Synthesis and Biological Activity of Strongly Fluorescent Tricyclic Analogues of Acyclovir and Ganciclovir

Tomasz Goslinski,[†] Bozenna Golankiewicz,*,[†] Erik De Clercq,[‡] and Jan Balzarini[‡]

Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznań, Poland, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

In search of strongly fluorescent tricyclic analogues of acyclovir (ACV, **1**) and ganciclovir (GCV, **2**), derivatives of the 3,9-dihydro-9-oxo-5*H*-imidazo[1,2-*a*]purine system, several 6-[4-(acyloxy)-phenyl], 6-[4-(acylamino)phenyl], and 6-[4-(phenoxycarbonyloxy)phenyl]-substituted TACV and TGCV analogues were synthesized and evaluated for their activity against herpes simplex virus types 1 and 2 in cell culture. All TACV and TGCV analogues showed strong fluorescence (quantum yield of 30−65% vs 2-aminopurine 100%). The 6-[4-(phenoxycarbonyloxy)phenyl]-substituted compounds **11** and **19** displayed the best combination of the fluorescence and antiviral potency.

We have previously reported the alkylation−condensation reaction of acyclovir (ACV, **1**) and ganciclovir (GCV, **2**) with phenacyl bromide, transforming **1** and **2** into their tricyclic derivatives 3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-6-phenyl-5*H*-imidazo[1,2-*a*]purine (6-Ph-TACV, **3**) and 3,9-dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-9-oxo-6-phenyl-5*H*-imidazo[1,2-*a*]-purine (6-Ph-TGCV, **4**), respectively.[1] The activity of compound **4** against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), thymidine kinase deficient (TK−) HSV-1, and varicella-zoster virus (VZV) was very similar to that of the parent ganciclovir, while compound **3** was on average approximately 15-fold less active than the parent acyclovir.[1] Both compounds are intrinsically fluorescent (quantum yield of ∼8% of that of 2-aminopurine), which makes them promising for application in the noninvasive diagnosis of herpes virus infections.

Our recent structure−activity studies on a series of diverse 6-aryl-substituted TACV and TGCV analogues led to the finding of 6-(4-MeOPh)-substituted derivatives **5** and **6** showing higher antiviral potency than **3** and **4**. However, the observed increase in antiviral potency of **5** and **6** was not accompanied by an increase in fluorescence intensity, the quantum yield remaining below 10%.[2] The aforementioned study has also demonstrated that the tolerance of the 6-aryl substituent to modifications is quite low and only variations in the 4 (para) position of the phenyl ring seem to be permitted.

We envisioned that introduction of an ester or amide group at this position may enhance the intensity of fluorescence. In the present paper, we describe the synthesis and evaluation of the antiherpetic activity of a series of strongly fluorescent tricyclic analogues derived from 6-(4-HOPh)-TACV, 6-(4-H$_2$NPh)-TACV, and their ganciclovir (TGCV) counterparts.

We also anticipated that the ester derivatives may be split by esterases into the parental substituted TACV or TGCV analogues. While in this case their fluorescence may be reduced to the level of the weakly fluorescent 6-(4-HOPh)-substituted compounds, they could still be of interest because they might serve as prodrugs of parent compounds. They would then constitute a new type of prodrug that, in contrast to the majority of the prodrugs of acyclovir and ganciclovir,[3] would not be blocked at the side chain hydroxy group involved in phosphorylation and would be crucial for converting this class of compounds to their antivirally active metabolites.
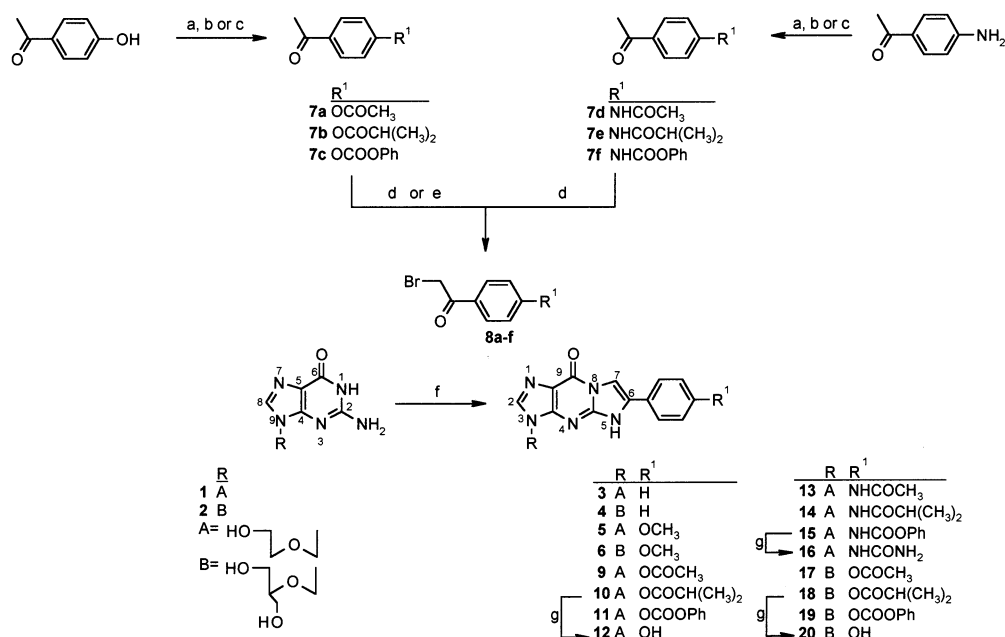
Chemistry

The synthesis of the 6-(4-R^{1}Ph)-substituted tricyclic analogues of acyclovir **9**−**16** and ganciclovir **17**−**20** is depicted in Scheme 1. The yields of their preparation, physical properties, and fluorescence characteristics are given in Table 1.

