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Polymethylene Derivatives of Nucleic Bases with ω-Functional Groups: II. Adenine and Hypoxanthine Derivatives

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Abstract—N^9-Polymethylene derivatives of adenine and hypoxanthine with various functional groups in the ω-position of the alkyl substituent were synthesized. Their physicochemical properties and effect on the HIV reverse transcriptase and DNA topoisomerase I were studied.

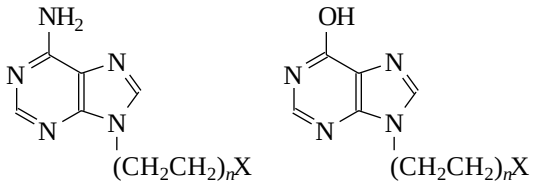
Key words: nucleosides, polymethylene analogues, alkylation; HIV reverse transcriptase; human DNA topoisomerase I

INTRODUCTION

In the previous communication [1] we described synthesis, some physicochemical characteristics, and the effect on the human HIV reverse transcriptase and the human DNA topoisomerase I of polymethylene derivatives of uracil, thymine, and cytosine containing a substituent in the N^1-position of the nucleic base, which is a hydrophobic chain with 5, 7, or 9 carbon atoms bearing various functional groups in the ω-position.[2] It was for the first timefound that some of these thymine and uracil derivatives can effectively interact with the site of the HIV reverse transcriptase responsible for recognition of the $tRNA^{Lys}$ anticodon (UUC) and activate this enzyme to promote the polymerization reaction. In this connection, it was appropriate to obtain the analogous derivatives of adenine and hypoxanthine.

RESULTS AND DISCUSSION

Adenine and hypoxanthine derivatives with a polymethylene hydrophobic chain in the N^9-position were obtained by alkylation of the nucleic bases with alkyl δ-chlorovalerate, ω-chloroenanthoate, and ω-chloropelargonate [2]. Potassium or cesium carbonate is usually used as a dehydrohalogenizing agent. In the last few years, DBU is widely used for this purpose [3, 4]. In the previous communication [1] we showed that using DBU as a dehydrohalogenizing agent offers advantages over other nitrogen-containing organic bases, such as 1,5-diazabicyclo[4.3.0]non-5-ene and 1,5,7-triazabicyclo[4.4.0]dec-5-ene, as well as over potassium carbonate. The reaction mixture (adenine or hypoxanthine, ethyl ω-chlorocarboxylate, and DBU in DMF) was kept for 15–20 h at 80–100°C (method A). The N^9-ethoxycarbonyl derivatives of adenine (**Ia**), (**Id**), and (**Ig**) and hypoxanthine (**IIa),** (**IId**), and (**IIg**) were isolated from the reaction mixture by column chromatography of Silica gel (Tables 1 and 2). The use of potassium carbonate as a dehydrohalogenizing agent hinders the isolation of target products.



(**Ia–Ii**) (**IIa–IIi**)

a, b, c: $n = 2$; **d, e, f**: $n = 3$; **g, h, i**: $n = 4$

a, d, g: X = COOEt; **b, e, h**: X = COOH;

c, f, i: X = CH_2OH

The corresponding carboxylic acids (**Ib**), (**Ie**), and (**Ih**) and (**IIb**), (**IIe**), and (**IIh**) were obtained from ethoxycarbonyl derivatives by reflux in 3 M hydrochloric acid (method B).

The ester group was reduced to the hydroxymethyl using lithium aluminum hydride in THF (method C). The hydroxy derivatives were also synthesized by alkylation of adenine and hypoxanthine with either the corresponding α,ω-polymethylene chlorohydrins (method D) or their *O*-acyl derivatives (method E). Derivatives (**Ic**), (**If**), and (**Ii**) and (**IIc**), (**IIf**), and (**IIi**) obtained by

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[2] Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; SDS, sodium dodecyl sulfate; Tris, tris(hydroxymethyl)aminomethane.

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Table 1. Synthetic methods, yields, melting temperatures, and UV spectral data for N^9-derivatives of adenine (**Ia**)–(**Ii**)

Compound	Synthetic method*	Yield, %	T_m, °C	UV, λ_{max}, nm (ε)		
				pH 1	pH 7	pH 14
(**Ia**)	A	31	125–126	261(14600)	262(14700)	262(15000)
(**Ib**)	B	93	>300	260(9500)	262(9800)	262(10000)
(**Ic**)	C	60	185–187	261(13800)	262(13200)	262(12900)
	D	36				
(**Id**)	A	67	90–91	261(13000)	262(13500)	262(13500)
(**Ie**)	B	92	198–199	260(11400)	260(12000)	262(13500)
(**If**)	C	76	183–185	261(15500)	262(14300)	262(13700)
	D	51				
(**Ig**)	A	63	94–95	261(13000)	262(12500)	262(13000)
(**Ih**)	B	90	214–216	260(10900)	262(11100)	262(10500)
(**Ii**)	C	70	160–163	261(13000)	262(13100)	263(12500)
	D	58				

* See the Experimental section.

