ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2015, Vol. 41, No. 1, pp. 37–45. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © V.V. Komissarov, V.T. Valuev-Elliston, O.N. Ivanova, S.N. Kochetkov, A.M. Kritzyn, 2015, published in Bioorganicheskaya Khimiya, 2015, Vol. 41, No. 1, pp. 44–53.

The Synthesis of ω-(2-Aryl-1,3-Dioxolan-2-yl)Alkyl Purine Derivatives and Their Activity towards HIV Reverse Transcriptase

V. V. Komissarov, V. T. Valuev-Elliston, O. N. Ivanova, S. N. Kochetkov, and A. M. Kritzyn[1]

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, ul. Vavilova 32, Moscow, 119991 Russia

Received May 8, 2014; in final form, June 23, 2014

Abstract—Novel derivatives of 6-substituted purines were synthesized by alkylation of 6-substituted purines with various 2-(chloroalkyl)-2-aryl-1,3-dioxolanes and related compounds. Their inhibitory properties toward HIV reverse transcriptase were studied. The structure-activity relationship within the synthesized compounds was found.

Keywords: alkylation, HIV reverse transcriptase, non-competitive inhibitors, polymethylene purine derivatives, purines

DOI: 10.1134/S1068162015010069

INTRODUCTION

Medicines capable of inhibiting the human immunodeficiency virus (HIV) replication play an important role for the therapy of acquired immunodeficiency syndrome. Such drugs include inhibitors of the absorption of the virus on the cell surface (entry inhibitors), fusion inhibitors, protease inhibitors, integrase inhibitors, and HIV reverse transcriptase inhibitors of two types, nucleoside- and nonnucleoside-based (NNRTI) compounds.

More than 50 structurally different types of NNRTI are known. Among them there are structures with three aromatic rings (for example, rilpivirin approved by FDA in 2011) or two aromatic fragments joined with a linker. Compounds HI-238 and R100943 [1], which displayed a high antiviral activity and improved resistance profile if compared with the first NNRTI generation (nevirapine), pertain to the latter type.

It is noteworthy that compound R100943 containing two aromatic rings joined with a flexible linker takes a "horseshoe" conformation in the enzyme hydrophobic pocket [1], which differs greatly from the butterfly-like model inherent for nevirapine and related tricyclic derivatives [2].

Despite the hydrolytical instability of compound R100943 due to a thiourea fragment in the linker [1], which was found in the course of clinical trials, interest to the compounds of this type was not lost. It was soon demonstrated that the presence of a thiourea or urea motifs in the linker structure was not mandatory for the inhibitory activity [3].

Polymethylene derivatives of nucleic bases bearing various ω-functional groups in the hydrophobic hydrocarbon chain make possible the elucidation of the function–structure relationship upon the interaction with various proteins. Particularly, earlier we searched for HIV integrase inhibitors among 5-(4-halophenyl)-5-oxopentyl derivatives of nucleic bases [4].

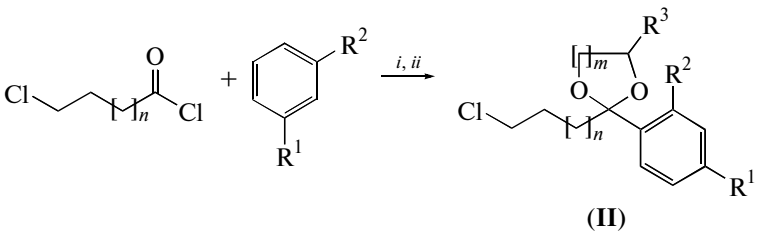
In this work, for the search of new HIV RT inhibitors we used a concept, according to which the presence of two π-systems and a conformational flexibility provided by an extended linker are necessary for interactions with the enzyme hydrophobic pocket.

RESULTS AND DISCUSSION

Compound (**I**) was the starting structure for the search of new HIV RT inhibitors. The inhibitory activity of this compound toward HIV RT was found during the screening of the library of nucleic base derivatives synthesized earlier [5]. The following structural elements can be discriminated in the molecule of compound (**I**): an adenine residue, a polymethylene linker, an aryl radical, and a dioxolane cycle, whereas it was found in preliminary experiments that pyrimidine and guanine derivatives similar to (**I**) did not inhibit HIV RT. A dioxolane fragment in the inhibitor molecule is also necessary, because the corresponding phenone obtained by acid hydrolysis of compound (**I**) did not inhibit the HIV RT activity.

Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TSA, toluenesulphonic acid; HIV, human immunodeficiency virus type 1; RT, reverse transcriptase; NNRTI, nonnucleoside reverse transcriptase inhibitors.

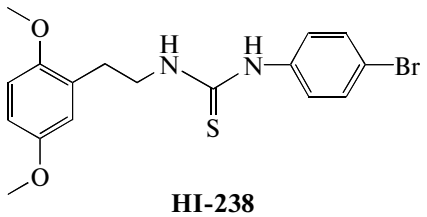
[1] Corresponding author: phone: +7 (499) 135-1405; e-mail: amk@eimb.ru.



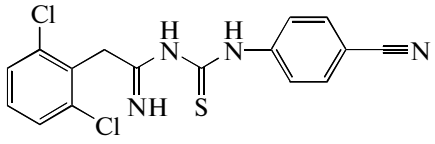
(II)

a: $R^1 = R^3 = H$, $n = 0$, $m = 1$
b: $R^1 = R^3 = H$, $n = 2$, $m = 1$
c: $R^1 = R^3 = H$, $n = 3$, $m = 1$
d: $R^1 = F$, $R^3 = H$, $n = m = 1$
e: $R^1 = Cl$, $R^3 = H$, $n = m = 1$
f: $R^1 = Br$, $R^3 = H$, $n = m = 1$
g: $R^1 = Me$, $R^3 = H$, $n = m = 1$
h: $R^1 = R^{2\#} = Me$, $R^3 = H$, $n = m = 1$
i: $R^1 = Et$, $R^3 = H$, $n = m = 1$
j: $R^1 = i\text{-}Pr$, $R^3 = H$, $n = m = 1$
k: $R^1 = OMe$, $R^3 = H$, $n = m = 1$
l: $R^1 = R^3 = H$, $n = 1$, $m = 2$
iii → **m**: $R^1 = H$, $R^3 = CH_2OH$, $n = 1$, $m = 1$
iii → **n**: $R^1 = H$, $R^3 = CH_2OAc$, $n = 1$, $m = 1$
\# for all the compounds except (**IIh**), $R^2 = H$

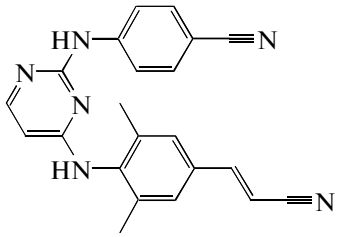
Scheme 1. The synthetic scheme for alkylating agents (**IIa**)–(**IIn**). (*i*) $AlCl_3$, the varied solvent (see the Experimental section), 0–20°C; (*ii*) diol, *p*-TSA, benzene, Δ; (*iii*) AcCl, NEt_3, CH_2Cl_2, 0°C.