The tricyclic analogues incorporating the ester or amide functions were prepared by reacting the 1-sodium derivative of acyclovir or ganciclovir with an appropriate bromo ketone according to a previously described method for an alkylation−condensation reaction using simple bromo ketones.[1,2,4] The synthesis of the bromo ketones started from treatment of either 4-hydroxyacetophenone or 4-aminoacetophenone in pyridine with acylating agent (i.e., acetic anhydride, isobutyric anhydride, or phenylchloroformate) to give 4-acyloxy (**7a**−**c**) or 4-acylamino (**7d**−**f**) acetophenones, respectively, in over 85% yield. With the exception of **7c**, the following compounds were obtained previously by diverse methods: **7a**,**b**,[5] **7d**,[6] **7e**,[7] **7f**.[8] For the bromination procedures to be convenient for converting **7a**−**f** into the desired 4-substituted phenacyl bromides **8a**−**f** (of which only **8a**[9] and **8d**[6] were reported so far), literature approaches[6,10,11] were explored. 4-Acyloxyphenacyl bromides could be prepared either by reaction of **7a**−**c** with bromine in tetrahydrofurane solution in the presence of catalytic amounts of aluminum chloride[6] or in a heterogeneous system consisting of copper(II) bromide in chloroform−ethyl acetate.[11] The second method was more selective; the first one was less time-consuming and did not

* To whom correspondence should be addressed. Phone: 4861 8528503. Fax: 4861 8520532. E-mail: bogolan@ibch.poznan.pl.
  † Polish Academy of Sciences.
  ‡ Katholieke Universiteit Leuven.

Scheme 1[a]

R[1]
7a OCOCH$_3$
7b OCOCH(CH$_3$)$_2$
7c OCOOPh

R[1]
7d NHCOCH$_3$
7e NHCOCH(CH$_3$)$_2$
7f NHCOOPh

8a–f

R
1 A
2 B

A = HO—⟍O⟍

B = HO—⟍O⟍...O⟍ HO

R	R[1]		R	R[1]
3 A	H		**13** A	NHCOCH$_3$
4 B	H		**14** A	NHCOCH(CH$_3$)$_2$
5 A	OCH$_3$		**15** A	NHCOOPh
6 B	OCH$_3$		**16** A	NHCONH$_2$
9 A	OCOCH$_3$		**17** B	OCOCH$_3$
10 A	OCOCH(CH$_3$)$_2$		**18** B	OCOCH(CH$_3$)$_2$
11 A	OCOOPh		**19** B	OCOOPh
12 A	OH		**20** B	OH

[a] Reagents and conditions: (a) (CH$_3$CO)$_2$O, Py, room temp, 5 h; (b) [(CH$_3$)$_2$CHCO]$_2$O, Py, room temp, 5 h; (c) ClCOOPh, Py, room temp, 5 h; (d) Br$_2$, AlCl$_3$, THF, 0–20 °C, 2 h; (e) CuBr$_2$, EtOAc–CHCl$_3$ 1:1, reflux, 5 h; (f) NaH/DMF, then **8a–f**, room temp, 4 h; (g) NH$_3$–MeOH, room temp, 3 h.

Table 1. Physical Properties and Analytical and Fluorescence Data of Compounds **9–20**

compd	yield,[a] %	recryst solvent[b]	mp, °C	formula, anal. CHN[c]	fluorescence (MeOH) emission λ_{max}, nm (excitation at 305 nm) (φ, %)[g]
9	53	A	218	C$_{18}$H$_{17}$N$_5$O$_5$	384 (43.4)
10	62	MeOH	224 dec	C$_{20}$H$_{21}$N$_5$O$_5$	383 (40.0)
11	34	A	158 dec	C$_{23}$H$_{19}$N$_5$O$_6$·0.5H$_2$O[d]	388 (54.1)
12	96	A or B	200 dec	C$_{16}$H$_{15}$N$_5$O$_4$·H$_2$O	369 (7.0)
13	33	A	220 dec	C$_{18}$H$_{18}$N$_6$O$_4$·0.5H$_2$O[e]	375 (40.2)
14	35	A	250 dec	C$_{20}$H$_{22}$N$_6$O$_4$·0.75H$_2$O	372 (37.4)
15	18	EtOH	166 dec	C$_{23}$H$_{20}$N$_6$O$_5$·H$_2$O	364 (65.4)
16	67	A	>300 dec	C$_{17}$H$_{17}$N$_7$O$_4$·0.75CH$_3$OH	363 (55.7)
17	59	EtOH	176–178	C$_{19}$H$_{19}$N$_5$O$_6$·0.75H$_2$O	384 (30.6)
18	55	MeOH	190–193 efferv	C$_{21}$H$_{23}$N$_5$O$_6$[f]	383 (30.8)
19	29	EtOH	157–159 efferv	C$_{24}$H$_{21}$N$_5$O$_7$·2.5H$_2$O	388 (48.0)
20	57	C	197–199 dec	C$_{17}$H$_{17}$N$_5$O$_5$·1.5H$_2$O	371 (8.1)

[a] After chromatography. [b] (A) CH$_2$Cl$_2$–MeOH, 1:1; (B) EtOH–EtOAc, 4:1; (C) EtOH–H$_2$O, 1:1. [c] Elemental compositions (%) were found to be within ±0.4% of the theoretical values for C, H, N unless stated otherwise. [d] N: calcd, 14.89; found, 14.31. [e] N: calcd, 21.47; found 20.96. [f] Purity is 99.05% and 99.15% according to HPLC in two solvent systems. [g] Relative to 2-aminopurine as 100% standard.

require heating. It was superior to the copper(II) bromide approach in those cases in which the dibromide side product was easily removed by crystallization. For preparation of 4-acylaminophenacyl bromides **8d–f**, only the bromine–tetrahydrofuran approach was suitable.

Routine thin-layer chromatography following of the reaction progress of **1** or **2** with bromo ketones **8a–f** indicated that, in contrast to alkylation–condensation reactions previously described, the present reactions went to completion without addition of aqueous ammonia.

The most efficient way toward 6-(4-HOPh)-TACV (**12**) and 6-(4-HOPh)-TGCV (**20**), parent compounds of esters **9–11** and **17–19**, respectively, was treatment of isobutyric esters **10** and **18** with saturated methanolic ammonia. Reaction of phenyl carbamate **15** with NH$_3$–MeOH (satd) led smoothly to the 6-(4-ureidophenyl) derivative **16**.

Alternatively, 6-(4-acetylaminophenyl)-TACV **13** was prepared from the recently reported[2] 6-(4-nitrophenyl)-TACV (**21**), which was subjected to, consecutively, O-acetylation in the acyclic moiety and reduction to the 6-aminophenyl derivative **22**, acetylation of the amino function to give **23**, and O-deacetylation to **13** (Scheme 2). This approach, however, was more tedious and less efficient than one employing the alkylation–condensation reaction of **1** with the appropriate ketone.

