLC: 0.139 g (96%); white microcrystals (ethanol/$CHCl_3$ 2:1), m.p. 207 °C (dec.). UV (MeOH), λ_{max}: 238, 314, 333 (43 000, 31 400, 29 400). ESIMS, *m/z* (rel.%) ES^+: 436 (86) $[M + H]^+$, 458 (100) $[M + Na]^+$; ES^-: 434 (22) $[M - H]^-$, 470 (100) $[M + Cl]^-$. ^1H NMR (DMSO-d_6): 1.92 pent, *J* = 6.6, 2 H (CH_2); 2.35 s, 3 H (CH_3); 2.46 s, 3 H (6-CH_3); 3.42–3.58 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.15 t, *J* = 6.6, 2 H (NCH_2); 4.64, 4.70 2 × t, *J* = 4.8, 5.1, 2 H (2 × OH); 5.51 s, 2 H (OCH_2N); 7.75 d, *J* = 8.1, 2 H (H-arom.); 7.43 d, *J* = 8.1, 2 H (H-arom.); 8.05 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 9.34 (6-CH_3); 21.03 (CH_3); 30.80 (CH_2); 40.27 (NCH_2); 57.69, 59.85 (CH_2OH); 70.88 (CH_2O); 72.15 (CH_2N); 77.86 (-C≡); 96.63 (≡C-); 101.21 (C-7); 116.19 (C-9a); 119.59, 129.34, 130.60, 138.31 (C-arom.); 134.05 (C-6); 139.33 (CH-2); 144.58 (C-4a); 149.19 (C-3a); 152.03 (C-9). For $C_{23}H_{25}N_5O_4$ (435.5) calculated: 63.44% C, 5.79% H, 16.08% N; found: 63.49% C, 5.75% H, 15.99% N.

7-Ethynyl-3[(2-hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**22a**) homogeneous in TLC: 97 mg (88%); white microcrystals (aqueous propan-2-ol), m.p. 188 °C (dec.). UV (MeOH), λ_{max}: 232, 256, 296 (30 900, 4300, 23 200). ESIMS, *m/z* (rel.%) ES^+: 332 (8) $[M + H]^+$, 354 (73) $[M + Na]^+$; ES^-: 330 (27) $[M - H]^-$, 366 (100) $[M + Cl]^-$. ^1H NMR (DMSO-d_6): 1.95 pent, *J* = 6.6, 2 H (CH_2); 3.41–3.57 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.11 t, *J* = 6.6, 2 H (NCH_2); 4.62 m, 2 H (OH, C≡CH); 4.69 t, *J* = 5.1, 1 H (OH); 5.50 s, 2 H (OCH_2N); 7.96 s (H-6); 8.06 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 30.90 (CH_2); 42.33 (NCH_2); 57.60, 59.77 (CH_2OH); 70.75 (CH_2O); 72.10 (OCH_2N); 72.18 (-C≡); 86.98 (≡CH); 103.07 (C-7); 115.85 (C-9a); 126.34 (CH-6); 139.41 (CH-2); 144.61 (C-4a); 149.54 (C-3a); 152.11 (C-9). For $C_{15}H_{17}N_5O_4$ (331.3) calculated: 54.38% C, 5.17% H, 21.14% N; found: 54.23% C, 5.20% H, 21.05% N.

3-[(2-Hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-7-(phenylethynyl)-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**22b**) homogeneous in TLC: 0.125 g (92%); white microcrystals (MeOH/$CHCl_3$ 2:1), dec. above 120 °C. UV (MEOH), λ_{max}: 235, 314, 332 (39 500, 30 800, 29 450). ESIMS, *m/z* (rel.%) ES^+: 408 (8) $[M + H]^+$, 430 (46) $[M + Na]^+$; ES^-: 406 (13) $[M - H]^-$, 442 (100) $[M + Cl]^-$. ^1H NMR (DMSO-d_6): 1.97 pent, *J* = 6.6, 2 H (CH_2); 3.43–3.58 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.14 t, *J* = 6.6, 2 H (NCH_2); overlap. 4.65, 4.70 2 × t, *J* = 5.1, 5.6, 2 H (2 × OH); 5.52 s, 2 H (OCH_2N); 7.44–7.47 m, 3 H (H-arom.); 7.53–7.56 m, 2 H (H-arom.); 8.00 s, 1 H (H-6); 8.07 s, 1 H (H-2). ^{13}C NMR (DMSO-d_6): 30.97 (CH_2); 42.44 (NCH_2); 57.66, 59.85 (CH_2OH); 70.84 (CH_2O); 72.19 (OCH_2N); 78.62 (-C≡); 94.64 (≡C-); 103.66 (C-7); 116.09 (C-9a); 122.28, 128.79 (2C); 130.78 (C-arom.); 125.34 (CH-6); 139.53 (CH-2); 144.82 (C-4a); 149.60 (C-3a); 152.38 (C-9). For $C_{21}H_{21}N_5O_4$ (407.4) calculated: 61.91% C, 5.20% H, 17.19% N; found: 61.95% C, 5.01% H, 17.22% N.