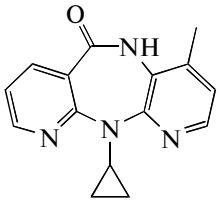
HI-238



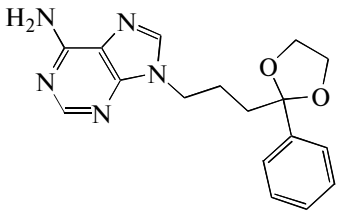
R100943



Rilpivirin



Nevirapine



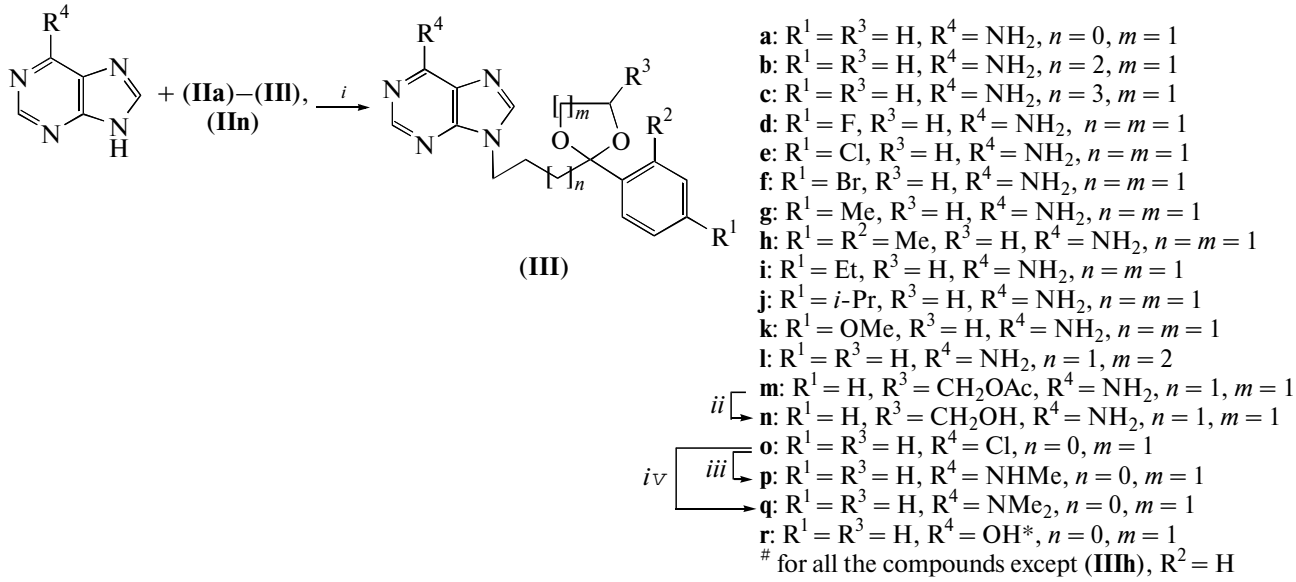
(I)

The Synthesis of 6-Substituted Purines

It seemed us interesting to synthesize compounds with a 6-substituted purine residue separated from the phenyl radical and the dioxolane (or analogous) fragment by a polymethylene linker and study their capacity to inhibit HIV RT. The synthesis of target compounds based on of alkylation reactions seemed to be the most rational approach. Thus, the first step was the preparation of alkylating agents by acylation of benzene or its substituted derivatives with ω-chloroacyl chlorides using the Friedel–Crafts reaction [6, 7]. The acyl chlorides of 3-chloropropanoic, 5-chloropentanoic, and 6-chlorohexanoic acid were used. As aryl components, benzene, toluene, *m*-xylene, fluoro-, chloro-, bromo-, ethyl-, isopropyl-, and methoxybenzene were taken. The long time refluxing of the phenones obtained with the corresponding diols in the presence of TSA with a Dean–Stark trap resulted in the target dioxolanes (**IIa**)–(**IIm**) in good yields (Scheme 1). Dioxolane (**IIn**) was prepared by acylation of derivative (**IIm**) in a good yield.

Alkylation of 6-substituted purines was performed in dimethylformamide in the presence of DBU. For the isolation and purification of the target compounds, column chromatography on silica gel was used. Derivative (**IIIm**) was obtained by alkaline hydrolysis of compound (**IIIn**) under mild conditions (Scheme 2). Compounds with 6-methylamino- (**IIIp**) and 6-dimethylamino-(**IIIq**) groups were obtained by aminolysis of 6-chloropurine derivative (**IIIo**). Hypoxantine derivative (**IIIr**) was described earlier [5].

^1H and ^{13}C NMR spectra of the synthesized compounds fully confirmed their structures and purity (see the Experimental section).



Scheme 2. The synthetic scheme for ω-(2-aryl-1,3-dioxolan-2yl)alkyl derivatives of adenine and relative compounds. (*i*) DBU, DMF, 80°C; (*ii*) NEt_3, $EtOH/H_2O$, Δ; (*iii*) $NH_2Me \cdot HCl$, DBU, MeOH, 20°C; (*iv*) $NHMe_2 \cdot HCl$, DBU, MeOH, 20°C.
* Compound (**IIIr**) is in the keto form.

The Activity of the Synthesized Compounds toward HIV RT

The synthesized compounds were tested as HIV RT inhibitors as described in [8]. The measure of inhibitory activity was the enzyme inhibition constant (K_I) (the table).

The comparison of activities of compounds (**I**) and (**IIIa**)–(**IIIc**) demonstrated that the optimal length of the linker joining a purine cycle and a dioxolane fragment is three methylene units. It is also noteworthy that the dioxolane fragment can affect the activity. The replacement of the five-membered cycle by a six-membered one resulted in a decreased activity [cf. (**I**) and (**IIIl**)].

It is likely that both an increased length of the linker between the dioxolane and purine fragments of (**IIIb**) and (**IIIc**) and a more bulky dioxolane ring (**IIIl**) hindered the placement of the inhibitor in the HIV RT hydrophobic pocket.

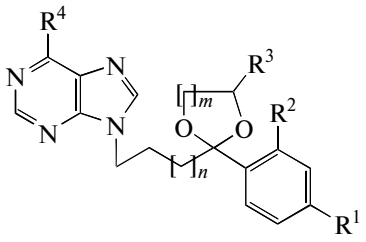
Compounds (**IIIm**) and (**IIIn**) exemplify the fact that the introduction of substituents into the dioxolane cycle position 3 resulted in a complete loss of activity.

The study of the influence of the benzene ring substituent on the anti-HIV RT activity demonstrated some common relationships. It was found for *p*-halosubstituted derivatives (**IIId**)–(**IIIf**) that only chlorosubstituted (**IIIe**) was active. Halogens can impact the inhibitor interaction with the "pocket" amino acids both directly, due to hydrophobic and dispersion interactions as well as hydrogen bonds, and indirectly, by effecting the distribution of the electron density in the benzene ring. It is most likely that a low activity of bromosubstituted (**IIIf**) is related with the steric factor reason, whereas the fluorine atom in the *p*-position of the (**IIId**) benzene ring negatively affected the redistribution of the electron density thus hindering stacking interactions of the benzene ring with the side groups of the hydrophobic pocket amino acids.

Compound (**IIIg**) containing a methylene group in the *p*-position of the benzene ring proved to be most active. Similarly to compound (**IIIe**), an increased activity can be probably explained by dispersion interactions of the substituent in the *p*-position of the benzene ring with amino acids of the hydrophobic pocket. However, the introduction of more bulky hydrophobic substituents [(**IIIi**) and (**IIIj**)] caused the loss of activity, which is most probably the result of steric hindrances for the inhibitor placing in the binding site. Probably, compound (**IIIk**) was inactive for the same reason. The introduction of an additional methyl substituent to the *o*-position of the benzene fragment (**IIIh**) also resulted in a decrease in the inhibitory activity. Thus, the introduction of small hydrophobic groups to the *p*-position of the benzene fragment only allowed an insignificant increase in the activity [cf. (**IIIe**), (**IIIg**), and (**I**)].

With the goal of corroborating that the synthesized compounds noncompetitively inhibited HIV RT by interacting with the binding site of nonnucleoside inhibitors, we tested the most effective compound (**IIIg**) containing two amino acid replacements (Lys103Asn and Tyr181Cys) as an HIV RT inhibitor. These mutations are located in the enzyme binding site of nonnucleoside inhibitors and are characteristic for viral

Inhibitory activity of the synthesized compounds toward HIV RT



Compound	R^1	R^2	R^3	R^4	*n*/*m*	K_I, μM
(I)	H	H	H	NH_2	1/1	16
(IIIa)	H	H	H	NH_2	0/1	>100
(IIIb)	H	H	H	NH_2	2/1	>100
(IIIc)	H	H	H	NH_2	3/1	>100
(IIId)	F	H	H	NH_2	1/1	>100
(IIIe)	Cl	H	H	NH_2	1/1	14.7
(IIIf)	Br	H	H	NH_2	1/1	>100
(IIIg)	Me	H	H	NH_2	1/1	13.4*
(IIIh)	Me	Me	H	NH_2	1/1	18.4
(IIIi)	CH_2CH_3	H	H	NH_2	1/1	>100
(IIIj)	*i*-Pr	H	H	NH_2	1/1	35.6
(IIIk)	O-CH_3	H	H	NH_2	1/1	>100
(IIIl)	H	H	H	NH_2	1/2	26
(IIIm)	H	H	CH_2-OAc	NH_2	1/1	>100
(IIIn)	H	H	CH_2-OH	NH_2	1/1	>100
(IIIo)	H	H	H	Cl	1/1	>100
(IIIp)	H	H	H	NHMe	1/1	19.7
(IIIq)	H	H	H	NMe_2	1/1	>100
(IIIr)	H	H	H	OH	1/1	>100
Nevirapin	–	–	–	–	–	4.2

* For the mutant HIV RT (K103N + Y181C) K_I = 1.1 mM.

strains resistant to HIV RT nonnucleoside inhibitors [9]. We demonstrated in this experiment that the inhibitory activity of derivative **(IIIg)** toward the mutant enzyme was 80 times lower than that toward the wild-type enzyme (the table). This fact supported our assumption.