The fluorophoric potential of the 6-phenyl substituent for the TACV and TGCV systems was significantly increased with acyloxy, acylamino, phenoxycarbonyloxy, and phenoxycarbonylamino groups in its 4-position. The strongest effect was observed for the phenoxycarbonyl unit; its presence resulted in an enhancement of the fluorescence quantum yield from below 10% for **3**,[1] **4**,[1] **12**, and **20** to around 50% (**19**, 48%) or more (**11**, 54%; **15**, 65%), relative to 2-aminopurine (100%).

Scheme 2[a]
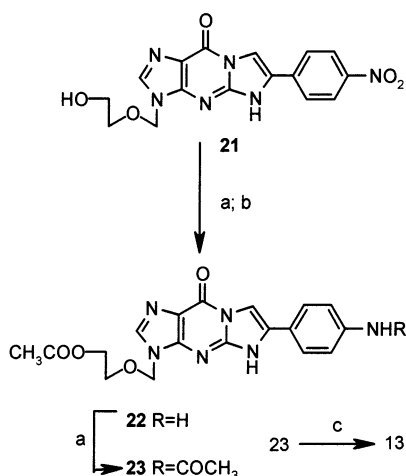
[a] Reagents and conditions: (a) $(CH_3CO)_2O$, Py, room temp, 5 h; (b) Pd/C, MeOH, $HCOONH_4$, Ar, room temp, 2 h; (c) NH_3-MeOH, room temp, 24 h.

The majority of the compounds, synthesized as described above, showed strong affinity for water, which could not be completely removed from analytical samples under drying conditions (Büchi drying oven, P_2O_5, 45 °C, 5 mmHg, 2 h), established beforehand for the whole series in terms of decomposition. The remaining water was observed in ^{1}H NMR spectra of these samples in anhydrous DMSO-d_6 solution prepared in a drybox. The structural character of water was demonstrated in the sample of the 6-(4-hydroxyphenyl) derivative **20**, which, in contrast to its ester or amide congeners, was stable under heating at 90 °C for 2 h. An attempt at drying **20** at 90 °C for 2 h, followed by drying at 45 °C for 0.5 h resulted in a compound with identical water content as that dried under routine conditions.

Antiviral Activity

The antiherpetic properties of the TACV and TGCV derivatives were determined in E_6SM cell cultures (Table 2). All tricyclic compounds showed activity against three different HSV-1 and three different HSV-2 strains. Although the antiviral potency markedly differed from one compound to another, each compound showed similar activity against HSV-1 and HSV-2. No activity was noted with any of the compounds against a TK-deficient HSV-1 strain. This points to the role of the HSV-encoded thymidine kinase (TK) in the metabolic activation of the test compounds. As a rule, the ester derivatives of **12** (i.e., **9**−**11**) were more active anti-HSV agents than the corresponding amide derivatives (i.e., **13**−**16**). The TGCV derivatives (**17**−**20**) were usually more inhibitory to HSV replication than the TACV derivatives, which is in line with our present and previous observations that GCV is also more effective than ACV. The most effective TACV and TGCV derivatives showed an antiviral activity that was the same order of magnitude as that of ACV and GCV, respectively. The ester derivatives **11** and **19** showed an activity that was comparable to that of the free TACV and TGCV derivatives **12** and **20**, pointing to an efficient conversion of the ester derivatives to the parental compounds by cellular esterases. None of the compounds was markedly cytotoxic to the E_6SM cell cultures (minimum cytotoxic concentration ranging between 100 and 1000 μM).

Conclusion

The 6-[4-(acyloxy)phenyl] and 6-[4-(phenoxycarbonyl-oxy)phenyl] derivatives of TACV and TGCV displayed both high antiherpetic activity and strong fluorescence. They should be considered as antiherpetic drug candidates worthy of further evaluation.

Experimental Section

Chemical Procedures. Melting points were determined on a Laboratory Devices Mel-Temp II micromelting point apparatus in open capillaries and are uncorrected. Elemental analyses were performed by Microanalytical Laboratories of the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw, Poland; the results are within 0.4% of the theoretical values unless otherwise stated. UV spectra were measured on a Perkin-Elmer LAMBDA Ez 201 spectrophotometer in CH_3OH; λ_{max} is reported in nm, and the extinction coefficient is reported as $\epsilon \times 10^{-3}$ dm^{-3} mol^{-1} cm^{-1} in parentheses. Fluorescence spectra Fl were measured on a Hitachi L-2000 fluorescence spectrophotometer in CH_3OH; $\lambda_{exc} = 305$ nm. The quantum yield of the reference 2-aminopurine (H_2O) φ is 1.0, and λ_{em} (relative intensity in %) is reported.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 FT NMR spectrometer in DMSO-d_6 at 299.95 and 75.43 MHz, respectively. Chemical shifts are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Capital letters refer to the pattern resulting from directly bonded [13]C−[1]H couplings.

For LR-MS, the EI mass spectra were recorded on an AMD-402 two-sector mass spectrometer (AMD Intectra, Germany). LR- and HR-MS were recorded on an AMD-604 mass spectrometer (Cs gun, 10 kV, 2 A) by the liquid secondary-ionization MS(LSIMS) method in positive mode with 3-nitrobenzyl alcohol (NBA) as the matrix; m/z (rel intensity in %) is reported. Metastable ions were analyzed with B/E linked scans.

Thin-layer chromatography (TLC) was conducted on Merck precoated silica gel F_{254} type 60 plates. Column chromatography (CC) was performed on silica gel 60H with particle size 40−60 μm (Merck). The following solvent systems (measured by volume) were used for TLC: hexane−EtOAc, 7:3 (A), CH_2Cl_2−CH_3OH, 5:1 (B), 9:1 (C), 95:5 (D). Analytical HPLC was performed on a Waters 600E multisolvent delivery system instrument with a 486 tunable absorbance detector using a Nova Pak C_{18} column (8 mm × 100 mm Radial-Pak cartridge).

