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# The Search of Novel Inhibitors of HIV-1 Integrase among 5-(4-Halogenophenyl)-5-oxopentyl Derivatives of Nucleic Bases

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**Abstract**—New nucleic base derivatives were obtained by alkylation of uracil, thymine, cytosine, adenine, 6-chloropurine, and 2-amino-6-chloropurine with 5-chloro-1-(4-halogenophenyl)-1-pentanones, and their physical and chemical properties were studied. The influence of the compounds synthesized on the HIV-1 integrase activity was studied.

*Keywords: alkylation, HIV-1integrase, nucleosides, polymethylene analogues*

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## INTRODUCTION

A series of drugs used for the therapy of various human diseases has been developed on the basis of nonglycoside nucleoside analogues. Nonglycoside guanine analogues applied for the treatment of herpes infections can serve an example. Particularly, 2HM-HBG is effective against *Varicella zoster* virus, penciclovir, against type 1 and 2 *Herpes simplex* and *V. zoster* viruses, Epstein-Barr virus, and cytomegalovirus [1].

Heterocyclic base derivatives are used in the treatment of HIV infection: along with standard nucleoside-based drugs (azidothymidine, dideoxyinosine, dideoxycytidine, emtricitabine, and tenofovir) bound in the HIV-1 reverse transcriptase active site, nonnucleoside inhibitors of the HEPT family [2] bound in the hydrophobic pocket adjacent to the enzyme active site [3] are intensely studied.

In addition, nonglycoside derivatives of heterocyclic bases are convenient models for studying the mechanisms of action of various enzymes involved in the nucleic acid exchange. Among these compounds, derivatives of both natural and modified heterocyclic bases bearing various functional groups in the ω-position of the hydrocarbon chain attract much attention. For example, some compounds of a general structural formula (**I**) were effective inhibitors of *E. coli* thymidine phosphorylase [4]. The analogous human enzyme is involved in angiogenesis and apoptosis [5]. Compounds (**II**), whose synthesis and properties were described earlier [6], inhibited both *E. coli* thymidine and uridine phosphorylases with an efficacy close to that of the known inhibitors of these enzymes.

Similar adenine and hypoxantine derivatives with a hydrocarbon chain of nine atoms in length were cytotoxic toward K562 and HCT116 tumor cells [7].

Earlier, we described ω-oxo-ω-phenylalkyl pyrimidines and purines with a varied length of the polymethylene chain [8]. It was shown in [9, 10] that polymethylene derivatives of heterocyclic bases bearing hydroxyl, alkoxycarbonyl, or carboxyl groups in the ω-position can be successfully used for studies of such significant enzymes as human topoisomerase I and/or HIV-1 reverse transcriptase. Another key HIV-1 enzyme is integrase, which provides incorporation of viral DNA into the genome of the infected cell [11].

The first integrase inhibitor approved for the therapy of HIV infection was raltegravir [12]. The critical element of its structure is derived from the pyrimidine cycle and is responsible for the binding of metal ions in the enzyme active site [13]. The other important structural element of raltegravir is a *p*-fluorophenyl substituent [14]. It is noteworthy that the halogenated aromatic residue is a part of the most effective HIV-1 integrase inhibitors [15]. Normally, a fluorine atom is used as a halogen, but some inhibitors (elvitegravir, MK-2048) also contain a chlorine atom.

Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; HIV-1, human immunodeficiency virus type 1.

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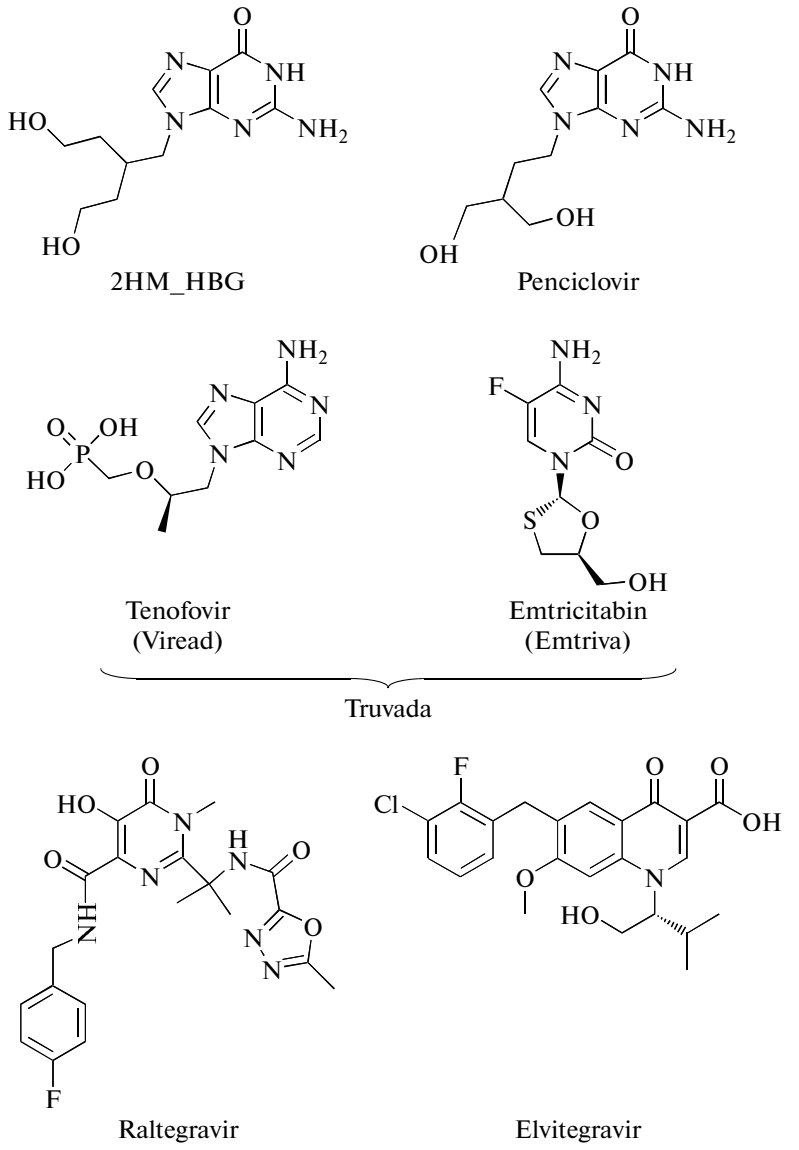
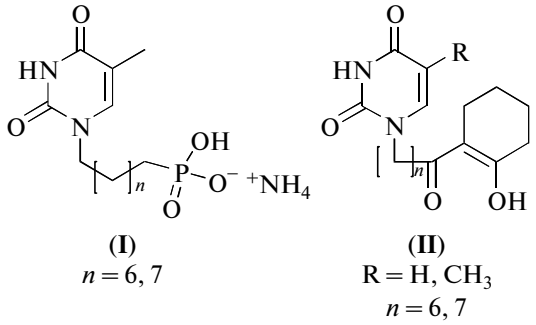