The comparison of analogues of compound **(I)** bearing various substituents in position 6 of the purine cycle **(IIIo)**–**(IIIr)** showed that the introduction of methyl residues into amino groups caused a decrease in the inhibitory activity and the replacement of amino groups by a chlorine atom **(IIIo)** or oxygen **(IIIr)** led to a complete loss of the activity. It is likely that the purine amino group formed hydrogen bonds with oxygen atoms of the main protein chain and, therefore, the introduction of amino group substituents or its replacement resulted in the loss of activity.

EXPERIMENTAL

In this work we used adenine, hypoxantine, 6-chloropurine, 3-chloropropionyl chloride, and 6-chlrohexanoyl chloride (Sigma, United States); 1,8-diazabicyclo[5.4.0]undec-7-ene, *p*-toluene sulfonic acid monohydrate, $CDCl_3$, DMSO-d_6, benzene, toluene, ethylbenzene, cumene, xylene, anisole, fluorobenzene, chlorobenzene, bromobenzene, aluminum chloride, methylamine hydrochloride, dimethylamine hydrochloride, ethylene glycol, glycerol, acetyl chloride, and triethylamine (Acros Organics, Belgium). 4-Chlorobutanoyl chloride and 5-chloropentanoyl chloride were prepared as described in [6, 7]. The solvents were purified and dried according to standard protocols [7]. TLC was carried out on Kieselgel 60 F_{254} plates (Merck, Germany) in the following systems: 1 : 1 methylene chloride–heptane (A), 18 : 2 chloroform–ethanol (B); and 18.5 : 1.5 chloroform–ethanol (C).

The compounds were detected by UV absorption at 254 nm. Column chromatography was performed on silica gel 60 (0.040–0.063 mm) (Merck, Germany).

Mass spectra were registered on a MS-30 mass spectrometer (Kratos, Japan) using the electron impact as an ionization method. NMR spectra were registered on a Bruker AMXIII-400 spectrometer in $CDCl_3$ if not stated otherwise with the working frequency 400 MHz for ^1H and 100 MHz for ^{13}C spectra at 300 K (δ, ppm, Hz).

The following reagents were used in biological experiments: [α-^{32}P]dATP (5000 Ci/mol, Isotop, Russia), 2'-deoxyribonucleoside 5'-triphosphates (Promega, United States), cellulose Whatman 3MM filters (Whatman, Great Britain). Other reagents of the highest purity were purchased from Sigma-Aldrich or Fluka. Activated DNA was obtained from salmon sperm (Pharmacia Biotech, United States) by treatment with calf pancreas DNase (Fermentas, Lithuania) as described in [10]. The plasmid encoding the wild type HIV-1 RT was a kind gift of Prof. S. Le Grice (National Cancer Institute, Frederick, Maryland, United States). The plasmid encoding RT with two amino acid replacements (Lys103Asn and Tyr181Cys) was described in [11]. The wild type HIV-1 RT and the mutant form (K103N+Y181C) were isolated and purified using Ni-NTA agarose according to the standard protocol [12].

Preparation of alkylating agents (IIa)–(IIm). Anhydrous aluminum trichloride (3 g, 22 mmol) was added in portions under stirring to a solution of ω-chlorocarboxylic acid chloride (20 mmol) and aromatic hydrocarbon (25 mmol) in a solvent (an excess of the same aromatic hydrocarbon or methylene chloride, 10 mL) cooled to 0°C for 5 min, and the resulting solution was stirred for 1 h at 0°C and then 1 h at 20°C. The mixture was poured onto ice (20 g), the organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The extracts were united, dried with anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by column chromatography (l = 5 cm, d = 5 cm) on silica gel eluting with methylene chloride. The chromatographically homogeneous product was used without further purification for the synthesis of alkylating agents (**IIa**)–(**IIm**) as described below.

A solution of the phenone prepared at the previous step (10 mmol), the corresponding diol (100 mmol), and TSA (0.5 g, 2.6 mmol) were mixed in dry benzene (70 mL). The resulting solution was refluxed for 10 h using a Dean–Stark trap. The reaction mixture was cooled and a solution semisaturated sodium hydrocarbonate (50 mL) was added. The organic layer was separated, and the aqueous phase was extracted with benzene (3 × 30 mL). The united organic extracts were dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was purified by column chromatography (l = 5 cm, d = 5 cm) on silica gel eluting with methylene chloride.

2-(2-Chloroethyl)-2-phenyl-1,3-dioxolane (IIa) was obtained in a yield of 35%, R_f 0.46 (A). Mass: m/z 212.1 [M^+]. Calc. M 212.7 ($C_{11}H_{13}ClO_2$). ^1H NMR: 2.84 (2 H, m, CH_2CH_2Cl); 3.68 (2 H, t, J 6.5, CH_2Cl); [3.76; 3.99] (2 H × 2, m × 2, OCH_2CH_2O); 7.27–7.46 (5 H, m, Ph). ^{13}C NMR: 39.13 (*C*H_2CH$_2$Cl); 43.47 (*C*H_2Cl); 64.57 (2 C, O*C*H_2*C*H_2O); 108.95 (O*C*O); [125.47 (2 C, C3 and C5); 128.02 (C4); 128.28 (2 C, C2 and C6); 141.58 (C1)] (Ph).

2-(4-Chlorobutyl)-2-phenyl-1,3-dioxolane (IIb) was obtained in a yield of 61%, R_f 0.49 (A). Mass: m/z 240.1 [M^+]. Calc. M 240.7 ($C_{13}H_{17}ClO_2$). ^1H NMR: 1.49 (2 H, m, CH_2CH$_2$Cl); 1.73 (2 H, m, CH_2CH$_2$CH$_2$Cl); 1.91 (2 H, m, CH_2CH$_2$CH$_2$CH$_2$Cl); 3.47 (2 H, t, J 6.7, CH_2Cl); [3.75; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); 7.29–7.47 (5 H, m, Ph). ^{13}C NMR: 21.18 (*C*H_2CH$_2$CH$_2$Cl); 32.70 (*C*H_2CH$_2$Cl); 39.75 (*C*H_2CH$_2$CH$_2$CH$_2$Cl); 44.89 (*C*H_2Cl); 64.57 (2 C, O*C*H_2*C*H_2O); 110.26 (O*C*O); [125.73 (2 C, C3 and C5); 128.06 (C4); 128.14 (2 C, C2 and C6); 142.56 (C1)] (Ph).

2-(5-Chloropentyl)-2-phenyl-1,3-dioxolane (IIc) was obtained in a yield of 62%, R_f 0.51 (A). Mass: m/z 254.1 [M^+]. Calc. M 254.7 ($C_{14}H_{19}ClO_2$). ^1H NMR: 1.38 (4 H, m, CH_2CH_2CH$_2$ CH$_2$Cl); 1.72 (2 H, m, CH_2CH$_2$Cl); 1.89 (2 H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$Cl); 3.47 (2 H, t, J 6.7, CH_2Cl); [3.75; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); 7.25–7.44 (5 H, m, Ph). ^{13}C NMR: 22.98 (*C*H_2CH$_2$CH$_2$CH$_2$Cl); 26.98 (*C*H_2CH$_2$CH$_2$Cl); 32.62 (*C*H_2CH$_2$Cl); 40.40 (*C*H_2CH$_2$CH$_2$CH$_2$CH$_2$Cl); 45.01 (*C*H_2Cl); 64.56 (2 C, O*C*H_2*C*H_2O); 110.43 (O*C*O); [125.78 (2 C, C3 and C5); 127.85 (C4); 128.14 (2 C, C2 and C6); 142.66 (C1)] (Ph).