General Procedure for the Preparation of 4-Substituted Derivatives of 4-Hydroxy- and 4-Aminoacetophenone 7a−f. 4-Hydroxy- or 4-aminoacetophenone (4 mmol) dried by successive coevaporations with anhydrous pyridine (2 × 20 mL) was dissolved in anhydrous pyridine (20 mL). The solution was concentrated to 10 mL, stirred, and treated at room temperature under argon with an appropriate acylating agent (6 mmol): acetic anhydride, isobutyric anhydride, or phenyl chloroformate. After 2 h, an additional portion of the acylating agent was added (4 mmol). The reaction was judged to be complete by TLC (solvent A) in approximately 5 h. Then, anhydrous ethanol was added dropwise (5 mL), the solvents were coevaporated, and the residue was subjected to successive coevaporations with dry ethanol (2 × 5 mL) and toluene (2 × 50 mL). The remaining solid was extracted with EtOAc−H_2O (1:1, 50 mL). The water layer was subsequently extracted with EtOAc (2 × 50 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a crude product, which could be further purified by crystallization from EtOAc or EtOAc−hexane. The yields ranged from 85% to 95%.

The following reactants prepared as above, with the exception of **7c**, have been obtained previously by diverse methods:

Table 2. Activity against Human Herpes Simplex Virus Types 1 and 2 and Cytotoxicity of Compounds **9**−**20**

compd	minimum cytotoxic concentration[a] (μM)	minimum inhibitory concentration[b] (μM)						
		herpes simplex virus-1 (KOS)	herpes simplex virus-1 (F)	herpes simplex virus-1 (McIntyre)	herpes simplex virus-2 (G)	herpes simplex virus-2 (196)	herpes simplex virus-2 (Lyons)	herpes simplex virus-1 TK⁻ (KOS) (ACVʳ)
9	1043	0.601	0.200	0.200	0.601	0.200	0.200	626
10	972	0.560	0.311	0.187	0.622	0.933	0.933	583
11	867	0.832	0.166	0.166	0.830	0.832	0.832	694
12	703	0.675	0.225	0.225	0.675	0.375	0.225	234
13	126	6.7	5.0	25	8.4	25	25	25
14	975	2.8	4.7	4.7	4.4	4.7	4.7	780
15	869	1.1	0.834	0.834	2.5	1.4	1.4	174
16	209	15	5.0	5.0	15	8.3	8.3	126
17	968	0.049	0.062	0.186	97	0.186	0.186	23
18	906	0.116	0.035	0.1740	0.116	0.870	0.174	22
19	814	0.008	0.031	0.781	0.417	0.781	0.156	19
20	1077	0.041	0.041	0.207	0.960	0.207	0.207	69
ACV	1776	0.341	0.341	0.341	0.242	1.0	1.0	249
GCV	392	0.030	0.045	0.040	0.060	0.100	0.045	7.5

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%.

4-acetyloxyacetophenone, **7a**,[5] 4-isobutyryloxyacetophenone, **7b**,[5] 4-acetylaminoacetophenone, **7d**,[6] 4-isobutyrylaminoacetophenone, **7e**,[7] 4-[(phenoxycarbonyl)amino]acetophenone, **7f**.[8]

4-[(Phenoxycarbonyl)oxy]acetophenone (7c). Recrystallized from EtOAc−hexane, white solid; mp 41−44 °C. MW = 256.26. MS (EI) (*m*/*z*, %): (256.2, 17.56). ¹H NMR (DMSO-d_6): δ 8.08, 7.55 (d, d, 2H, 2H, 4-PhOCOO*Ph*), 7.16−7.52 (m, 5H, 4-*Ph*OCOOPh), 2.61 (s, 3H, CH₃).

General Procedure for the Bromination of 4-Substituted Derivatives of 4-Hydroxy- and 4-Aminoacetophenone. Method A. For Derivatives of 4-Hydroxy- and 4-Aminoacetophenone. To a solution of the appropriate ketone (4 mmol) in THF (30 mL) containing a catalytic amount of AlCl₃ (20 mg) was added Br₂ (5.2 mmol in 5 mL of THF) dropwise for 30 min at 0 °C. Then the mixture was allowed to warm to room temperature. After 60 min, the solvent was removed in vacuo followed by extraction of the resulting solid with EtOAc−H₂O (1:1, 50 mL). The water layer was subsequently extracted with EtOAc (2 × 50 mL), and the organic layers were combined, concentrated, and purified by crystallization or silica gel column chromatography (EtOAc−hexane), giving the appropriate bromo ketone.

Method B. For Derivatives of 4-Hydroxyacetophenone. All bromination reactions were performed under Ar. The compound to be brominated (4 mmol) and ground copper(II) bromide (6 mmol) were placed in a flask fitted with a reflux condenser. A mixture of chloroform and ethyl acetate (1:1, 30 mL) was added, and the resulting reaction mixture was refluxed with vigorous stirring. The completion of the reaction was judged by the disappearance of all of the black solid and cessation of hydrogen bromide formation (after 4−5 h). The copper(I) bromide was removed by filtration and was washed well with ethyl acetate. The solvents were removed from the filtrate under reduced pressure. The product was purified by crystallization or silica gel column chromatography (EtOAc−hexane, 3:7).

The yields of both methods ranged from 50% to 70%. Two of the bromo ketones prepared as above (method A) have been described previously: 4-acetyloxyphenacyl bromide **8a**[9] and 4-acetylaminophenacyl bromide **8d**.[6]

4-Isobutyryloxyphenacyl Bromide (8b) from Methods A and B. Recrystallized from hexane−EtOAc 10:1, white needles, mp 46−49 °C. TLC with solvent A. MW = 285.14. MS (EI) (*m*/*z*, %): (283.9, 6.78), (285.9, 7.09). ¹H NMR (DMSO-d_6): δ 8.07, 7.32 (d, d, 2H, 2H, 4-(CH₃)₂CHCOO*Ph*), 4.95 (s, 2H, CH₂), 2.84 (dq, 1H, CH), 1.25 (d, 6H, 2 × CH₃).

4-[(Phenoxycarbonyl)oxy]phenacyl Bromide (8c) from Methods A and B. CC, hexane−EtOAc 7:1 → 7:1.5, white fluffy crystals, mp 84 °C. TLC with solvent A. MW = 335.15. MS (EI) (*m*/*z*, %): (333.8, 6.41), (335.8, 6.22). ¹H NMR (DMSO-d_6): δ 8.12, 7.59 (d, d, 2H, 2H, 4-PhOCOO*Ph*), 7.46−7.52, 7.30−7.43 (m, m, 2H, 3H, 4-*Ph*OCOOPh), 4.97 (s, 2H, CH₂).