**Formulas 1.** Some inhibitors of HIV-1 reverse transcriptase and integrase.

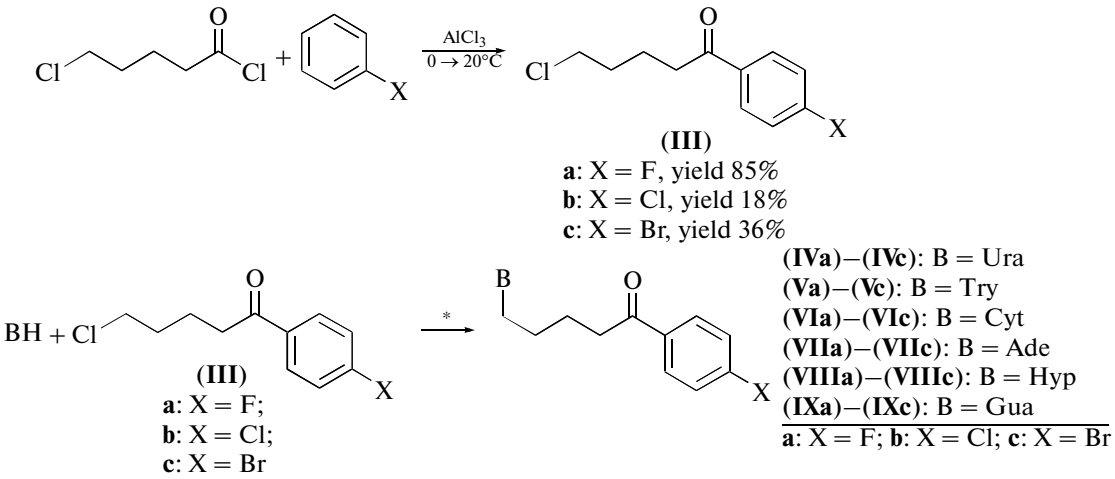



**Formulas 2.** Some inhibitors of thymidine and uridine phosphorylases.

On the basis of the above facts, we believe it reasonable to study whether nucleic base derivatives containing a *p*-halogenated phenone fragment in the ω-position can affect the activity of HIV-1 integrase.

## RESULTS AND DISCUSSION

In this work we set a task to prepare compounds (**IVa–c**)–(**IXa–c**), in which the heterocyclic base **B** was linked to a *p*-halogenophenone fragment with a chain of four methylene units (Scheme). We obtained six series of compounds (**IVa–c**)–(**IXa–c**) based on six heterocyclic bases, thymine, uracil, cytosine, adenine, guanine, and hypoxanthine. Since the role of the halogen atom for the inhibitory properties toward integrase is not clear, we prepared three compounds in each series containing atoms of different halogens in the *p*-position of the aromatic ring.




**Scheme 1.** A scheme of synthesis of some heterocyclic base derivatives with a terminal (*p*-halogenophenyl) oxo group.

The compounds were synthesized as shown in the scheme. Compounds **(III)** served starting alkylating agents. They were obtained by the Friedel–Crafts reaction by acylation of fluoro-, chloro-, or bromobenzene with δ-chloropentanoyl chloride similar the procedure described in [16]. Aluminum chloride was used as a catalyst. Unlike benzene, acylation of halobenzenes proceeded more slowly and was accompanied by considerable resinification of the reaction mixture [17], which resulted in a substantial reduction of product yields.

Heterocyclic bases were alkylated using the previously developed method of heating the mixture of a pyrimidine or purine base, compound **(III)** and DBU in DMF (method A). For the preparation of cytidine derivatives we used alkylation of its Na salt in DMF (method B).

Final products were isolated by column chromatography on silica gel. Their structures were confirmed by mass and NMR spectra.

Alkylation of uracil and thymine resulted in 1-substituted derivatives together with a small amount of 1,3-bis-substituted pyrimidines. The major product of adenine alkylation was its 9-substituted isomer, although its 3-substituted derivatives were also isolated in insignificant yields. Alkylation of hypoxanthine proceeded typically to give the target 9-substituted derivative together with the corresponding 7-derivative. In the case of compound **(VIIIa)**, the 7-isomer was separated by multistep crystallization from ethyl acetate. Since this procedure is rather labor consuming, for the preparation of compounds **(VIIIb)** and **(VIIIc)** we used alkylation of 6-chloropurine followed by hydrolysis (see the Experimental section).

In the NMR spectra of the compounds synthesized there are three resonance groups clearly observed: resonances of heterocyclic bases, resonances of polymethylene chains, and those of aryl residues (see the Experimental section). $^{1}H$ and $^{13}C$ NMR spectra of fluorobenzene derivatives **(IVa)**–**(IXa)** are characterized by the presence of additional resonances of the aromatic radical due to spin-spin interactions with the fluorine atom.

NMR spectra of the compounds synthesized allowed us to identify the substituent positions in the heterocyclic bases due to significant differences in the sets of chemical shifts of the base atoms and atoms of the first methylene unit of the side chain for various position isomers. Critical differences in the spectra of 3- and 9-adenine substituents were described by Holy et al. [18]. For 7- and 9-substituted hypoxanthine and guanine the differences were also essential. Due to these differences the position of the purine side chain once determined by the HMBC method (Heteronuclear Multiple Bond Correlation) can be used for unambiguous assignment of the structure of isomeric purine derivatives using their one-dimensional NMR spectra.

For the studies of the capacity of the compounds to inhibit HIV-1 integrase we took 1-substituted pirimidine isomers and 9-substituted purine isomers with the highest solubility. The inhibitory properties of these compounds were analyzed using the standard protocols [19]. Integrase catalyzes two reactions of the virus replication: 3'-terminal processing resulting in the removal of GT nucleotides from both viral DNA 3'-ends and strand transfer resulting in the incorporation of the viral DNA into cell DNA. The capacity of *p*-halogenated phenone derivatives of heterocyclic compounds to inhibit the integrase catalytic activity was studied in both reactions with a recombinant protein and DNA U5B/U5A and U5B-2/U5A duplexes corresponding to the terminal region of the U5 fragment of the long DNA repeat before and after the cleavage of the GT nucleotide. Accordingly, an integrase substrate in the reaction of 3'-terminal process-

* For the conditions, see the Experimental section.