2-(3-Chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (IId) was obtained in a yield of 55%, R_f 0.49 (A). Mass: m/z 244.1 [M^+]. Calc. M 244.7 ($C_{12}H_{14}ClFO_2$). ^1H NMR: 1.84 (2 H, m, CH_2CH$_2$Cl); 2.01 (2 H, m, CH_2CH$_2$CH$_2$Cl); 3.52 (2 H, t, J 6.7, CH_2Cl); [3.75; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); [7.01 (2 H, m, [H3 and H5]; 7.41 (2 H, m, (H2 and H6)] (Ph). ^{13}C NMR: 27.19 (*C*H_2CH$_2$Cl); 38.00 (*C*H_2CH$_2$CH$_2$Cl); 45.18 (*C*H_2Cl); 64.75 (2 C, O*C*H_2*C*H_2O); 109.87 (O*C*O); [115.10 (2 C, d, J 21.5, C3 and C5); 127.65 (2 C, d, J 8.1, C2 and C6); 130.82 (d, J 9.4, C1); 161.61 (d, J 245.9, C4)] (Ph).

2-(3-Chloropropyl)-2-(4-chlorophenyl)-1,3-dioxolane (IIe) was obtained in a yield of 12%, R_f 0.50 (A). Mass: m/z 260.0 [M^+]. Calc. M 261.1 ($C_{12}H_{14}Cl_2O_2$). ^1H NMR: 1.84 (2 H, m, CH_2CH$_2$Cl); 2.00 (2 H, m, CH_2CH$_2$CH$_2$Cl); 3.52 (2 H, t, J 6.7, CH_2Cl); [3.74; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); 7.23–7.39 (4 H, m, Ph). ^{13}C NMR: 27.05 (*C*H_2CH$_2$Cl); 37.76 (*C*H_2CH$_2$CH$_2$Cl); 45.05 (*C*H_2Cl); 64.69 (2 C, O*C*H_2*C*H_2O); 109.70 (O*C*O); [127.27 (2 C, C3 and C5); 128.46 (2 C, C2 and C6); 133.98 (C1); 141.07 (C4)] (Ph).

2-(3-Chloropropyl)-2-(4-bromophenyl)-1,3-dioxolane (IIf) was obtained in a yield of 10%, R_f 0.50 (A). Mass: *m/z* 304.0 [M^+]. Calc. *M* 305.6 ($C_{12}H_{14}BrClO_2$). ^{1}H NMR (DMSO-d_6): 1.83 (2 H, m, CH_2CH$_2$Cl); 1.98 (2 H, m, CH_2CH$_2$CH$_2$Cl); 3.51 (2 H, t, *J* 6.7, CH_2Cl); [3.95; 4.12] (2 H × 2, m × 2, OCH_2CH_2O); [7.29 (2 H, m, H2 and H6); 7.52 (2 H, m, H3 and H5)] (Ph). ^{13}C NMR (DMSO-d_6): 27.13 (*C*H$_2$CH$_2$Cl); 37.75 (*C*H$_2$CH$_2$CH$_2$Cl); 45.03 (*C*H$_2$Cl); 64.27 (2 C, OCH$_2$*C*H$_2$O); 108.89 (O*C*O); [121.14 (C4); 127.67 (2 C, C2 and C6); 131.04 (2 C, C3 and C5); 140.79 (C1)] (Ph).

2-(3-Chloropropyl)-2-(4-methylphenyl)-1,3-dioxolane (IIg) was obtained in a yield of 71%, R_f 0.52 (A). Mass: *m/z* 240.1 [M^+]. Calc. *M* 240.7 ($C_{13}H_{17}ClO_2$). ^{1}H NMR: 1.86 (2 H, m, CH_2CH$_2$Cl); 2.03 (2 H, m, CH_2CH$_2$CH$_2$Cl); 2.35 (3 H, s, CCH_3Ph); 3.58 (2 H, t, *J* 6.7, CH_2Cl); [3.77; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); [7.15 (2 H, m, H-3 and H-5); 7.83 (2 H, m, H-2 and H-6)] (Ph). ^{13}C NMR: 21.02 (*C*H$_3$Ph); 27.09 (*C*H$_2$CH$_2$Cl); 37.49 (*C*H$_2$CH$_2$CH$_2$Cl); 45.07 (*C*H$_2$Cl); 64.44 (2 C, OCH$_2$*C*H$_2$O); 109.99 (O*C*O); [125.54 (2 C, C, and C6); 128.81 (2 C, C3 and C5); 137.56 (C4); 139.27 (C1)] (Ph).

2-(3-Chloropropyl)-2-(2,4-dimethylphenyl)-1,3-dioxolane (IIh) was obtained in a yield of 40%, R_f 0.55 (A). Mass: *m/z* 254.1 [M^+]. Calc. *M* 254.7 ($C_{14}H_{19}ClO_2$). ^{1}H NMR: 1.88 (2 H, m, CH_2CH$_2$Cl); 2.06 (2 H, m, CH_2CH$_2$CH$_2$Cl); [2.29; 2.44] ((3 H × 2, s × 2, (CH_3)$_2$Ph); 3.53 (2 H, t, *J* 6.7, CH_2Cl); [3.73; 3.98] (2 H × 2, m × 2, OCH_2CH_2O); 6.96–7.40 (3 H, m, Ph). ^{13}C NMR: [20.66; 20.92] ((*C*H$_3$)$_2$Ph); 27.13 (*C*H$_2$CH$_2$Cl); 36.31 (*C*H$_2$CH$_2$CH$_2$Cl); 45.36 (*C*H$_2$Cl); 64.21 (2 C, OCH$_2$*C*H$_2$O); 110.82 (O*C*O); [126.22; 126.84; 129.15; 132.91; 135.66; 137.74] (Ph).

2-(3-Chloropropyl)-2-(4-ethylphenyl)-1,3-dioxolane (IIi) was obtained in a yield of 76%, R_f 0.52 (A). Mass: *m/z* 254.1 [M^+]. Calc. *M* 254.7 ($C_{14}H_{19}ClO_2$). ^{1}H NMR: 1.24 (3 H, t, *J* 7.6, CH_3CH$_2$Ph); 1.86 (2 H, m, CH_2CH$_2$Cl); 2.02 (2 H, m, CH_2CH$_2$CH$_2$Cl); 2.64 (2 H, q, *J* 7.6, CH$_3$CH_2Ph); 3.52 (2 H, t, *J* 6.7, CH_2Cl); [3.77; 4.00] (2 H × 2, m× 2, OCH_2CH_2O); [7.16 (2 H, m, H3 and H5); 7.35 (2 H, m, H2 and H6)] (Ph). ^{13}C NMR: 15.47 (*C*H$_3$CH$_2$Ph); 27.21 (*C*H$_2$CH$_2$Cl); 28.57 (CH$_3$*C*H$_2$Ph); 37.89 (*C*H$_2$CH$_2$CH$_2$Cl); 45.23 (*C*H$_2$Cl); 64.59 (2 C, OCH$_2$*C*H$_2$O); 110.15 (O*C*O); [125.69 (2 C, C2 and C6); 127.71 (2 C, C3 and C5); 139.63 (C1); 144.02 (C4)] (Ph).

2-(3-Chloropropyl)-2-(4-isopropylphenyl)-1,3-dioxolane (IIj) was obtained in a yield of 45%, R_f 0.53 (A). Mass: *m/z* 268.1 [M^+]. Calc. *M* 268.8 ($C_{15}H_{21}ClO_2$). ^{1}H NMR: 1.24 (6 H, d, *J* 6.8, (CH_3)$_2$CHPh); 1.87 (2 H, m, CH_2CH$_2$Cl); 2.01 (2 H, m, CH_2CH$_2$CH$_2$Cl); 2,90 (1 H, hept, *J* 6.8, (CH$_3$)$_2$C*H*Ph); 3.52 (2 H, t, *J* 6.7, CH_2Cl); [3.78; 4.00] (2 H × 2, m × 2, OCH_2CH_2O); [7.19 (2 H, m, H3 and H5); 7.35 (2 H, m, H2 and H6)] (Ph). ^{13}C NMR: 24.02 (2 C, (*C*H$_3$)$_2$CHPh); 27.21 (*C*H$_2$CH$_2$Cl); 33.85 ((CH$_3$)$_2$*C*HPh); 37.90 (*C*H$_2$CH$_2$CH$_2$Cl); 45.24 (*C*H$_2$Cl); 64.62 (2 C, OCH$_2$*C*H$_2$O); 110.15 (O*C*O); [125.64 (2 C, C2 and C6); 126.28 (2 C, C3 and C5); 139.75 (C1); 148.63 (C4)] (Ph).