4-Isobutyrylaminophenacyl Bromide (8e) from Method A. Recrystallized from hexane−EtOAc 7:3, cream colored solid, mp 138−140 °C. TLC with solvent A. MW = 284.15. MS (EI) (*m*/*z*, %): (282.9, 25.17), (284.9, 24.60). ¹H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.97, 7.77 (d, d, 2H, 2H, 4-(CH₃)₂-CHCONH*Ph*), 4.85 (s, 2H, CH₂), 2.64 (dq, 1H, CH), 1.11 (d, 6H, 2 × CH₃).

4-[(Phenoxycarbonyl)amino]phenacyl Bromide (8f) from Method A. CC, hexane−EtOAc 7:3, white fluffy crystals, mp 168−171 °C dec. TLC with solvent A. MW = 334.17. MS (EI) (*m*/*z*, %): (332.9, 1.16), (334.9, 1.17). ¹H NMR (DMSO-d_6): δ 10.72 (s, 1H, NH), 8.00, 7.67 (d, d, 2H, 2H, 4-PhOC-ONH*Ph*), 7.42−7.49, 7.24−7.32 (m, m, 2H, 3H, 4-*Ph*OCONHPh), 4.86 (s, 2H, CH₂).

General Procedure for the Preparation of 3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purines and 3,9-Dihydro-3-[1,3-dihydroxypropoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purines Substituted in the 6-Position with Ester or Amidophenyl Group. All alkylation−condensation reactions were performed under Ar. To an anhydrous suspension of acyclovir or ganciclovir (2 mmol) in dimethylformamide was added sodium hydride in 60% suspension in oil (2.2 mmol). After being stirred with exclusion of moisture for 1 h at room temperature, the resulting solution was treated with bromo ketone (2 mmol). The reaction mixture was stirred for the next 4 h. Volatile materials were removed under reduced pressure, and the residual oil was chromatographed in an appropriate gradient of CH₂Cl₂−CH₃OH. Fractions containing the main product were evaporated to dryness and recrystallized.

Detailed data on yields, recrystallization solvents, melting points, combustion analyses, and fluorescence spectra are presented in Table 1, and purification methods, UV, ¹H and ¹³C NMR, and mass spectra are given below.

6-[4-(Acetyloxy)phenyl]-3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5*H*-imidazo[1,2-*a*]purine (9). CC, CH₂Cl₂−CH₃OH, 97:3 → 9:1, white small crystals. TLC with solvents B and C. UV: 254 (31.4), 310 (9.9). ¹H NMR (DMSO-d_6): δ 13.14 (s, 1H, N-5-H), 8.23 (s, 1H, H-7), 8.08 (s, 1H, H-2), 7.95, 7.26 (d, d, 2H, 2H, 6-(4-CH₃COO*Ph*)), 5.53 (s, 2H, NCH₂O), 4.71 (t, 1H, OH), 3.55, 3.51 (m, m, 2H, 2H, CH₂CH₂), 2.31 (s, 3H, CH₃). ¹³C NMR (DMSO-d_6): δ 169.08 (Sq, C=O), 151.24 (Ss, C-9), 150.65 (Sm, C4′), 150.40 (Sm, C-3a), 146.52 (Sd, C-4a), 139.33 (Dt, C-2), 128.46 (Sdt, C-6), 126.27, 122.50 (Dd, Dd, C2′C3′), 125.56 (Sdt, C1′), 115.45 (Sd, C-9a), 103.37 (Ds, C-7), 72.38 (Ts, NCH₂O), 70.56, 59.93 (Tm, Td, CH₂CH₂), 20.83 (Qs, CH₃).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-[4-(isobutyryloxy)phenyl]-9-oxo-5*H*-imidazo[1,2-*a*]purine (10). CC,

CH$_2$Cl$_2$−CH$_3$OH, 7:1 → 6:1, white small crystals. TLC with solvents B and C. UV: 254 (33.5), 310 (10.5). ^{1}H NMR (DMSO-d_6): δ 13.14 (d, 1H, N-5-H), 8.24 (d, 1H, H-7), 8.08 (s, 1H, H-2), 7.96, 7.25 (d, d, 2H, 2H, 6-(4-(CH$_3$)$_2$CHCOOPh)), 5.53 (s, 2H, NCH$_2$O), 4.71 (s, 1H, OH), 3.55, 3.51 (m, m, 2H, 2H, CH$_2$CH$_2$), 2.84 (m, 1H, CH), 1.25 (d, 6H, 2 × CH$_3$). ^{13}C NMR (DMSO-d_6): δ 174.92 (Sdq, C=O), 151.22 (Ss, C-9), 150.75 (Sm, C-3a), 150.39 (Sdt, C4′), 146.51 (St, C-4a), 139.33 (Ds, C-2), 128.46 (Sm, C-6), 126.29, 122.42 (Dd, Dd, C2′C3′), 125.55 (St, C1′), 115.43 (Sd, C-9a), 103.38 (Dd, C-7), 72.37 (Tm, NCH$_2$O), 70.57, 59.92 (Tm, Tt, CH$_2$CH$_2$), 33.31 (Ddq, CH), 18.61 (Qdq, 2 × CH$_3$).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-6-[4-(phenoxycarbonyloxy)phenyl]-5H-imidazo[1,2-a]purine (11). CC, CH$_2$Cl$_2$−CH$_3$OH, 97:3 → 9:1, yellowish solid. TLC with solvents B, C, D. UV: 254 (21.0), 310 (6.2). ^{1}H NMR (DMSO-d_6): δ 13.18 (s, 1H, N-5-H), 8.29 (s, 1H, H-7), 8.07 (s, 1H, H-2), 8.02, 7.53 (d, d, 2H, 2H, 6-(4-PhOCOOPh)), 7.48, 7.34−7.42 (d, m, 5H, 6-(4-PhOCOOPh)), 5.52 (s, 2H, NCH$_2$O), 4.68 (t, 1H, OH), 3.53, 3.49 (m, m, 2H, 2H, CH$_2$CH$_2$). ^{13}C NMR (DMSO-d_6): δ 151.41 (Ss, C=O), 151.24 (Ss, C-9), 150.69 (Sm, C-3a), 150.64 (Sm, C1′′), 150.43 (Sm, C4′), 146.55 (Sd, C-4a), 139.36 (Dm, C-2), 129.70, 126.52, 121.18 (Dd, D, Dm, C2′′C3′′C4′′), 128.25 (Sdt, C-6), 126.44, 121.98 (Dd, Dd, C2′C3′), 126.29 (St, C1′), 115.45 (Sd, C-9a), 103.72 (Dd, C-7), 72.38 (Ts, NCH$_2$O), 70.56, 59.92 (Tm, Ts, CH$_2$CH$_2$).