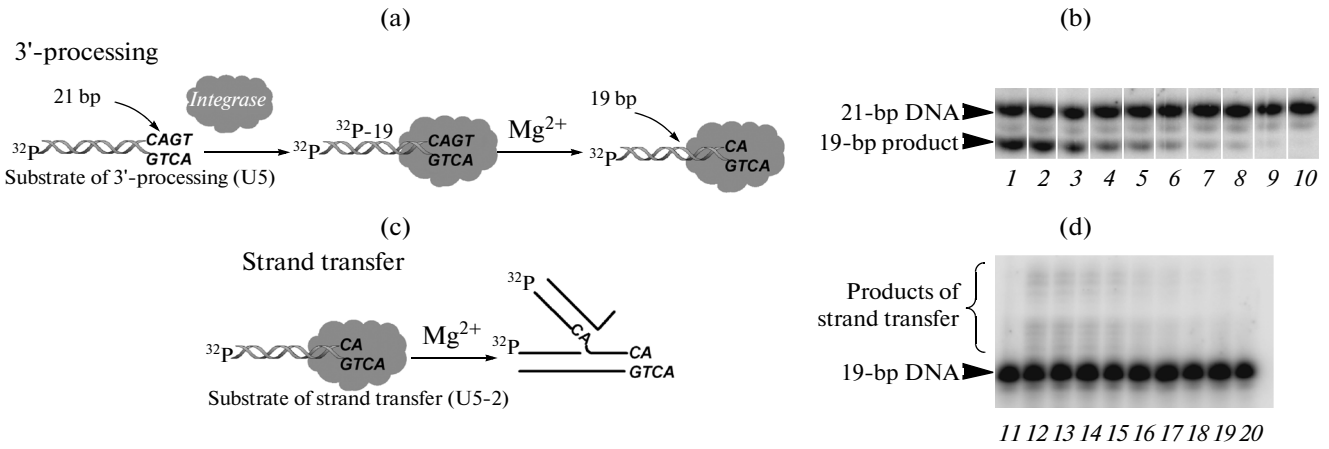



**Fig. 1.** The influence of compound (**IXb**) on the HIV-1 integrase activity in the 3'-processing and strand transfer reactions. (a) A scheme of the 3'-processing catalyzed by HIV-1 integrase in vitro. (b) A representative radioautogram of the inhibition of the 3'-processing reaction in the presence of increasing concentrations of compound (**IX**) in PAG under denaturing conditions (7 M urea). Lane *1*, without inhibitors; lanes *2–10*, increasing inhibitor concentrations shown in the table. (c) A scheme of the strand transfer reaction catalyzed by HIV-1 integrase in vitro. (d) A representative radioautogram of the inhibition of the strand transfer reaction in the presence of increasing concentrations of compound (**IX**) in PAG under denaturing conditions (7 M urea). Lane *11*, without inhibitors; lanes *12–20*, increasing inhibitor concentrations shown in the table.

ing was the U5B/U5A duplex and in the reaction of strand transfer, the U5B-2/U5A duplex. It is noteworthy that integrase interacts with cell DNA without regard to its primary structure. Therefore, in the reaction of strand transfer the enzyme can incorporate the U5B-2/U5A substrate into any DNA including the substrate itself. The schemes of 3'-terminal processing and strand transfer with these substrates are shown in Fig. 1a and 1b.

None of the 1-substituted derivatives of the pyrimidine series inhibited the integrase catalytic activity to a concentration of 1 mM in any of the reactions. Similar adenine and hypoxanthine derivatives did not display inhibitory properties within the concentration range tested (10–1500 μM) either. At the same time, the guanine Cl-derivative (**IXb**) inhibited both of the integrase-catalyzed reactions (Fig. 1b and 1d, table), the inhibitory efficacy for the reaction of strand transfer being somewhat higher than that of the 3'-processing: the (**IXb**) concentration, at which the reaction efficiency was reduced by 50% ($IC_{50}$) was 516 ± 107 μM for the 3'-processing reaction and 284 ± 59 μM for the strand transfer.

As a reference compound we used raltegravir, an inhibitor of the strand transfer reaction ($IC_{50}$ 0.5 μM for the 3'-processing reaction and 0.01 μM for the strand transfer [20]). Compound (**IXb**) also inhibited this reaction more effectively. It is noteworthy that analogues of this compound containing fluorine (**IXa**) and bromine (**IXc**) atoms were ineffective as integrase inhibitors. However, in the mechanism of integrase inhibition the role of a halogen atom, which is borne by nearly all inhibitors of the strand transfer [15], is still unclear [21].

## EXPERIMENTAL

In this work we used adenine, hypoxantine, guanine, uracil, thymine, cytosine, and 6-chloropurin purchased from Sigma (United States); DBU, sodium hydride 60% suspension in mineral oil, from Fluka (Switzerland); $CDCl_3$, DMSO-$d_6$, fluorobenzene, chlorobenzene, bromobenzene, and aluminum chloride, from Acros Organics (Belgium). 5-Chloropentanoyl chloride was obtained as described in [16]. The solvents were purified using standard procedures [22]. TLC was carried out on Kieselgel 60 $F_{254}$ plates (Merck, Germany) with the following systems: 19 : 1 chloroform–ethanol (A), 18 : 2 (B), 17 : 3 (C), and 19.5 : 0.5 (D). The compounds were detected by UV at 254 nm. Column chromatography was performed on silica gel 60 (0.040–0.063 mm) (Merck, Germany).

Mass spectra were registered on an MS-30 mass-spectrometer (Kratos, Japan) using electron impact as the ionization method. NMR spectra were registered on an AMXIII-400 Bruker spectrometer (Germany) (δ, ppm, *K*, Hz) with the working frequency of 400 MHz for $^1H$ and 100 MHz for $^{13}C$ spectra at 300 K in $CDCl_3$ and DMSO-$d_6$.

Recombinant HIV-1 integrase was isolated from the *E. coli* producer strain Rosetta and purified without a detergent as described in [23].

Oligodeoxyribonucleotides U5B (5'-GTGTGGAAAATCTCTAGCAGT-3'), U5B-2 (5'-GTGTGGAAAATCTCTAGCA-3'), and U5A (5'-ACTGCTAGAGATTTTCCACAC-3') were synthesized by the phosphoamidite procedure on an automatic ABI 3400 DNA synthesizer (Applied Biosystems, United States) using a standard protocol and commercial reagents (Glen Research, United States).

Yields of the 3'-processing and strand transfer reactions at varied concentrations of compound (**IXb**). The reaction effectiveness is given relative to the reaction without inhibitors

| Inhibition of 3'-processing | | | Inhibition of strand transfer | | |
|---|---|---|---|---|---|
| lane number on figure b | concentration of compound (**IXb**), μM | reaction effectiveness, % | lane number on figure d | concentration of compound (**IXb**), μM | reaction effectiveness, % |
| 2 | 200 | 81.27 ± 14.3 | 11 | 10 | 98.04 ± 16.6 |
| 3 | 350 | 70.02 ± 14 | 12 | 100 | 80.88 ± 15.3 |
| 4 | 500 | 52.76 ± 12.1 | 13 | 200 | 60.19 ± 13.3 |
| 5 | 750 | 34.2 ± 6.8 | 14 | 300 | 50.98 ± 10 |
| 6 | 900 | 17.76 ± 3.7 | 15 | 400 | 39.22 ± 8.5 |
| 7 | 1100 | 9.4 ± 1.2 | 16 | 500 | 26.08 ± 5.2 |
| 8 | 1300 | 3.27 ± 0.5 | 17 | 750 | 22.94 ± 1 |
| 9 | 1500 | 2.81 ± 0.52 | 18 | 1000 | 17.65 ± 2.9 |

**Preparation of 5-halogeno-1-(4-fluorophenyl)pentanone-1 (IIIa)–(IIIc)**. Anhydrous aluminum chloride (6.7 g, 50 mmol) was added in portions under stirring to a solution of 5-chloropentanoyl chloride (43.3 g, 50 mmol) in the proper halobenzene (20 mL) cooled to 0°C. The mixture was stirred at 0°C for 30 min and then at room temperature for 1 h. The solution was poured onto ice (150 g), the organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 15 mL).The extracts were united, washed with saturated sodium hydrocarbonate (20 mL), dried with anhydrous sodium sulfate, and the solvent was evaporated. The residue was chromatographed on a silica gel column (5 × 10 cm, 70 g) eluting with methylene chloride.