Table 2. Synthetic methods, yields, melting temperatures, and UV spectral data for N^9-derivatives of hypoxanthine (**IIa**)–(**IIi**)

Compound	Synthetic method*	Yield, %	T_m, °C	UV, λ_{max}, nm (ε)		
				pH 1	pH 7	pH 14
(**IIa**)	A	42	120–122	249(10400)	250(10900)	254(11200)
(**IIb**)	B	92	204–206	250(10200)	251(10800)	255(10200)
(**IIc**)	D	15	220–221	249(10000)	250(10100)	253(11400)
(**IId**)	A	64	159–160	250(11600)	251(12200)	253(12400)
(**IIe**)	B	97	104–106	251(9600)	252(10000)	254(10500)
(**IIf**)	E	40	170–172	250(9700)	251(9400)	255(9800)
(**IIg**)	A	43	98–99	251(10500)	252(10400)	255(10500)
(**IIh**)	B	87	139–141	250(9900)	251(9900)	254(10300)
(**IIi**)	C	65	155–156	250(10000)	251(9800)	255(10100)
	D	12				
	E	57				

* See the Experimental section.

various methods (C, D, or E) had the same characteristics.

The structure of compounds synthesized was confirmed by UV and ^{1}H NMR spectroscopy and mass spectrometry data (see Tables 1 and 2 and the Experimental section). These compounds were studied in the reactions catalyzed by the HIV reverse transcriptase and human DNA topoisomerase I, which are the targets of the majority of well-known antiviral [5] and antitumor [6–8] drugs, respectively. The data for these enzymes are given in Table 3.

Most of the compounds under study except (**Ih**) and (**IIh**) even in a rather high concentration (1 mM) do not affect or only slightly inhibit the reaction of polymerization, whereas some compounds in this concentration not only lack an inhibitory effect on the reverse transcriptase, but promote polymerization. The particularly noticeable enzyme activation (21–30%) is observed in the case of (**Ig**), (**Ii**), (**IIf**), and (**IIi**). All these compounds contain 8 methylene groups in the alkyl chain and uncharged ethoxycarbonyl or hydroxyl functions. The strongest enzyme inhibitors, (**Ih**) and (**IIh**), also

Table 3. Relative activity of the HIV reverse transcriptase (RT) and the human DNA topoisomerase I (TOPO) (the enzyme activity in the absence of (**I**)–(**II**) is taken as 100%; the concentration of compounds is 10^{-3} M)

Compound	Relative activity, %		Compound	Relative activity, %	
	RT	TOPO		RT	TOPO
(**Ia**)	94	100	(**IIa**)	97	93
(**Ib**)	89	79	(**IIb**)	92	92
(**Ic**)	79	97	(**IIc**)	100	83
(**Id**)	102	97	(**IId**)	97	32
(**Ie**)	89	74	(**IIf**)	121	30
(**If**)	95	42	(**IIg**)	100	63
(**Ig**)	130	57	(**IIh**)	45	71
(**Ih**)	56	56	(**IIi**)	124	74
(**Ii**)	121	60			

contain eight methylene groups, but they include a negatively charged carboxyl group. Apparently, the spacer between the base and the functional group of precisely the same length ensures interaction of the base analogues under study with some functional sites of this enzyme.

$tRNA^{Lys}$ is the natural primer of the HIV reverse transcriptase. In the model polymerization reactions, the poly(A) · oligo(dT) complex usually serves as a primer. Previously we showed [9, 10] that the primer interacts with the regulatory p51 subunit of the functional p51/p66 dimer of the enzyme to cause its conformational changes and thus activates polymerization. Later, the primer molecule was found to contain two regions responsible for the activation of the HIV reverse transcriptase. The removal of the 3'-terminal CCA sequence from the $tRNA^{Lys}$ molecule markedly decreases the activating ability of the primer. On the other hand, 7–10-membered fragments of the tRNA anticodon loop activate the enzyme [11, 12]. Nucleosides, their monophosphates, or short oligonucleotides are known to be incapable of activating the HIV reverse transcriptase. Exceptions are the N^1-acyclic derivatives of uracil and thymine with hydrophobic polymethylene chains bearing various functional groups in the ω-position of the chain reported by us in [1]. In the present study we found adenine and hypoxanthine derivatives capable of effective interaction with the recognition site of reverse transcriptase for the $tRNA^{Lys}$ (UUC) anticodon and of activation of the enzyme. The activation level in the case of some pyrimidine derivatives (30–50%) [1] correlates with that for the aforementioned adenine and hypoxanthine derivatives (20–30%). Note that activation of reverse transcriptase by (**Ig**) (30%) is approximately 10- and 3-fold lower than by $tRNA^{Lys}$ and its oligonucleotide analogues, respectively.