6-[4-(Acetylamino)phenyl]-3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-5H-imidazo[1,2-a]purine (13). CC, CH$_2$Cl$_2$−CH$_3$OH, 9:1 → 7:1, white solid. TLC with solvents B and C. UV: 274 (17.3), 316 (9.8). ^{1}H NMR (DMSO-d_6): δ 13.04 (d, 1H, N-5-H), 10.13 (s, 1H, NH), 8.11 (d, 1H, H-7), 8.07 (s, 1H, H-2), 7.83, 7.68 (d, d, 2H, 2H, 6-(4-CH$_3$CONHPh)), 5.52 (s, 2H, NCH$_2$O), 4.70 (t, 1H, OH), 3.53, 3.49 (m, m, 2H, 2H, CH$_2$CH$_2$), 2.08 (s, 3H, CH$_3$). ^{13}C NMR (DMSO-d_6): δ 168.50 (Sdq, C=O), 151.21 (Ss, C-9), 150.31 (Sm, C-3a), 146.39 (Sdt, C-4a), 139.74 (St, C4′), 139.26 (Dt, C-2), 129.04 (Sm, C-6), 125.56, 119.07 (Dd, Dm, C2′C3′), 122.39 (St, C1′), 115.42 (Sd, C-9a), 102.27 (Dd, C-7), 72.36 (Tm, NCH$_2$O), 70.54, 59.91 (Tm, Td, CH$_2$CH$_2$), 24.04 (Qs, CH$_3$).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-[4-(isobutyrylamino)phenyl]-9-oxo-5H-imidazo[1,2-a]purine (14). CC, CH$_2$Cl$_2$−CH$_3$OH, 8:1 → 6:1, yellowish solid. TLC with solvents B and C. UV: 274 (26.8), 316 (15.5). ^{1}H NMR (DMSO-d_6): δ 13.04 (s, 1H, N-5-H), 10.03 (s, 1H, NH), 8.12 (s, 1H, H-7), 8.07 (s, 1H, H-2), 7.84, 7.72 (d, d, 2H, 2H, 6-(4-(CH$_3$)$_2$-CHCONHPh)), 5.53 (s, 2H, NCH$_2$O), 4.70 (t, 1H, OH), 3.54, 3.50 (m, m, 2H, 2H, CH$_2$CH$_2$), 2.63 (m, 1H, CH), 1.13 (d, 6H, 2 × CH$_3$). ^{13}C NMR (DMSO-d_6): δ 175.42 (Sm, C=O), 151.22 (Ss, C-9), 150.31 (Sdt, C-3a), 146.41 (Sd, C-4a), 139.88 (St, C4′), 139.27 (Dt, C-2), 129.07 (Sdt, C-6), 125.54, 119.23 (Dd, Dt, C2′C3′), 122.36 (St, C1′), 115.43 (Sd, C-9a), 102.28 (Ds, C-7), 72.36 (Ts, NCH$_2$O), 70.55, 59.92 (Ts, Td, CH$_2$CH$_2$), 34.98 (Ddq, CH), 19.43 (Qdq, 2 × CH$_3$).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-6-[4-(phenoxycarbonylamino)phenyl]-5H-imidazo[1,2-a]purine (15). CC, CH$_2$Cl$_2$−CH$_3$OH, 7.5:1 → 6:1, white solid. TLC with solvents B and C. UV: 271 (26.7), 315 (13.6). ^{1}H NMR (DMSO-d_6): δ 13.06 (s, 1H, N-5-H), 10.47 (s, 1H, NH), 8.15 (s, 1H, H-7), 8.06 (s, 1H, H-2), 7.88, 7.62 (d, d, 2H, 2H, 6-(4-PhOCONHPh)), 7.44, 7.25−7.31 (d, m, 5H, 6-(4-PhOCON-HPh)), 5.52 (s, 2H, NCH$_2$O), 4.70 (t, 1H, OH), 3.54, 3.50 (m, m, 2H, 2H, CH$_2$CH$_2$). ^{13}C NMR (DMSO-d_6): δ 151.59 (Ss, C=O), 151.22 (Ss, C-9), 150.40 (Sm, C1′′), 150.32 (Sm, C-3a), 146.41 (Sd, C-4a), 139.28 (Dt, C-2), 139.09 (St, C4′), 129.43, 125.51, 121.90 (Dd, Dm, Dm, C2′′C3′′C4′′), 128.93 (Sdt, C-6), 125.77, 118.56 (Dm, Dm, C2′C3′), 122.46 (St, C1′), 115.43 (Sd, C-9a), 102.41 (Ds, C-7), 72.36 (Ts, NCH$_2$O), 70.55, 59.91 (Tm, Td, CH$_2$CH$_2$).

6-[4-(Acetyloxy)phenyl]-3,9-dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-9-oxo-5H-imidazo[1,2-a]purine (17). CC, CH$_2$Cl$_2$−CH$_3$OH, 7:1 → 5:1, white solid. TLC with solvent B. UV: 255 (34.0), 310 (10.7). ^{1}H NMR (DMSO-d_6): δ 13.15 (s, 1H, N-5-H), 8.23 (s, 1H, H-7), 8.06 (s, 1H, H-2), 7.95, 7.26 (d, d, 2H, 2H, 6-(4-CH$_3$COOPh)), 5.62 (s, 2H, NCH$_2$O), 4.64 (t,

1H, OH), 3.64 (m, 1H, CH), 3.44, 3.34 (m, m, 2H, 2H, 2 × CH$_2$), 2.30 (s, 3H, CH$_3$). ^{13}C NMR (DMSO-d_6): δ 169.09 (Sq, C=O), 151.25 (Ss, C-9), 150.66 (Sm, C4′), 150.31 (Sdt, C-3a), 146.51 (Sd, C-4a), 139.31 (Dt, C-2), 128.49 (Sdt, C-6), 126.29, 122.52 (Dd, Dd, C2′C3′), 125.61 (St, C1′), 115.41 (Sd, C-9a), 103.34 (Ds, C-7), 80.18 (Ds, CH), 71.83 (Td, NCH$_2$O), 60.92 (Ts, 2 × CH$_2$), 20.84 (Qs, CH$_3$).