**5-Chloro-1-(4-fluorophenyl)pentanone-1 (IIIa).** The yield 85%; bp 135–137°C (1 mm Hg). Mass: *m/z* 214.7 [$M^+$]. Calculated *M* 214.7 ($C_{11}H_{12}ClFO$). $^1$H NMR ($CDCl_3$): 1.65–1.85 (4 H, m, $CH_2CH_2CH_2Cl$); 2.86 (2 H, t, *J* 6.8, $COCH_2$); 3.45 (2 H, t, *J* 6.2, $CH_2Cl$); 6.99 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.7, $J_{m\text{-H},\,F}$ 8.7, *m*-H, PhF); 7.86 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.7, $J_{o\text{-H},\,F}$ 5.3, *o*-H, PhF). $^{13}$C NMR ($CDCl_3$): 21.38 ($CH_2CH_2CO$); 31.95 ($CH_2CH_2Cl$); 37.34 ($COCH_2$); 44.65 ($CH_2Cl$); [115.50 (2 C, d, $J_{3\text{-C},\,F}$ 22.1, C3 and C5); 130.54 (2 C, d, $J_{2\text{-C},\,F}$ 9.1, C2 and C6); 133.30 (C1); 165.56 (1 C, d, $J_{4\text{-C},\,F}$ 254.1, C4)] ($C_6H_4Cl$); 198.25 (*C*O).

**5-Chloro-1-(4-chlorophenyl)pentanone-1 (IIIb).** The yield 49%. Mass: *m/z* 275.6 [$M^+$]. Calculated *M* 231.1 ($C_{11}H_{12}Cl_2O$). $^1$H NMR ($CDCl_3$): 1.80–1.95 (4 H, m, $CH_2CH_2CH_2Cl$); 2.97 (2 H, t, *J* 6.8, $COCH_2$); 3.57 (2 H, t, *J* 6.2, $CH_2Cl$); 7.42 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.7, *m*-H, PhCl); 7.88 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.7, *o*-H, PhCl). $^{13}$C NMR ($CDCl_3$): 21.43 ($CH_2CH_2CO$); 31.97 ($CH_2CH_2Cl$); 37.52 ($COCH_2$); 44.59 ($CH_2Cl$); [128.19 (2 C, C3, and C5); 129.40 (2 C, C2, and C6); 135.19 (C1); 139.50 (C4)] ($C_6H_4Cl$); 198.55 (*C*O).

**5-Chloro-1-(4-bromophenyl)pentanone-1 (IIIc).** The yield 39%. Mass: *m/z* 275.6 [$M^+$]. Calculated *M* 275.6 ($C_{11}H_{12}ClBrO$). $^1$H NMR ($CDCl_3$): 1.75–1.95 (4 H, m, $CH_2CH_2CH_2Cl$); 2.96 (2 H, t, *J* 6.8, $COCH_2$); 3.57 (2 H, t, *J* 6.1, $CH_2Cl$); 7.59 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr), 7.80 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhBr). $^{13}$C NMR ($CDCl_3$): 21.52 ($CH_2CH_2CO$); 32.06 ($CH_2CH_2Cl$); 37.61 ($COCH_2$); 44.68 ($CH_2Cl$); [128.32 (C4); 129.62 (2 C, C2, and C6); 132.02 (2 C, C3, and C5); 135.69 (C1)] ($C_6H_4Br$); 198.55 (*C*O).

**Alkylation of heterocyclic bases using DBU (method A).** An alkylating agent (5.5 mmol) and DBU (0.78 mL, 5.5 mmol) were added to a suspension of a heterocyclic base or its protected derivative (5 mmol) in anhydrous DMF (10 mL). The mixture was heated at 80–100°C for 20 h (TLC control). The reaction mixture was cooled and evaporated in vacuum. The residue was suspended in a minimal volume of methylene chloride and chromatographed on a silica gel column (70 g, 5 × 10 cm) eluting in a gradient of ethanol in methylene chloride (0 → 20%). The target fractions were evaporated and the residue was recrystallized.

**Alkylation of cytosine sodium salt (method B).** A suspension of sodium hydride (0.21 g, 5.2 mmol) in mineral oil was added to a suspension of cytosine (0.55 g, 5 mmol) in anhydrous DMF (10 mL). The reaction mixture was heated at 80–100°C for 20 h (TLC control). The reaction mixture was cooled and evaporated in vacuum. The residue was suspended in a minimal volume of methylene chloride and chromatographed on a silica gel column (70 g, 5 × 10 cm) eluting in a gradient of ethanol in methylene chloride (0 → 20%). The target fractions were evaporated and the residue was recrystallized.

**1-[5-(4-Fluorophenyl)-5-oxopentyl] uracil (IVa)** was obtained by method **A** in a yield of 28%; $R_f$ 0.25 (19.5 : 0.5); mp 101–102°C (ethyl acetate). Mass: *m/z* 290.3 [$M^+$], 291.3 [$M + H^+$]. Calculated *M* 290.3 ($C_{15}H_{15}FN_2O_3$). $^1$H NMR ($CDCl_3$): 1.68–1.83 (4 H, m, H2' and H3'); 2.99 (2 H, t, *J* 6.4, H4'); 3.76 (2 H, t, *J* 6.7, H 1'); 5.68 (1 H, d, $J_{5,\,6}$ 7.8, H5); 7.10 (2 H, dd,

$J_{m\text{-H},\,o\text{-H}}$ 8.6, $J_{m\text{-H},\,F}$ 8.6, *m*-H, PhF); 7.18 (1 H, d, $J_{6,5}$ 7.8, H6); 7.95 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.9, $J_{o\text{-H},\,F}$ 5.4, *o*-H, PhF), 9.48 (1 H, br s, H3). $^{13}$C NMR ($CDCl_3$): 20.74 (C3'); 28.54 (C2'); 37.54 (C4'); 48.55 (C1'); 102.33 (C5); [115.79 (2 C, d, $J_{C,F}$ 22.0); 130.69 (2 C, d, $J_{C,F}$ 8.9); 133.27 (1 C, d, $J_{C,F}$ 3.1); 165.84 (1 C, d, $J_{4\text{-C},F}$ 254.9)] ($C_6H_4F$); 144.39 (C6); 151.06 (C2); 163.87 (C4); 197.86 (C5').