Deprotection of Compounds **19c**, **21c**. General Procedure

The compound (0.3 mmol) was dissolved in absolute methanol (10 ml) and treated with 1 M solution of NaOMe in methanol (100 µl, 0.1 mmol). The reaction mixture was stored at room temperature overnight. According to TLC ($CHCl_3$/MeOH 6:1), a starting material was consumed. The reaction mixture was cooled to 0 °C and its pH was adjusted to 4.5 with 99.9% acetic acid (15 µl). The solution was evaporated in vacuo and the obtained solid was purified on a silica gel column (15 g) to give products **20c** or **22c**, respectively.

3-[(2-Hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-6-methyl-7-[3-(trifluoroacetamido)prop-1-yn-1-yl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**20c**) homogeneous in TLC: 0.129 g (82%); white crystals (ethanol/$CHCl_3$ 2:1), m.p. 195 °C (dec.). UV (MeOH), λ_{max}: 235, 296 (31 700, 21 500). ESIMS, *m/z* (rel.%) ES^+: 471 (11) $[M + H]^+$, 493 (100) $[M + Na]^+$; ES^-: 469 (100) $[M - H]^-$, 505 (62) $[M + Cl]^-$. ^{1}H NMR (DMSO-d_6): 1.89 pent, *J* = 6.6, 2 H (CH_2); 2.39 s, 3 H (6-CH_3); 3.40–3.57 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.12 t, *J* = 6.6, 2 H (NCH_2); 4.35 s, 2 H (CH_2NH); 4.62 t, *J* = 4.8, 1 H (OH); 4.68 t, *J* = 5.4, 1 H (OH); 5.50 s, 2 H (OCH_2N); 8.04 s, 1 H (H-2); 10.15 brs, 1 H (NH). ^{13}C NMR (DMSO-d_6): 9.04 (6-CH_3); 29.88 (CH_2NH); 30.72 (CH_2); 40.23 (NCH_2); 57.65, 59.83 (CH_2OH); 70.83 (CH_2O); 71.52 (-C≡); 72.13 (OCH_2N); 92.25 (≡C-); 100.40 (C-7); 115.85 q, *J*(C,F) = 288 (CF_3); 116.04 (C-9a); 135.16 (C-6); 139.26 (CH-2); 144.44 (C-4a); 149.17 (C-3a); 151.81 (C-9); 156.12 q, *J*(C,F) = 36 (C=O). ^{19}F NMR (DMSO-d_6): 1.83 (CF_3). For $C_{38}H_{44}F_6N_{12}O_{11}$ (2 M + H_2O; 958.8) calculated: 47.60% C, 4.63% H, 17.53% N; found: 47.99% C, 4.67% H, 17.26% N.

3-[(2-Hydroxyethoxy)methyl]-5-(3-hydroxypropyl)-7-[3-(trifluoroacetamido)prop-1-yn-1-yl]-3,9-dihydro-5H-imidazo[1,2-a]purin-9-one (**22c**) homogeneous in TLC: 0.131 g (86%); white crystals (ethanol/$CHCl_3$ 2:1), m.p. 180 °C (dec.). UV (MeOH), λ_{max}: 232, 297 (29 200, 23 000). ESIMS, *m/z* (rel.%) ES^+: 457 (7) $[M + H]^+$, 479 (100) $[M + Na]^+$; ES^-: 455 (68) $[M - H]^-$, 491 (100) $[M + Cl]^-$. ^{1}H NMR (DMSO-d_6): 1.94 pent, *J* = 6.6, 2 H (CH_2); 3.40–3.56 m, 6 H (2 × C**H**$_2$OH, CH_2O); 4.10 t, *J* = 6.6, 2 H (NCH_2); 4.33 s, 2 H (CH_2NH); 4.62 t, *J* = 5.1, 1 H (OH); 4.68 t, *J* = 5.7, 1 H (OH); 5.50 s, 2 H (OCH_2N); 7.92 s, 1 H (H-6); 8.06 s, 1 H (H-2); 10.16 brs, 1 H (NH). ^{13}C NMR (DMSO-d_6): 29.69 (CH_2NH); 30.93 (CH_2); 42.37 (NCH_2); 57.64, 59.84 (CH_2OH); 70.80 (CH_2O); 71.42 (-C≡); 72.16 (OCH_2N); 90.54 (≡C-); 103.04 (C-7); 115.77 q, *J*(C,F) = 288 (CF_3); 115.92 (C-9a); 126.06 (CH-6); 139.43 (CH-2); 144.68 (C-4a); 149.56 (C-3a); 152.17 (C-9); 156.12 q, *J*(C,F) = 36 (C=O). ^{19}F NMR (DMSO-d_6): 1.89 (CF_3). For $C_{18}H_{19}F_3N_6O_5$ (456.4) calculated: 47.37% C, 4.20% H, 18.41% N; found: 47.40% C, 4.23% H, 18.22% N.

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