3,9-Dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-6-[4-(isobutyryloxy)phenyl]-9-oxo-5H-imidazo[1,2-a]purine (18). CC, CH$_2$Cl$_2$−CH$_3$OH, 6:1 → 5:1, white solid. TLC with solvents B and C. UV: 255 (40.2), 310 (12.7). ^{1}H NMR (DMSO-d_6): δ 13.15 (s, 1H, N-5-H), 8.23 (s, 1H, H-7), 8.06 (s, 1H, H-2), 7.96, 7.25 (d, d, 2H, 2H, 6-(4-(CH$_3$)$_2$CHCOOPh)), 5.62 (s, 2H, NCH$_2$O), 4.64 (t, 1H, OH), 3.64 (s, 1H, CH), 3.43, 3.34 (m, m, 2H, 2H, 2 × CH$_2$), 2.84 (m, 1H, CH), 1.25 (d, 6H, 2 × CH$_3$). ^{13}C NMR (DMSO-d_6): δ 174.88 (Sm, C=O), 151.20 (Ss, C-9), 150.67 (Sm, C4′), 150.26 (Sdt, C-3a), 146.51 (Sd, C-4a), 139.22 (Dm, C-2), 128.59 (Sm, C-6), 126.24, 122.36 (Dd, Dd, C2′C3′), 125.65 (St, C1′), 115.28 (Sd, C-9a), 103.22 (Ds, C-7), 80.09 (Dm, CH), 71.73 (Td, NCH$_2$O), 60.83 (Tm, 2 × CH$_2$), 33.24 (Ddq, CH), 18.55 (Qdq, 2 × CH$_3$). LSIMS (positive mode): 442.6 (92, [MH]$^+$), 464.5 (72, [MNa]$^+$). MS (linked scan): 442.0, 371.1, 367.1, 350.1, 338.1, 267.1. HR-MS (formula C$_{21}$H$_{24}$O$_6$N$_5$): calcd 442.172 67; found 442.174 54. For HPLC, elution was performed in two systems: (1) CH$_3$OH (A)−H$_2$O (B), from 10% A to 60% A in 20 min, continued with 60% A for the next 15 min, retention time of 29.36 min, purity of 99.05%; (2) 10 mM NH$_4$Ac (C)−10 mM NH$_4$Ac−CH$_3$CN 1:1 (D), from 20% D to 100% D in 20 min, continued at 100% D for the next 15 min, retention time of 21.59 min, purity of 99.15%, flow rate of 1 mL/min. UV: detection at 257 nm.

3,9-Dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-9-oxo-6-[4-(phenoxycarbonyloxy)phenyl]-5H-imidazo[1,2-a]purine (19). CC, CH$_2$Cl$_2$−CH$_3$OH, 7:1 → 5:1, white solid. TLC with solvents B and C. UV: 255 (25.4), 310 (7.5). ^{1}H NMR (DMSO-d_6): δ 13.19 (s, 1H, N-5-H), 8.28 (s, 1H, H-7), 8.07 (s, 1H, H-2), 8.03, 7.53 (d, d, 2H, 2H, 6-(4-PhOCOOPh)), 7.49 (d, 2H, C2′′), 7.41 (m, 2H, C3′′), 7.35 (m, 1H, C4′′), 5.62 (s, 2H, NCH$_2$O), 4.65 (t, 1H, OH), 3.64 (m, 1H, CH), 3.44, 3.34 (m, m, 2H, 2H, 2 × CH$_2$). ^{13}C NMR (DMSO-d_6): δ 151.41 (C=O), 151.28 (C-9), 150.68 (C4′), 150.64 (C1′′), 150.36 (C-3a), 146.60 (C-4a), 139.33 (C-2), 129.73 (C2′′), 128.39 (C-6), 126.55 (C4′′), 126.47 (C2′), 126.44 (C1′), 122.00 (C3′), 121.21 (C3′′), 115.39 (C-9a), 103.66 (C-7), 80.18 (CH), 71.83 (NCH$_2$O), 60.92 (2 × CH$_2$). LSIMS (positive mode): 492.7 (10, [MH]$^+$), 514.6 (5, [MNa]$^+$). MS (linked scan): 492.0, 416.9, 399.9, 387.9, 267.0. HR-MS (formula C$_{24}$H$_{22}$O$_7$N$_5$): calcd 492.151 92; found 492.148 90.

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-6-(4-ureidophenyl)-5H-imidazo[1,2-a]purine (16). Compound **15** (47.5 mg, 0.1 mmol) was stirred with saturated methanolic ammonia (3 mL) for 4 h under Ar and strictly anhydrous conditions. Upon removal of NH$_3$ under reduced pressure, a brown precipitate of **16** separated out (26.6 mg, 0.07 mmol, 67%). Recrystalllized from solvent A, brown solid. TLC with solvent B. UV: 273 (2.3), 314 (1.5). ^{1}H NMR (DMSO-d_6): δ 12.92 (s, 1H, N-5-H), 8.73 (s, 1H, NH), 8.05 (s, 1H, H-7), 8.04 (s, 1H, H-2), 7.76, 7.50 (d, d, 2H, 2H, 6-(4-H$_2$NCONHPh)), 5.96 (s, 2H, NH$_2$), 5.51 (s, 2H, NCH$_2$O), 4.69 (t, 1H, OH), 3.53, 3.49 (m, m, 2H, 2H, CH$_2$CH$_2$).