In this reaction 1,3-bis[5-(4-fluorophenyl)-5-oxopentyl]uracil, $R_f$ 0.61 (19.5 : 0.5), oil, was obtained in a yield of 15% as a side product.

**1-[5-(4-Fluorophenyl)-5-oxopentyl] thymine (Va)** was obtained by method **A** in a yield of 32%; $R_f$ 0.33 (19.5 : 0.5); mp 121–122°C (ethyl acetate). Mass: *m/z* 304.3 [$M^+$], 305.3 [$M + H^+$]. Calculated *M* 304.3 ($C_{16}H_{17}FN_2O_3$). $^1$H NMR ($CDCl_3$): 1.68–1.82 (4 H, m, H2' and H3'); 1.89 (3 H, s, 5-C$H_3$); 2.98 (2 H, t, *J* 6.4, H4'); 3.72 (2 H, t, *J* 6.7, H1'); 6.99 (1 H, s, H6); 7.09 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.7, $J_{m\text{-H},\,F}$ 8.7, *m*-H, PhF); 7.95 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.7, $J_{o\text{-H},\,F}$ 5.3, *o*-H, PhF), 9.45 (1 H, br s, H3). $^{13}$C NMR ($CDCl_3$): 12.21 (5-$CH_3$), 20.69 (C3'); 28.45 (C2'); 37.46 (C4'); 48.09 (C1'); 110.72 (C5); [115.66 (2 C, d, $J_{C,F}$ 22.0); 130.58 (2 C, d, $J_{C,F}$ 9.4); 133.20 (1 C, d, $J_{C,F}$ 2.7); 165.71 (1 C, d, $J_{4\text{-C},F}$ 254.9)] ($C_6H_4F$); 140.22 (C6); 151.05 (C2); 164.97 (C4); 197.85 (C5').

In this reaction 1,3-bis[5-(4-fluorophenyl)-5-oxopentyl]thymine, $R_f$ 0.64 (19.5 : 0.5), oil, was obtained in a yield of 14% as a side product.

**1-[5-(4-Fluorophenyl)-5-oxopentyl] cytosine (VIa)** was obtained by method **B** in a yield of 41%; $R_f$ 0.47 (17 : 3); mp 197–198°C (ethanol). Mass: *m/z* 289.3 [$M^+$], 290.3 [$M + H^+$]. Calculated *M* 289.3 ($C_{15}H_{16}FN_3O_2$). $^1$H NMR (DMSO-$d_6$): 1.50–1.70 (4 H, m, H2' and H3'); 3.04 (2 H, t, *J* 6.7, H4'); 3.66 (2 H, t, *J* 6.7, H1'); 5.63 (1 H, d, $J_{5,6}$ 7.2, H5); 6.93 (2 H, br s, 4-N$H_2$); 7.33 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.9, $J_{m\text{-H},\,F}$ 8.9, *m*-H, PhF); 7.57 (1 H, d, $J_{6,5}$ 7.2, H6); 8.03 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.9, $J_{o\text{-H}}$ 5.6, *o*-H, PhF). $^{13}$C NMR (DMSO-$d_6$): 20.54 (C3'); 28.18 (C2'); 37.29 (C4'); 48.18 (C1'); 92.97 (C5); [115.56 (2 C, d, $J_{C,F}$ 22.0); 130.75 (2 C, d, $J_{C,F}$ 9.4); 133.38 (1 C, d, $J_{C,F}$ 2.7); 164.87 (1 C, d, $J_{4\text{-C},F}$ 251.8)] ($C_6H_4F$); 145.88 (C6); 155.74 (C2); 165.81 (C4); 198.33 (C5').

**9-[5-(4-Fluorophenyl)-5-oxopentyl] adenine (VIIa)** was obtained by method **A** in a yield of 35%; $R_f$ 0.33 (18 : 2); mp 197–198°C (ethyl acetate). Mass: *m/z* 313.3 [$M^+$], [$M + H^+$], 314.3 [$M + H^+$]. Calculated *M* 313.3 ($C_{16}H_{16}FN_5O$). $^1$H NMR (DMSO-$d_6$): 1.58 (2 H, m, H2'); 1.88 (2 H, m, H3'); 3.05 (2 H, t, *J* 7.2, H4'); 4.19 (2 H, t, *J* 7.0, H1'); 7.11 (2 H, br s, 6-N$H_2$); 7.30 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.9, $J_{m\text{-H},\,F}$ 8.9, *m*-H, PhF); 8.00 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.7, $J_{o\text{-H},\,F}$ 5.6, *o*-H, PhF); 8.14 (2 H, br s, H2 and H8). $^{13}$C NMR (DMSO-$d_6$): 20.57 (C3'); 28.76 (C2'); 37.00 (C4'); 42.57 (C1'); [115.46 (2 C, d, $J_{C,F}$ 22.0); 130.65 (2 C, d, $J_{C,F}$ 9.4); 133.32 (1 C, d, $J_{C,F}$ 2.7); 164.82 (1 C, d, $J_{4\text{-C},F}$ 251.3)] ($C_6H_4F$); 118.70 (C5); 140.71 (C8); 149.51 (C4); 152.23 (C2); 155.85 (C6); 198.15 (C5').

In this reaction3-[5-(4-fluorophenyl)-5-oxopentyl]adenine, $R_f$ 0.09 (18 : 2), was obtained in a yield of 6% as a side product.

**9-[5-(4-Fluorophenyl)-5-oxopentyl] hypoxantine (VIIIa)** was obtained by method **A** in a yield of 21%; $R_f$ 0.40 (18 : 2); mp 202–203°C (ethyl acetate). Mass: *m/z* 314.3 [$M^+$], 315.3 [$M + H^+$]. Calculated *M* 314.3 ($C_{16}H_{15}FN_4O_2$). $^1$H NMR (DMSO-$d_6$): 1.56 (2 H, m, H2'); 1.86 (2 H, m, H3'); 3.05 (2 H, t, *J* 7.0, H4'); 4.18 (2 H, t, *J* 6.8, H1'); 7.32 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.6, $J_{m\text{-H},\,F}$ 8.6, *m*-H, PhF); 8.01 (3 H, m, *o*-H, PhF and H8); 8.10 (1 H, s, H2); 12.22 (1 H, br s, H1). $^{13}$C NMR (DMSO-$d_6$): 20.52 (C3'); 28.96 (C2'); 37.01 (C4'); 43.06 (C1'); [115.56 (2 C, d, $J_{C,F}$ 22.0); 130.74 (2 C, d, $J_{C,F}$ 9.4); 133.32 (1 C, d, $J_{C,F}$ 2.7); 164.89 (1 C, d, $J_{4\text{-C},F}$ 251.3)] ($C_6H_4F$); 123.91 (C5); 140.21 (C8); 145.31 (C2); 148.33 (C4); 156.60 (C6); 198.18 (C5').