2-(3-Chloropropyl)-2-(4-methoxyphenyl)-1,3-dioxolane (IIk) was obtained in a yield of 51%, R_f 0.48 (A). Mass: *m/z* 256.1 [M^+]. Calc. *M* 256.7 ($C_{13}H_{17}ClO_3$). ^{1}H NMR: 1.83 (2 H, m, CH_2CH$_2$Cl); 2.00 (2 H, m, CH_2CH$_2$CH$_2$Cl); 3.50 (2 H, t, *J* 6.7, CH_2Cl); [3.76; 3.98] (2 H × 2, m × 2, OCH_2CH_2O); 3.79 (3 H, s, PhOCH_3) [6.85 (2 H, m, H3 and H5); 7.34 (2 H, m, H2 and H6)] (Ph). ^{13}C NMR: 27.13 (*C*H$_2$CH$_2$Cl); 37.81 (*C*H$_2$CH$_2$CH$_2$Cl); 45.11 (*C*H$_2$Cl); 55.21 (PhO*C*H$_3$); 64.44 (2 C, OCH$_2$*C*H$_2$O); 109.92 (O*C*O); [113.47 (2 C, C3 and C5); 126.87 (2 C, C2 and C6); 130.25 (C1); 159.33 (C4)] (Ph).

2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane (IIl) was obtained in a yield of 70%, R_f 0.49 (A). Mass: *m/z* 240.09 [M^+]. Calc. *M* 240.7 ($C_{13}H_{17}ClO_2$). ^{1}H NMR: 1.79–1.90 (4 H, m, CH_2CH_2CH$_2$Cl); 1.99 (2 H, m, OCH$_2$CH_2CH$_2$O); 3.47 (2 H, t, *J* 6.5, CH_2Cl); 3.76–3.87 (4 H, m, OCH_2CH$_2$CH_2O); 7.27–7.41 (5 H, m, Ph); ^{13}C NMR: 25.59 (OCH$_2$*C*H$_2$CH$_2$O); 26.61 (*C*H$_2$CH$_2$Cl); 38.51 (*C*H$_2$CH$_2$CH$_2$Cl); 45.32 (*C*H$_2$Cl); 61.11 (2 C, OCH$_2$*C*H$_2$O); 101.52 (O*C*O); [127.36 (2 C, C3 and C5); 128.06 (C4); 128.61 (2 C, C2 and C6); 139.96 (C1)] (Ph).

2-(3-Chloropropyl)-2-phenyl-4-hydroxymethyl-1,3-dioxolane (IIm) was obtained in a yield of 79%, R_f 0.31 (A). Mass: *m/z* 256.1 [M^+]. Calc. *M* 256.7 ($C_{13}H_{17}ClO_3$). ^{1}H NMR: 1.86 (2 H, m, CH_2CH$_2$Cl); 1.89 (1 H, m, O*H*); 2.04 (2 H, m, CH_2CH$_2$CH$_2$Cl); 3.52 (2 H, t, *J* 6.7, CH_2Cl); 3.63 (2 H, m, CH_2OH); 3.80 (2 H, m × 2, OCH_2CH); 4.04–4.18 (1 H, m × 2, OC*H*); 7.25–7.48 (5 H, m, Ph). ^{13}C NMR: 26.90 (*C*H$_2$CH$_2$Cl); 37.85 (*C*H$_2$CH$_2$CH$_2$Cl); 44.98 (*C*H$_2$Cl); 63.32 (*C*H$_2$OH); 65.69 (*C*H$_2$O); 77.82 (*C*HO); 110.72 (O*C*O); [125.64 (2 C, C3 and C5); 128.10 (C4); 128.25 (2 C, C2 and C6); 141.86 (C1)] (Ph).

2-(3-Chloropropyl)-2-phenyl-4-acetoxymethyl-1,3-dioxolane (IIn). Triethylamine (3 mL, 21 mmol) and was added to a solution of 4-hydroxymethyl derivative (**IIm**) in dry CH_2Cl_2 (25 mL) (4.3 g, 17 mmol). The solution was cooled on an ice bath and a solution of AcCl (1.5 mL, 21 mmol) in methylene chloride (5 mL) was added dropwise under stirring for 5 min. The reaction mixture was stirred for 1 h at 0°C, kept for 14 h at room temperature, and poured onto ice (30 g). The organic layer was separated and the aqueous layer was extracted with methylene chloride (3 × 30 mL). The extracts were combined, dried with anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by column chromatography (l = 5 cm, d = 5 cm) on silica gel eluting with methylene chloride to give 41% of derivative (**IIn**), R_f 0.62 (A). Mass: *m/z* 298.1 [M^+]. Calc. *M* 298.8 ($C_{15}H_{19}ClO_4$). ^{1}H NMR: 1.87 (2 H, m, CH_2CH$_2$Cl); 2.02 (2 H, m, CH_2CH$_2$CH$_2$Cl); 2.10 (3 H, s, COCH_3), 3.52 (2 H, t,

J 6.7, CH_2Cl); 3.67 (2 H, m, CH_2OAc); 3.80 (2 H, m × 2, OCH_2CH); 4.18 (1 H, m, OCH); 7.27–7.48 (5 H, m, Ph). ^{13}C NMR: 20.76 (*C*H_3CO); 26.84 (*C*H_2CH$_2$Cl); 37.82 (*C*H_2CH$_2$CH$_2$Cl); 44.98 (*C*H_2Cl); 64.47 (*C*H_2OAc); 66.29 (*C*H_2O); 73.25 (*C*HO); 111.01 (O*C*O); [125.56 (2 C, C3 and C5); 128.10 (C4); 128.24 (2 C, C2 and C6); 141.98 (C1)] (Ph); 170.72 (CH$_3$*C*O).

Alkylation of adenine and other 6-substituted purines with (IIa)–(III) and (IIn) in the presence of DBU. The corresponding alkylating agent (6 mmol) and DBU (6 mmol, 0.86 mL) were added to a suspension of a nucleic base or its protected derivative (5 mmol) in absolute DMF (10 mL) and the mixture was heated at 80–100°C for 20 h. The reaction course was monitored by TLC. The mixture was cooled and evaporated, and the residue was suspended in a minimal volume of CH_2Cl_2 and chromatographed on a silica gel column (5 × 10 cm, ~70 g) eluting in a gradient of ethanol in chloroform (0 → 20%). The target fractions were evaporated and the residue was recrystallized from EtOAc or a 2 : 1 EtOAc–heptane mixture.

9-[2-(2-Phenyl-1,3-dioxolan-2-yl)ethyl]adenine (IIIa) was obtained in a yield of 30%, R_f 0.44 (B); mp 172–173°C (EtOAc). Mass: *m/z* 312.1 [*M* + H$^+$]. Calc. *M* 311.3 ($C_{16}H_{17}N_5O_2$). ^{1}H NMR: 2.50 (2 H, t, *J* 7.2, H2'); [3.77; 4.01] (2 H × 2, m × 2, OCH_2CH_2O); 4.34 (2 H, t, *J* 7.2, H1'); 5.74 (2 H, br s, 6-NH_2); 7.25–7.45 (5 H, m, Ph); 7.74 (s, 1 H, H8); 8.34 (s, 1 H, H2). ^{13}C NMR: 39.20 (C2'); 39.73 (C1'); 64.64 (2 C, OCH_2*C*H_2O); 108.95 (O*C*O); 119.73 (C5); [125.55 (2 C, C3 and C5); 128.39 (C4); 128.43 (2 C, C2 and C6); 141.30 (C1)] (Ph); 140.75 (C8); 150.23 (C4); 152.90 (C2); 155.56 (C6).