3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-(4-hydroxyphenyl)-9-oxo-5H-imidazo[1,2-a]purine (12). **12** was obtained from **10** (474.7 mg, 1.15 mmol) and NH$_3$−MeOH (10 mL), according to the procedure described above for **15** → **16**. White solid (379 mg, 1.11 mmol, 96.2%). Recrystallized from solvent A or B. TLC with solvent B. UV: 262 (31.2), 308 (13.7). ^{1}H NMR (DMSO-d_6): δ 12.95 (s, 1H, N-5-H), 9.86 (s, 1H, HOPh), 8.06 (s, 1H, H-2), 7.99 (d, 1H, H-7), 7.72, 6.85 (d, d, 2H, 2H, 6-(4-HOPh)), 5.51 (s, 2H, NCH$_2$O), 4.68 (s, 1H, OH), 3.52, 3.49 (m, m, 2H, 2H, CH$_2$CH$_2$). ^{13}C NMR (DMSO-d_6): δ 158.11 (St, C4′), 151.26 (Ss, C-9), 150.24 (Sdt, C-3a), 146.33 (Sd, C-4a), 139.24 (Dt, C-2), 129.57 (Sdt, C-6), 126.68, 115.80 (Dd, Dm, C2′C3′), 118.72 (St, C1′), 115.43 (Sd, C-9a), 101.17 (Ds, C-7), 72.38 (Ts, NCH$_2$O), 70.55, 59.94 (Ts, Td, CH$_2$-CH$_2$).

3,9-Dihydro-3-[(1,3-dihydroxy-2-propoxy)methyl]-6-(4-hydroxyphenyl)-9-oxo-5H-imidazo[1,2-a]purine (20). 20 was obtained from **18** (208.7 mg, 0.47 mmol) and NH_3−MeOH (8 mL) according to the procedure described above for **15** → **16**. Yellowish solid (100.1 mg, 0.27 mmol, 57%). Recrystallized from solvent C. TLC with solvent B. UV: 261 (30.8), 308 (13.8). ^{1}H NMR (DMSO-d_6): δ 12.95 (d, 1H, N-5-H), 9.85 (s, 1H, *HO*Ph), 8.04 (s, 1H, H-2), 7.99 (d, 1H, H-7), 7.72, 6.85 (d, d, 2H, 2H, 6-(4-HO*Ph*)), 5.60 (s, 2H, NCH$_2$O), 4.62 (t, 1H, OH), 3.62 (m, 1H, CH), 3.32, 3.42 (m, m, 2H, 2H, 2 × CH$_2$). ^{13}C NMR (DMSO-d_6): δ 158.01 (C4′), 151.14 (C-9), 150.03 (C-3a), 146.21 (C-4a), 139.12 (C-2), 129.46 (C-6), 126.59, 115.70 (C2′C3′), 118.63 (C1′), 115.70 (C-9a), 101.07 (C-7), 80.08 (CH), 71.75 (NCH$_2$O), 60.84 (2 × CH$_2$).

Alternative Route to 13. From 3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-(4-nitrophenyl)-9-oxo-5H-imidazo-[1,2-a]purine (21). Compound **21**, described previously,[2] was converted into the corresponding 3-[(2-acetyloxyethoxy)methyl] derivative using the acetylation procedure in pyridine described above for 4-hydroxy- and 4-aminoacetophenone. Crude, dried acetate (43.4 mg, 0.1 mmol) was dissolved in anhydrous MeOH (10 mL) and subjected to reduction with a Pd/C ammonium formate system[12] (40 mg Pd/C and 64 mg, 1 mmol HCOONH$_4$) for 2 h. The reaction mixture was filtered through Celite, methanol was removed from the filtrate by evaporation, and the excessive ammonium formate was removed by sublimation under reduced pressure. The resulting solid was purified by CC using a CH$_2$Cl$_2$−MeOH gradient of 95:5 → 9:1 to give 3-[(2-acetyloxyethoxy)methyl]-6-(4-aminophenyl)-3,9-dihydro-9-oxo-5H-imidazo[1,2-a]purine (**22**) (20.3 mg, 0.053 mmol, 50.4%). CC, CH$_2$Cl$_2$−CH$_3$OH, 95:5 → 9:1, tan solid. TLC with solvents C and D. UV: 273 (21.5), 314 (14.3). ^{1}H NMR (DMSO-d_6): δ 12.80 (s, 1H, N-5-H), 8.05 (s, 1H, H-2), 7.84 (s, 1H, H-7), 7.54, 6.62 (d, d, 2H, 2H, 6-(4-H$_2$N*Ph*)), 5.51 (s, 2H, NCH$_2$O), 5.48 (s, 2H, NH$_2$), 4.09, 3.72 (t, t, 2H, 2H, CH$_2$CH$_2$), 1.95 (s, 3H, CH$_3$).

Compound **22** (16.6 mg, 0.043 mmol) was acetylated as described above to give after CC purification (CH$_2$Cl$_2$−MeOH, 95:5 → 9:1) 6-[4-(acetylamino)phenyl]-3-[(2-acetyloxyethoxy)-methyl]-3,9-dihydro-9-oxo-5H-imidazo[1,2-a]purine (**23**) (13.6 mg, 0.032 mmol, 74.5%). CC, CH$_2$Cl$_2$−CH$_3$OH, 95:5 → 9:1, white solid. TLC with solvents C and D. ^{1}H NMR (DMSO-d_6): δ 13.07 (s, 1H, N−5-H), 10.17 (s, 1H, NH), 8.12 (s, 1H, H-7), 8.08 (s, 1H, H-2), 7.84, 7.68 (d, d, 2H, 2H, 6-(4-CH$_3$CONH*Ph*)), 5.53 (s, 2H, NCH$_2$O), 4.09, 3.73 (t, t, 2H, 2H, CH$_2$CH$_2$), 2.08 (s, 3H, NHCOCH$_3$), 1.95 (s, 3H, OCOCH$_3$).

Compound **23** (13.6 mg, 0.032 mmol) was stirred with saturated NH_3−MeOH (1.5 mL) at room temperature for 24 h under Ar and strictly anhydrous conditions. Upon removal of NH$_3$ under reduced pressure, a chromatographically homogeneous white solid precipitated out (5.4 mg, 0.014, 44%) identical in all respects to **13** obtained from an alkylation−condensation reaction.

Antiviral Activity and Cytotoxicity Assays. The antiviral assays were based on inhibition of virus-induced cytopathicity in E$_6$SM fibroblasts following previously established procedures. Briefly, confluent cell cultures in 96-well microtiter plates were inoculated with 100 CCID$_{50}$ of virus, 1 CCID$_{50}$ being the virus dose required to infect 50% of virus-inoculated cell cultures. After a 1 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of 2- to 5-fold dilutions of the test compound solutions. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures (i.e., at day 3 postinfection).

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