In this reaction 20% 7-[5-(4-fluorophenyl)-5-oxopentyl]hypoxantine, $R_f$ 0.40 (18 : 2), was obtained as a side product. The target product (**VIIIa**) was separated from it by multiple crystallization from ethyl acetate.

**9-[5-(4-Fluorophenyl)-5-oxopentyl] guanine (IXa)** was obtained by method **A** by alkylation of 2-amino-6-chloropurine followed by hydrolysis of the resulting raw 2-amino-6-chloropurine derivative (reflux in 0.33 M NaOH, 3.5 h) in a total yield of 26%; $R_f$ 0.40 (18 : 2); mp 128–129°C (ethyl acetate). Mass: *m/z* 329.3 [$M^+$], 330.3 [$M + H^+$]. Calculated *M* 329.3 ($C_{16}H_{16}FN_5O_2$). $^1$H NMR ($CDCl_3$): 1.75 (2 H, m, H2'); 1.89 (2 H, m, H3'); 2.94 (2 H, t, *J* 7.2, H4'); 4.04 (2 H, t, *J* 7.0, H1'); 4.84 (2 H, br s, 2-N$H_2$); 7.02 (2 H, dd, $J_{m\text{-H},\,o\text{-H}}$ 8.6, $J_{m\text{-H},\,F}$ 8.6, *m*-H, PhF); 7.45 (1 H, s, H8); 7.91 (2 H, dd, $J_{o\text{-H},\,m\text{-H}}$ 8.7, $J_{o\text{-H},\,F}$ 5.5, *o*-H, PhF). $^{13}$C NMR ($CDCl_3$): 21.16 (C3'); 29.44 (C2'); 37.62 (C4'); 43.05 (C1'); 115.24 (C5) [115.70 (2 C, d, $J_{C,F}$ 22.0); 130.65 (2 C, d, $J_{C,F}$ 9.4); 133.34 (1 C, d, $J_{C,F}$ 2.7); 167.7 (1 C, d, $J_{4\text{-C},F}$ 254.5)] ($C_6H_4F$); 135.98 (C8); 152.43 (C4); 155.43 (C2); 159.25 (C6); 198.18 (C5').

**1-[5-(4-Chlorophenyl)-5-oxopentyl] uracil (IVb)** was obtained by method **A** in a yield of 30%; $R_f$ 0.4 (19 : 1); mp 171–172°C (ethyl acetate). Mass: *m/z* 306.7 [$M^+$], 307.7 [$M + H^+$]. Calculated *M* 306.7 ($C_{15}H_{15}ClN_2O_3$). $^1$H NMR ($CDCl_3$): 1.19–1.41 (4 H, m, H2' and H3'); 2.66 (2 H, t, *J* 6.5, H4'); 3.29 (2 H, t, *J* 6.5, H1'); 5.11 (1 H, d, $J_{5,6}$ 7.8, H5); 6.89 (1 H, d, $J_{6,5}$ 7.8, H6); 6.89 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhCl); 7.44 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *o*-H, PhCl); 10.54 (1 H, br s, H3). $^{13}$C NMR ($CDCl_3$): 19.54 (C3'); 27.33 (C2'); 36.54 (C4'); 46.81 (C1'); 100.72 (C5); [127.76 (2 C); 128.41 (2 C); 134.15; 137.99] ($C_6H_4Cl$); 143.53 (C6); 150.16 (C2); 163.08 (C4); 197.10 (C5').

**1-[5-(4-Chlorophenyl)-5-oxopentyl] thymine (Vb)** was obtained by method **A** in a yield of 28%; $R_f$ 0.54 (19 : 1); mp 172–173°C (ethyl acetate). Mass: *m/z* 320.7 [$M^+$], 321.7 [$M + H^+$]. Calculated *M* 320.7 ($C_{16}H_{17}ClN_2O_3$). $^1$H NMR ($CDCl_3$): 1.68–1.82 (4 H,

m, H2' and H3'); 1.89 (3 H, s, 5-C$H_3$); 2.98 (2 H, t, *J* 6.4, H4'); 3.72 (2 H, t, *J* 6.4, H1'); 6.98 (1 H, s, H6); 7.40 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhCl); 7.86 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhCl); 9.37 (1 H, br s, H3). $^{13}$C NMR ($CDCl_3$): 12.23 (5-*C*$H_3$), 20.63 (C3'); 28.44 (C2'); 37.53 (C4'); 48.08 (C1'); 110.74 (C5); [128.90 (2 C); 129.38 (2 C); 135.07; 139.55] ($C_6H_4Cl$); 140.19 (C6); 151.03 (C2); 164.26 (C4); 198.22 (C5').

In this reaction 1,3-bis[5-(4-chlorophenyl)-5-oxopentyl]thymine, $R_f$ 0.64 (19.5 : 0.5), oil, was obtained as a side product in a yield of 14%.

**1-[5-(4-Chlorophenyl)-5-oxopentyl] cytosine (VIb)** was obtained by method **B** in a yield of 3.6%; $R_f$ 0.47 (17 : 3); mp 213–214°C (ethanol). Mass: *m/z* 305.7 [$M^+$], 306.7 [$M$ + $H^+$]. Calculated *M* 305.7 ($C_{15}H_{16}ClN_3O_2$). $^1$H NMR (DMSO-$d_6$): 1.50–1.67 (4 H, m, H2' and H3'); 3.03 (2 H, t, *J* 6.7, H4'); 3.65 (2 H, t, *J* 6.7, H1'); 5.64 (1 H, d, $J_{5,\,6}$ 7.2, H5); 6.95 (2 H, br s, 4-N$H_2$); 7.56 (1 H, d, $J_{6,\,5}$ 7.2, H6); 7.70 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhCl); 7.87 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhCl). $^{13}$C NMR (DMSO-$d_6$): 20.47 (C3'); 28.16 (C2'); 37.38 (C4'); 48.18 (C1'); 93.03 (C5); [128.71 (2 C); 129.72 (2 C); 135.30; 137.90] ($C_6H_4Cl$); 145.89 (C6); 155.78 (C2); 165.82 (C4); 198.76 (C5').

**9-[5-(4-Chlorophenyl)-5-oxopentyl] adenine (VIIb)** was obtained by method **A** in a yield of 36%; $R_f$ 0.31 (18 : 2); mp 209–210°C (ethyl acetate). Mass: *m/z* 329.7 [$M^+$], 330.7 [$M$ + $H^+$]. Calculated *M* 329.7 ($C_{16}H_{16}ClN_5O$). $^1$H NMR (DMSO-$d_6$): 1.55 (2 H, m, H2'); 1.86 (2 H, m, H3'); 3.05 (2 H, t, *J* 7.2, H4'); 4.17 (2 H, t, *J* 7.0, H1'); 7.13 (2 H, br s, 6-N$H_2$); 7.55 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.4, *m*-H, PhCl); 7.92 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.4, *o*-H, PhCl); 8.12 (1 H, s, H8); 8.14 (1 H, s, H2). $^{13}$C NMR (DMSO-$d_6$): 20.50 (C3'); 28.77 (C2'); 37.11 (C4'); 42.59 (C1'); 118.71 (C5); [128.68 (2 C); 129.68 (2 C); 135.26; 137.89] ($C_6H_4Cl$); 140.76 (C8); 149.52 (C4); 152.28 (C2); 155.89 (C6); 198.63 (C5').