9-[2-(2-Phenyl-1,3-dioxolan-2-yl)butyl]adenine (IIIb) was obtained in a yield of 42%, R_f 0.48 (B); mp 146–147°C (EtOAc). Mass: *m/z* 340.2 [*M* + H$^+$]. Calc. *M* 339.4 ($C_{18}H_{21}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.20 (2 H, m, H2'); 1.77 (2 H, m, H3'); 1.83 (2 H, m, H4'); [3.63; 3.92] (2 H × 2, m × 2, OCH_2CH_2O); 4.07 (2 H, t, *J* 7.0, H1'); 7.12 (2 H, br s, 6-NH_2); 7.24–7.34 (5 H, m, Ph); 8.05 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 20.25 (C3'); 29.21 (C2'); 38.99 (C4'); 42.59 (C1'); 64.03 (2 C, OCH_2*C*H_2O); 109.50 (O*C*O); 118.68 (C5); [125.26 (2 11 C, C3 and C5); 127.61 (C4); 127.92 (2 C, C2 and C6); 142.25 (C1)] (Ph); 140.67 (C8); 149.46 (C4); 152.23 (C2); 155.86 (C6).

9-[5-(2-Phenyl-1,3-dioxolan-2-yl)pentyl]adenine (IIIc) was obtained in a yield of 43%, R_f 0.43 (B); mp 115–116°C (EtOAc). Mass: *m/z* 354.2 [*M* + H$^+$]. Calc. *M* 353.4 ($C_{19}H_{23}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.22 (4 H, m, H2' and H4'); 1.75 (4 H, m, H5' and H6'); [3.63; 3.92] (2 H × 2, m × 2, OCH_2CH_2O); 4.06 (2 H, t, J 7.2, H1'); 7.14 (2 H, br s, 6-NH$_2$); 7.28–7.35 (5 H, m, Ph); 8.08 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 22.72 (C4'); 25.98 (C2'); 29.18 (C3'); 39.55 (C4'); 42.78 (C1'); 64.02 (2 C, OCH_2*C*H_2O); 109.57 (O*C*O); 118.70 (C5); [125.29 (2 C, C3 and C5); 127.57 (C4); 127.93 (2 C, C2 and C6); 142.39 (C1)] (Ph); 140.69 (C8); 149.48 (C4); 152.25 (C2); 155.87 (C6).

9-{3-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIId) was obtained in a yield of 36%, R_f 0.42 (B); mp 168–169°C (EtOAc). Mass: *m/z* 344.1 [*M* + H$^+$]. Calc. *M* 343.4 ($C_{17}H_{18}FN_5O_2$). ^{1}H NMR (DMSO-d_6): 1.80 (4 H, m, H2', H3'); [3.65; 3.95] (2 H × 2, m × 2, OCH_2CH_2O); 4.12 (2 H, t, *J* 7.2, H1'); 7.15 (4 H, m, 6-NH_2, (H-3 and H-5) Ph); 7.37 (2 H, m, (H-2 and H-6) Ph); 8.08 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 24.09 (C2'); 36.83 (C3'); 42.71 (C1'); 64.17 (2 C, OCH_2*C*H_2O); 108.91 (O*C*O); 118.69 (C5); [115.10 (2 C, d, *J* 21.1, C-3 and C-5); 127.43 (2 C, d, *J* 8.1, C2 and C6); 138.44 (d, *J* 2, C1); 161.68 (d, *J* 243.7, C4)] (Ph); 140.74 (C8); 149.42 (C4); 152.27 (C2); 155.86 (C6).

9-{3-[2-(4-Chlorophenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIe) was obtained in a yield of 50%, R_f 0.64 (B); mp 130–131°C (EtOAc). Mass: *m/z* 360.1 [*M* + H$^+$]. Calc. *M* 359.8 ($C_{17}H_{18}ClN_5O_2$). ^{1}H NMR (DMSO-d_6): 1.79 (4 H, m, H2', H3'); [3.64; 3.95] (2 H × 2, m × 2, OCH_2CH_2O); 4.12 (2 H, t, *J* 7.2, H1'); 7.14 (2 H, br s, 6-NH_2); 7.37 (4 H, m, Ph); 8.08 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 24.07 (C2'); 36.69 (C3'); 42.71 (C1'); 64.25 (2 C, OCH_2*C*H_2O); 108.85 (O*C*O); 118.70 (C5); [127.30 (2 C, C3 and C5); 128.10 (2 C, C2 and C6); 132.56 (C-1); 141.20 (C4)] (Ph); 140.76 (C8); 149.43 (C4); 152.30 (C2); 155.88 (C6).

9-{3-[2-(4-Bromophenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIf) was obtained in a yield of 34%, R_f 0.46 (B); oil. Mass: *m/z* 404.1 [*M* + H$^+$]. Calc. *M* 405.3 ($C_{17}H_{18}BrN_5O_2$). ^{1}H NMR (DMSO-d_6): 1.79 (4 H, m, H2', H3'); [3.65; 3.95] (2 H × 2, m × 2, OCH_2CH_2O); 4.12 (2 H, t, *J* 7.2, H1'); 7.12 (2 H, br s, 6-NH_2); [7.29 (2 H, m, H-2 and H-6); 7.52 (2 H, m, H-3 and H-5)] (Ph); 8.08 (s, 1 H, H8); 8.11 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 24.06 (C2'); 36.65 (C3'); 42.71 (C1'); 64.26 (2 C, OCH_2*C*H_2O); 108.88 (O*C*O); 118.69 (C5); [121.13 (C4); 127.67 (2 C, C2 and C6); 131.04 (2 C, C3 and C5); 140.78 (C1);] (Ph); 141.63 (C8); 149.43 (C4); 152.30 (C2); 155.88 (C6).

9-{3-[2-(4-Methylphenylphenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIg) was obtained in a yield of 47%, R_f 0.44 (B); mp 174–175°C (EtOAc). Mass: *m/z* 340.2 [*M* + H$^+$]. Calc. *M* 339.4 ($C_{18}H_{21}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.78 (4 H, m, H2', H3'); 2.27 (3 H, s, CH_3Ph); [3.63; 3.93] (2 H × 2, m × 2, OCH_2CH_2O); 4.11 (2 H, t, *J* 7.2, H1'); 7.11–7.23 (6 H, m, 6-NH_2, [H-2, H-6, H-3, H-5](Ph)); 8.07 (s, 1 H, H8); 8.11 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 20.56 (*C*H$_3$Ph); 24.20 (C2'); 36.88 (C3'); 42.75 (C1'); 64.05 (2 C, OCH_2*C*H_2O); 109.25 (O*C*O); 118.69 (C5); [125.20 (2 C, C-2 and C-6); 128.61 (2 C, C-3 and C-5); 136.91 (C-4); 139.18 (C-1);] (Ph); 140.75 (C8); 149.42 (C4); 152.28 (C2); 155.87 (C6).

9-{3-[2-(4-Dimethylphenylphenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIh) was obtained in a yield of

37%, R_f 0.47 (B), mp 135–136°C (EtOAc). Mass: *m/z* 354.2 [*M* + H$^+$]. Calc. *M* 353.4 ($C_{19}H_{23}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.82 (4 H, m, H2', H3'); [2.21; 2.28] (3 H × 2, s × 2, $(CH_3)_2$Ph); [3.59; 3.92] (2 H × 2, m × 2, OCH_2CH_2O); 4.12 (2 H, t, *J* 7.2, H1'); 6.92 (2 H, br s, 6-NH_2), 7.12–7.25 (3 H, m, [H-3, H-5, H-6](Ph)); 8.07 (s, 1 H, H8); 8.11 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): [20.08; 20.33] ((CH_3)$_2$Ph); 24.11 (C2'); 35.36 (C3'); 42.77 (C1'); 63.72 (2 C, OCH_2CH_2O); 109.89 (O*C*O); 118.71 (C5); [125.93; 126.20; 132.41; 134.72; 136.51; 136.87] (Ph); 140.73 (C8); 149.44 (C4); 152.28 (C2); 155.87 (C6).

9-{3-[2-(4-Ethylphenylphenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIi) was obtained in a yield of 47%, R_f 0.39 (B); mp 161–162°C (EtOAc). Mass: *m/z* 354.2 [*M* + H$^+$]. Calc. *M* 353.4 ($C_{19}H_{23}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.15 (2 H, t, *J* 7.5, CH_3CH_2Ph); 1.79 (4 H, m, H2', H3'); 2.57 (2 H, q, *J* 7.5, CH_3CH_2Ph); [3.64; 3.93] (2 H × 2, m × 2, OCH_2CH_2O); 4.12 (2 H, t, *J* 7.2, H1'); 7.12–7.25 (6 H, m, 6-NH_2, [H-2, H-6, H-3, H-5](Ph)); 8.08 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 15.28 (CH_3CH$_2$Ph); 24.15 (C2'); 27.68 (CH_3CH_2Ph); 36.89 (C3'); 42.75 (C1'); 64.07 (2 C, OCH_2CH_2O); 109.23 (O*C*O); 118.70 (C5); [125.22 (2 C, C-2 and C-6); 127.39 (2 C, C-3 and C-5); 139.48 (C-1); 143.16 (C-4)] (Ph); 140.73 (C8); 149.42 (C4); 152.26 (C2); 155.86 (C6).

9-{3-[2-(4-Isopropylphenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIj) was obtained in a yield of 44%, R_f 0.62 (B); mp 119–120°C (EtOAc). Mass: *m/z* 368.2 [*M* + H$^+$]. Calc. *M* 367.4 ($C_{20}H_{25}N_5O_2$). ^{1}H NMR (DMSO-d_6): 1.17 (6 H, d, *J* 6.8, $(CH_3)_2$CHPh); 1.79 (4 H, m, H2', H3'); 2.84 (1 H, hept, *J* 6.8, $(CH_3)_2CH$Ph); [3.64; 3.92] (2 H × 2, m × 2, OCH_2CH_2O); 4.12(2 H, t, *J* 7.2, H1'); 7.14–7.27 (6 H, m, 6-NH_2, [H-2, H-6, H-3, H-5](Ph)); 8.09 (s, 1 H, H8); 8.12 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 23.75 (2 C, (CH_3)$_2$CHPh); 24.16 (C2'); 33.01 ((CH_3)$_2$CHPh); 36.94 (C3'); 42.78 (C1'); 64.13 (2 C, OCH_2CH_2O); 109.24 (O*C*O); 118.72 (C5); [125.23 (2 C, C2 and C6); 125.97 (2 C, C3 and C5); 139.71 (C1); 147.79 (C4)] (Ph); 140.78 (C8); 149.44 (C4); 152.30 (C2); 155.90 (C6).

9-{3-[2-(4-Methoxyphenyl)-1,3-dioxolan-2-yl]propyl}adenine (IIIk) was obtained in a yield of 35%, R_f 0.42 (B); mp 166–167°C (EtOAc). Mass: *m/z* 355.2 [*M* + H$^+$]. Calc. *M* 355.4 ($C_{18}H_{21}N_5O_3$). ^{1}H NMR (DMSO-d_6): 1.78 (4 H, m, H2', H3'); [3.63; 3.92] (2 H × 2, m × 2, OCH_2CH_2O); 3.73 (3 H, s, CH_3OPh); 4.11(2 H, t, *J* 7.2, H1'); 6.87 (2 H, m, H-3 and H-5); 7.15 (2 H, br s, 6-NH_2), 7.25 (2 H, m, H-2 and H-6)]; 8.08 (s, 1 H, H8); 8.11 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 24.26 (C2'); 36.98 (C3'); 42.76 (C1'); 54.97 (CH_3OPh); 64.04 (2 C, OCH_2CH_2O); 109.20 (O*C*O); 118.70 (C5); [113.40 (2 C, C3 and C5); 126.55 (2 C, C2 and C6); 134.13 (C1); 158.80 (C4)] (Ph); 140.76 (C8); 149.43 (C4); 152.30 (C2); 155.89 (C6).

9-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]adenine (IIIl) was obtained in a yield of 39%, R_f 0.45 (B); mp 153–154°C (EtOAc). Mass: *m/z* 340.2 [*M* + H$^+$]. Calc. *M* 339.4 ($C_{18}H_{21}N_5O_2$). ^{1}H NMR: 1.71 (2 H, m, H3'); 1.84 (2 H, m, H2'); 2.05 (2 H, m, $OCH_2CH_2CH_2O$); 3.69–3.85 (4 H, m, OCH_2CH_2 CH_2O); 4.15 (2 H, t, *J* 7.3, H1'); 5.89 (2 H, br s, 6-NH_2); 7.25–7.44 (5 H, m, Ph); 7.74 (s, 1 H, H8); 8.30 (s, 1 H, H2). ^{13}C NMR ($CDCl_3$): 23.80 ($OCH_2CH_2CH_2O$); 25.55 (C2'); 41.33 (C3'); 43.76 (C1'); 64.17 (2 C, OCH_2CH_2O); 101.48 (O*C*O); 119.62 (C5); [127.28 (2 C, C3 and C5); 127.85 (C4); 128.67 (2 C, C2 and C6); 139.69 (C-1)] (Ph); 140.57 (C8); 150.07 (C4); 152.78 (C2); 155.44 (C6).

9-[3-(2-Phenyl-1,3-dioxolan-2-yl)propyl]adenine (IIIm) was obtained in a yield of 26%, R_f 0.61 (C), oil. Mass: *m/z* 398.2 [*M* + H$^+$]. Calc. *M* 397.4 ($C_{20}H_{23}N_5O_4$). ^{1}H NMR ($CDCl_3$): 1.88–2.01 (4 H, m, H2', H3'); 2.04 (3 H, s, OCOCH_3); 3.77 (2 H, m, CH_2OAc); 4.12–4.22 (5 H, m, OCH_2CH, OC*H*, H1'); 6.11 (2 H, br s, 6-NH_2); 7.25–7.40 (5 H, m, Ph); 7.77 (s, 1 H, H8); 8.30 (s, 1 H, H2). ^{13}C NMR ($CDCl_3$): 20.83 (CH_3CO); 24.20 (C2'); 37.05 (C3'); 43.67 (C1'); 64.57 (CH_2OAc); 66.31 (CH_2O); 73.34 (*C*HO); 111.01 (O*C*O); 119.55 (C5); [125.60 (2 C, C3 and C5); 128.31 (C-4); 128.40 (2 C, C2 and C6); 141.67 (C1)] (Ph); 140.54 (C8); 150.05 (C4); 152.84 (C2); 155.59 (C6), 170.79 (CH_3*C*O).

9-[3-(2-Phenyl-4-hydroxymethyl-1,3-dioxolan-2-yl)propyl]adenine (IIIn) was obtained by refluxing of the solution of 4-acetoxymethyl derivative (**IIIn**) in a 1 : 1mixture of ethanol–water in the presence of NEt_3 (0.6 mL, 8.1 mmol) for 15 h. The solvents were evaporated and the residue was suspended in a minimal volume of methylene chloride and chromatographed on a silica gel column (5 × 2 cm, ~10 g) eluting in a gradient of ethanol in chloroform 0 → 40% to give 50% of the target compound; R_f 0.19 (C); mp 131–132°C (EtOAc). Mass: *m/z* 356.2 [*M* + H$^+$]. Calc. 355.4 ($C_{18}H_{21}N_5O_3$). ^{1}H NMR (DMSO-d_6): 1.76–1.91 (4 H, m, H2', H3'); 3.47 (2 H, m, CH_2OH); 3.72 (2 H, m × 2, OCH_2CH); 3.87 (1 H, m, OC*H*); 4.14 (2 H, t, *J* 6.5, H1'); 4.86 (1 H, t, *J* 5.7, O*H*); 7.13 (2 H, br s, 6-NH_2); 7.26–7.36 (5 H, m, Ph); 8.08 (s, 1 H, H8); 8.11 (s, 1 H, H2). ^{13}C NMR (DMSO-d_6): 23.99 (C2'); 37.03 (C3'); 42.80 (C1'); 61.84 (CH2OH); 61.84 (CH_2OH); 66.09 (CH_2O); 76.11 (CHO); 109.73 (OCO); 118.69 (C5); [125.24 (2 C, C-3 and C-5); 127.79 (C4); 128.11 (2 C, C2 and C6); 142.44 (C1)] (Ph); 140.80 (C8); 149.43 (C4); 152.29 (C2); 155.88 (C6).