**9-[5-(4-Chlorophenyl)-5-oxopentyl] hypoxantine (VIIIb)** was obtained by method **A** by alkylation of 6-chloropurine followed by hydrolysis of the resulting raw 6-chloropurine derivative (reflux in 4% HCl, 3 h) in a total yield of 27%; $R_f$ 0.28 (18 : 2); mp 231–232°C (ethyl acetate). Mass: *m/z* 330.7 [$M^+$], 331.7 [$M$ + $H^+$]. Calculated *M* 330.7 ($C_{16}H_{15}ClN_4O_2$). $^1$H NMR (DMSO-$d_6$): 1.55 (2 H, m, H2'); 1.85 (2 H, m, H3'); 3.04 (2 H, t, *J* 7.2, H4'); 4.17 (2 H, t, *J* 6.9, H1'); 7.55 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.7, *m*-H, PhCl); 7.93 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.7, *o*-H, PhCl); 8.00 (1 H, s, H8); 8.09 (1 H, s, H2); 12.22 (1 H, br s, H1). $^{13}$C NMR (DMSO-$d_6$): 20.42 (C3'); 28.93 (C2'); 37.07 (C4'); 43.03 (C1'); 123.91 (C5); [128.68 (2 C); 129.68 (2 C); 135.24; 137.91] ($C_6H_4Cl$); 140.20 (C8); 145.29 (C2); 148.32 (C4); 156.59 (C6); 198.58 (C5').

**9-[5-(4-Chlorophenyl)-5-oxopentyl] guanine (IXb)** was obtained by method **A** by alkylation of 2-amino-6-chloropurine followed by hydrolysis of the resulting raw 2-amino-6-chloropurine derivative (reflux in 0.33 N NaOH, 3.5 h) in a total yield of 11%; $R_f$ 0.11 (18 : 2); mp >250°C (ethanol). Mass: *m/z* 345.7 [$M^+$], 346.7 [$M$ + $H^+$]. Calculated *M* 345.7 ($C_{16}H_{16}ClN_5O_2$). $^1$H NMR (DMSO-$d_6$): 1.54 (2 H, m, H2'); 1.78 (2 H, m, H3'); 3.04 (2 H, t, *J* 7.2, H4'); 3.96 (2 H, t, *J* 7.0, H1'); 6.40 (2 H, br s, 2-N$H_2$); 7.56 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.7, *m*-H, PhCl); 7.68 (1 H, s, H8); 7.93 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.7, *o*-H, PhCl); 10.53 (1 H, brs, H2). $^{13}$C NMR (DMSO-$d_6$): 20.49 (C3'); 28.83 (C2'); 37.14 (C4'); 42.33 (C1'); 116.55 (C5); [128.70 (2 C); 129.70 (2 C); 135.26; 137.91] ($C_6H_4Cl$); 137.37 (C8); 151.10 (C4); 153.41 (C2); 156.77 (C6); 198.65 (C5').

**1-[5-(4-Bromophenyl)-5-oxopentyl] uracil (IVc)** was obtained by method **A** in a yield of 27%; $R_f$ 0.65 (18 : 2); mp 174–175°C (ethyl acetate). Mass: *m/z* 351.2 [$M^+$], 352.2 [$M$ + $H^+$]. Calculated *M* 351.2 ($C_{15}H_{15}BrN_2O_3$). $^1$H NMR (DMSO-$d_6$): 1.53–1.70 (4 H, m, H2' and H3'); 3.04 (2 H, t, *J* 6.8, H4'); 3.68 (2 H, t, *J* 6.8, H1'); 5.53 (1 H, d, $J_{5,\,6}$ 7.8, H5); 7.64 (1 H, d, $J_{6,\,5}$ 7.8, H6); 7.71 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr); 7.87 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhBr); 11.16 (1 H, br s, H3). $^{13}$C NMR (DMSO-$d_6$): 20.25 (C3'); 27.86 (C2'); 37.25 (C4'); 47.10 (C1'); 100.74 (C5); [127.05; 129.82(2 C); 131.66 (2 C); 135.60] ($C_6H_4Br$); 145.57 (C6); 150.87 (C2); 163.62(C4); 198.86 (C5').

**1-[5-(4-Bromophenyl)-5-oxopentyl] thymine (Vc)** was obtained by method **A** in a yield of 22%; $R_f$ 0.48 (19 : 1); mp 187–190°C (ethyl acetate). Mass: *m/z* 365.2 [$M^+$], 366.2 [$M$ + $H^+$]. Calculated *M* 365.2 ($C_{16}H_{17}BrN_2O_3$). $^1$H NMR ($CDCl_3$): 1.70–1.80 (4 H, m, H2' and H3'); 1.90 (3 H, s, 5-C$H_3$); 2.98 (2 H, t, *J* 6.4, H4'); 3.73 (2 H, t, *J* 7.0, H1'); 6.98 (1 H, s, H6); 7.68 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr); 7.79 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhBr); 9.09 (1 H, br s, H3). $^{13}$C NMR ($CDCl_3$): 12.36 (5-C$H_3$), 20.74 (C3'); 28.56 (C2'); 37.63 (C4'); 48.22 (C1'); 110.88 (C5); [128.40; 129.60 (2 C); 132.04 (2 C); 135.58] ($C_6H_4Br$); 140.28 (C6); 151.04 (C2); 164.23 (C4); 198.50 (C5').

**1-[5-(4-Bromophenyl)-5-oxopentyl] cytosine (VIc)** was obtained by method **B** in a yield of 8.2%; $R_f$ 0.47 (17 : 3); mp 217–218°C (ethanol). Mass: *m/z* 350.2 [$M^+$], 351.2 [$M$ + $H^+$]. Calculated *M* 350.2 ($C_{15}H_{16}BrN_3O_2$). $^1$H NMR (DMSO-$d_6$): 1.46–1.77 (4 H, m, H2' and H3'); 3.02 (2 H, t, *J* 6.8, H4'); 3.65 (2 H, t, *J* 6.6, H1'); 5.62 (1 H, d, $J_{5,\,6}$ 7.2, H5); 6.92 (2 H, br s, 4-N$H_2$); 7.57 (1 H, d, $J_{6,\,5}$ 7.2, H6); 7.71 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr); 7.87 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhBr);. $^{13}$C NMR (DMSO-$d_6$): 20.44 (C3'); 28.14 (C2'); 37.35 (C4'); 48.16 (C1'); 92.97 (C5); [127.02; 129.83 (2 C); 131.66 (2 C); 135.62] ($C_6H_4Br$); 145.88 (C6); 155.72 (C2); 165.79 (C4); 198.95 (C5').