6-Chloro-9-[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]purine (IIIo) was obtained in a yield of 56%, R_f 0.84 (B). Mass: *m/z* 345.1 [*M* + H$^+$]. Calc. 344.8 ($C_{17}H_{17}ClN_4O_2$). ^{1}H NMR (DMSO-d_6): 1.90 (2 H, m, H3'); 2.01 (2 H, m, H2'); [3.74; 3.99] (2 H × 2, m × 2, OCH_2CH_2O); 4.30 (2 H, t, *J* 7.2, H1'); 7.25–7.40 (5 H, m, Ph); 8.09 (s, 1 H, H8); 8.70 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): 24.20 (C2'); 36.93 (C3'); 44.33 (C1'); 64.59 (2 C, O*C*H$_2$*C*H$_2$O); 109.87 (O*C*O); [125.61 (2 C, C3 and C5); 128.23 (C4); 128.37 (2 C, C2 and C6); 141.91 (C1)] (Ph); 131.73 (C5); 145.35 (C8); 151.04 (C6); 151.94 (C2, C4); 155.95 (C6).

6-Methylamino-9-[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]purine (IIIp) was obtained by keeping a mixture of 6-chloro derivative (**IIIo**) (30 mg, 0.09 mmol), $NH_3CH_3 \cdot HCl$ (90 mg, 1.33 mmol), and DBU (0.2 mL, 1.33 mmol) in methanol (1.5 mL) for 14 h. The solvent was evaporated and the residue was suspended in a minimal volume of methylene chloride and chromatographed on a silica gel column (5 × 2 cm, ~10 g) eluting in a gradient of ethanol in chloroform 0 → 20%. The target fractions were evaporated and the residue was recrystallized from an ethyl acetate–octane mixture to give 96% of the target compound; R_f 0.65 (B); oil. Mass: *m/z* 340.2 [*M* + H$^+$]. Calc. 339.4 ($C_{18}H_{21}N_5O_2$). ^{1}H NMR:1.90 (4 H, m, H2', H3'); 3.18 (3 H, br s, 6-NHC*H*$_3$); [3.73; 3.98] (2 H × 2, m × 2, OC*H*$_2$C*H*$_2$O); 4.17 (2 H, t, *J* 6.7, H1'); 6.53 (1 H, br s, 6-N*H*CH$_3$); 7.25–7.40 (5 H, m, Ph); 7.70 (s, 1 H, H8); 8.36 (s, 1 H, H2). ^{13}C NMR ($CDCl_3$): 24.31 (C2'); 29.84 (6-NH*C*H$_3$); 36.95 (C3'); 43.60 (C1'); 64.47 (2 C, O*C*H$_2$*C*H$_2$O); 109.86(O*C*O); 119.45 (C5); [125.54 (2 C, C3 and C5); 128.01 (C4); 128.19 (2 C, C2 and C6); 142.01 (C1)] (Ph); 139.45 (C8); 151.02 (C4); 153.13 (C2); 155.35 (C6).

6-Dimethylamino-9-[3-(2-phenyl-1,3-dioxolan-2-yl)propyl]purine (IIIq) was obtained by keeping a mixture of 6-chloro derivative (**IIIo**) (30 mg, 0.09 mmol), $NH_2(CH_3)_2 \cdot HCl$ (110 mg, 1.35 mmol), and DBU (0.2 mL, 1.33 mmol) in methanol (1.5 mL) for 14 h. The solvent was evaporated and the residue was suspended in a minimal volume of methylene chloride and chromatographed on a silica gel column (5 × 2 cm, ~10 g) eluting in a gradient of ethanol in chloroform 0 → 20%. The target fractions were evaporated and the residue was recrystallized from an ethyl acetate–octane mixture to give 83%, R_f 0.81 (B), oil. Mass: *m/z* 353.2 [*M* + H$^+$]. Calc. 339.4 ($C_{19}H_{23}N_5O_2$). ^{1}H NMR: 1.91 (4 H, m, H2', H3'); 3.50 (6 H, br s, 6-N(C*H*$_3$)$_2$); [3.73; 3.97] (2 H × 2, m × 2, OC*H*$_2$C*H*$_2$O); 4.15 (2 H, t, *J* 6.8, H1'); 7.23–7.41 (5 H, m, Ph); 7.67 (s, 1 H, H8); 8.30 (s, 1 H, H2). ^{13}C NMR ($CDCl_3$): 24.28 (C2'); 37.02 (C3'); 38.45 (N(*C*H$_3$)$_2$); 43.36 (C1'); 64.47 (2 C, O*C*H$_2$*C*H$_2$O); 109.91(O*C*O); 120.15 (C5); [125.56 (2 C, C-3 and C-5); 127.97 (C-4); 128.16 (2 C, C-2 and C-6); 142.08 (C-1)] (Ph); 138.25 (C8); 150.51 (C4); 152.28 (C2); 154.95 (C6).

Evaluation of HIV-1 RT activity in the system of activated DNA. A standard reaction mixture (20 μL) contained 150 μg/mL activated DNA, HIV-1 RT (0.05 μg), 1.5 μM ATP, other nucleoside 5'-triphosphates (30 μM of each), 0.02 MBq [α-^{32}P]dATP, and the buffer for assaying HIV-1 RT activity (50 mM Tris-HCl, pH 8.0, 10 mM $MgCl_2$, and 200 mM KCl). For testing inhibitory properties the compounds were added into the reaction mixture as solutions in DMSO up to a final concentration of 10%; the control reactions were performed with the addition of the same volume of DMSO. The reaction was initiated by the addition of HIV RT and incubated for 20 min at 37°C. The aliquots were loaded onto Whatman 3MM filters (1 × 1 cm) impregnated with 0.5 M EDTA (1 μL). The filters were washed from the labeled nucleotide not incorporated into the DNA with 10% trichloroacetic acid (5 × 25 mL) for 5 min each, then ethanol (25 mL), and dried in air. The radioactivity absorbed on the filters was measured using the Cherenkov method on an Intertechnique Liquid Scintillation Counter SL-4000. Inhibition constants were calculated by the Dixon procedure [13].

REFERENCES

1. Ludovici, D.W.L., Kukla, M.J., Grous, P.G., Krishnan, S., Andries, K., de Buthune, M.P., Azijn, H., Pauwels, R., de Clercq, E., Arnold, E., and Janssen, P.A., *Bioorg. Med. Chem. Let.,* 2001, vol. 11, pp. 2225–2228.
2. Das, K.L., Lewi, P.J., Hughes, S.H., and Arnold, E., *Prog. Biophys. Mol. Biol.*, 2005, vol. 88, pp. 209–231.
3. Paramonova, M.P., Babkov, D.A., Valuev-Elliston, V.T., Ivanov, A.V., Kochetkov, S.N., Pannekuk, K., Ozerov, A.A., Bal'zarini, Ya., and Novikov, M.S., *Khim.-Farm. Zh.*, 2013, vol. 47, pp. 7–11.
4. Komissarov, V.V., Knyazhanskaya, E.S., Atrohova, A.V., Gottikh, M.B., and Kritzyn, A.M., *Russ. J. Bioorg. Chem.*, 2014, vol. 40, pp. 532–540.
5. Komissarov, V.V. and Kritzyn, A.M., *Russ. J. Bioorg. Chem.*, 2005, vol. 31, pp. 549–555.
6. Nesmeyanov, A.N. and Zakharkin, L.I., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1955, pp. 224–238.
7. Tietze, L.F. and Eicher, T., *Reaktionen und Synthesen im organische-chemischen Praktikum und Forschungslaboratorium*, New York: Georg Thieme Verlag Stutgart, 1991.
8. Dudding, L.R., Nkabinde, N.C., and Mizrahi, V., *Biochemistry*, 1991, vol. 30, pp. 10498–10506.
9. de Bŭthune, M.P., *Antiviral Res.*, 2010, vol. 85, pp. 75–90.
10. Baril, E., Mitchener, J., Lee, L., and Baril, B., *Nucleic Acids Res.*, 1977, vol. 4, pp. 2641–2654.
11. Novikov, M.S., Ivanova, O.N., Ivanov, A.V., Ozerov, A.A., Valuev-Elliston, V.T., Temburnikar, K., Gurskaya, G.V., Kochetkov, S.N., Pannecouque, C., Balzarini, J., and Seley-Radtke, K.L., *Bioorg. Med. Chem.*, 2011, vol. 19, pp. 5794– 5802.
12. Le Grice, S.F. and Grüninger-Leitch, F., *Eur. J. Biochem.*, 1990, vol. 187, p. 307.
13. Dixon, M., *Biochem. J.,* 1953, vol. 55, pp. 170–171.

Translated by E. Shirokova