**9-[5-(4-Bromophenyl)-5-oxopentyl] adenine (VIIc)** was obtained by method **A** in a yield of 34%; $R_f$ 0.39 (18 : 2); mp 206–207°C (ethyl acetate). Mass: *m/z* 374.2 [$M^+$], 375.2 [$M$ + $H^+$]. Calculated *M* 374.2 ($C_{16}H_{16}BrN_5O$). $^1$H NMR (DMSO-$d_6$): 1.55 (2 H, m, H2'); 1.86 (2 H, m, H3'); 3.04 (2 H, t, *J* 7.2, H4'); 4.17 (2 H, t, *J* 7.0, H 1'); 7.14 (2 H, br s, 6-N$H_2$); 7.70 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr); 7.85 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6,

*m*-H, PhBr); 8.12 (1 H, s, H8); 8.14 (1 H, s, H2). $^{13}$C NMR (DMSO-$d_6$): 20.48 (C3'); 28.77 (C2'); 37.08 (C4'); 42.58 (C1'); 118.71 (C5); [127.03; 129.79 (2 C); 131.63 (2 C); 135.57] ($C_6H_4Br$); 140.75 (C8); 149.51 (C4); 152.27 (C2); 155.88 (C6); 198.82 (C5').

**9-[5-(4-Bromophenyl)-5-oxopentyl] hypoxantine (VIIIc)** was obtained by method **A** by alkylation of 6-chloropurine followed by hydrolysis of the resulting raw 6-chloropurine derivative (reflux in 4% HCl, 3 h). The total yield 24%; $R_f$ 0.27 (18 : 2); mp 242°C (degr., ethanol). Mass: *m/z* 375.2 [$M^+$], 376.2 [$M + H^+$]. Calculated *M* 375.2 ($C_{16}H_{15}BrN_4O_2$). $^1$H NMR (DMSO-$d_6$): 1.54 (2 H, m, H2'); 1.84 (2 H, m, H3'); 3.04 (2 H, t, *J* 7.2, H4'); 4.17 (2 H, t, *J* 6.9, H 1'); 7.70 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.5, *o*-H, PhBr); 7.85 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.5, *m*-H, PhBr); 8.01 (1 H, s, H8); 8.10 (1 H, s, H2); 12.25 (1 H, br s, H1). $^{13}$C NMR (DMSO-$d_6$): 20.42 (C3'); 28.97 (C2'); 37.09 (C4'); 43.07 (C1'); 123.93 (C5); [127.13; 129.86 (2 C); 131.71 (2 C); 135.58] ($C_6H_4Br$); 140.29 (C8); 145.38 (C2); 148.36 (C4); 156.65 (C6); 198.84 (C5').

**9-[5-(4-Bromophenyl)-5-oxopentyl] guanine (IXc)** was obtained by method **A** by alkylation of 2-amino-6-chloropurine followed by hydrolysis of the resulting raw 2-amino-6-chloropurine derivative (reflux in 0.33 N NaOH, 3.5 h). The total yield 13%; $R_f$ 0.34 (A); mp 126–127°C (ethanol). Mass: *m/z* 390.2 [$M^+$], 391.2 [$M + H^+$]. Calculated *M* 390.2 ($C_{16}H_{16}BrN_5O_2$). $^1$H NMR (DMSO-$d_6$): 1.71 (2 H, m, H2'); 1.87 (2 H, H3'); 2.91 (2 H, t, *J* 7.2, H4'); 4.01 (2 H, t, *J* 7.0, H1'); 4.79 (2 H, br s, 2-N$H_2$); 7.43 (1 H, s, H8); 7.52 (2 H, d, $J_{o\text{-H},\,m\text{-H}}$ 8.6, *o*-H, PhBr); 7.71 (2 H, d, $J_{m\text{-H},\,o\text{-H}}$ 8.6, *m*-H, PhBr). $^{13}$C NMR ($CDCl_3$): 20.94 (C3'); 29.25 (C2'); 37.50 (C4'); 42.81 (C1'); 115.10 (C5); [120.06; 129.42 (2 C); 131.78 (2 C); 135.79] ($C_6H_4Br$); 135.44 (C8); 152.48 (C4); 155.27 (C2); 159.16 (C6); 198.35 (C5').

**Inhibition of the 3'-processing reaction.** For the preparation of a radioactive duplex U5B/U5A, oligonucleotide U5B/U5A (10 pmol) was incubated with T4 polynucleotide kinase (10 U, Fermentas, Lithuania) and 59 μCi γ-$^{32}$P ATP (3000 Ci/mmol, 16 pmol) in the reaction mixture (20 μ]L) containing the buffer (50 mM Tris-HCl,, pH 7.5, 10 mM $MgCl_2$, 5 mM dithiothreitol, 0.1 mM spermidine, and 0.1 mM EDTA) for 1 h at 37°C. The kinase was deactivated by the addition of 250 mM aqueous EDTA (2 μL) followed by heating to 65°C for 10 min. The complementary oligonucleotide U5A was added and the duplex U5B/U5A was formed by heating the mixture to 95°C followed by slow cooling to room temperature. The resulting duplex was purified from the excess of [γ-$^{32}$P]ATP and salts on a MicroSpin G-25 Columns column (Amersham Biosciences, United States) using the supplier's recommendations.

The $^{32}$P labeled U5B/U5A duplex was incubated with integrase (2 pmol) in the reaction mixture (20 μL) containing the buffer (20 mM HEPES, pH 7.2, 7.5 mM $MgCl_2$, 1 mM DTT, and 10% DMSO) in the presence of increasing concentrations of the inhibitor (1–1500 μM) for 2 h at 37°C. The reaction was stopped the addition of the stop solution (80 μL) (7 mM EDTA, 0.3 M sodium acetate, 10 mM Tris-HCl, pH 8.0, and 0.125 mg/mL glycogen). Integrase was extracted with a phenol/chloroform/isoamyl alcohol mixture (25 : 24 : 1), and the DNA duplex was precipitated with ethanol (250 μL) and analyzed by electrophoresis in 20% PAG with 7 M urea.

Radioautograms were registered on a GE Typhoon FLA 9500 scanner; densitometry was performed using the ImageQuant 5.0 software. For the calculation of the $IC_{50}$ the data on the reaction effectiveness were approximated using the function of exponential decay followed by the calculation at the point corresponding to 50%.

**Inhibition of the strand transfer reaction.** The $^{32}$P labeled U5B-2/U5A duplex was obtained as described above for U5B/U5A starting from the $^{32}$P labeled oligonucleotide U5B-2. The reaction was carried out in the same buffer as that for the 3'-processing using the $^{32}$P labeled U5B/U5A duplex (0.2 pmol) and integrase (2 pmol). The reaction was performed in the presence of increasing inhibitor concentrations (1–1500 μM) at 37°C for 2 h. The isolation and analysis of the products were performed as described above. For the calculation of the $IC_{50}$ the data on the reaction effectiveness were approximated using the function of exponential decay followed by the calculation at the point corresponding to 50%.

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