The inhibitors of DNA topoisomerase I are widely used as antitumor drugs [6–8]. We studied the inhibitory properties of the synthesized compounds by previously described procedures [13–15]. Most of them inhibited the enzyme, but the inhibitory effect was incomplete even at a high (1 mM) concentration of the compounds. The highest inhibitory activities were displayed by two hypoxanthine derivatives, (**IId**) and (**IIf**) (68–70%), and by an adenine derivative, (**If**) (58%), with six methylene units and uncharged functional groups. A close inhibitory effect (40–44%) was displayed by three adenine derivatives, (**Ig**), (**Ih**), and (**Ii**), containing eight methylene units and any one of three ω-functional groups. Hypoxanthine derivatives (**IIg**), (**IIh**), and (**IIi**) with a similar structure of the ω-functional groups demonstrated a somewhat lower but comparable inhibitory effect (26–37%). The derivatives containing four methylene groups had practically no inhibitory effect on both enzymes even in a concentration of 1 mM. Thus, the series of the purine derivatives studied exhibits a specific dependence of inhibitory properties on the polymethylene chain length, the nature of ω-functional groups, and the base structure.

EXPERIMENTAL

Solvents were purified and dried by the standard procedures. UV spectra were recorded on a Specord UV VIS spectrophotometer (Germany). Mass spectra were taken on a MS 902 AEI Manchester instrument (United States). ^{1}H NMR spectra were registered on a Bruker AMX 400 spectrometer (Germany) at 300 K. The chemical shifts (ppm) and coupling constants (Hz) are given. TLC was performed on precoated Silica gel 60 F_{254} plates (Merck, Germany) in (1) 19 : 1 chloroform–ethanol, (2) 18 : 2 chloroform–ethanol, (3) 17 : 3 chloroform–ethanol, and (4) 14 : 6 chloroform–ethanol systems. Column chromatography was carried out on Silica gel L 40/100 (Chemapol, Czech Republic). Radioactivity was measured on FN-16 Filtrac paper fil-

ters (Germany) using LKB-Vallac MINI-Beta counter (Sweden).

Adenine, hypoxanthine, Tris, and SDS were from Sigma (United States); EDTA was from Serva (Germany); and agarose was purchased from Lachema (Czech Republic). Electrophoresis was performed in 0.8% agarose gel in Tris–acetate buffer (pH 7.5). Gel was stained with a 0.5 μg/ml solution of ethidium bromide.

Activity of the HIV reverse transcriptase and the human DNA topoisomerase I was determined by the procedures described in [1].

Alkylation of adenine and hypoxanthine with ethyl ω-chlorocarboxylates in the presence of DBU (method A). An ethyl ω-chlorocarboxylate (30 mmol) and DBU (30 mmol) were added to a suspension of adenine or hypoxanthine (20 mmol) in anhydrous DMF (30 ml), and the reaction mixture was kept for 15–20 h at 80–100°C while being monitored by TLC. After evaporation in vacuum, the residue was dissolved in chloroform (25–30 ml), washed with water, dried with anhydrous sodium sulfate, evaporated, and chromatographed on a column (200 g of Silica gel, elution with a 0–10% ethanol gradient in chloroform).

Acid hydrolysis of ethoxycarbonyl derivatives (method B). An ethoxycarbonyl derivative (3 mmol) was added to 3 M hydrochloric acid (20 ml), and the mixture was refluxed for 3–4 h with TLC monitoring. The reaction mixture was evaporated and several times coevaporated with water. The products were crystallized from water–ethanol mixtures containing 5–50% of ethanol.

Reduction of ethoxycarbonyl derivatives with lithium aluminum hydride in THF (method C). A solution of an ethoxycarbonyl derivative (5 mmol) in anhydrous THF (15 ml) was added with stirring to a suspension of lithium aluminum hydride (500 mg) in anhydrous THF (50 ml). The reaction mixture was refluxed and TLC monitored. After cooling, ethyl acetate (60 ml) and then water (15 ml) were added. The resulting mixture was refluxed for 30 min, cooled, and evaporated. The target product was extracted with hot ethyl acetate. After evaporation, the residue was chromatographed on a column (70 g of Silica gel, elution with an 0–20% ethanol gradient in chloroform).

Alkylation of adenine and hypoxanthine with α,ω-chlorohydrins (method D). An α,ω-chlorohydrin (30 mmol) and powdered potassium carbonate or DBU (30 mmol) were added to a suspension of the nucleic base (20 mmol) in anhydrous DMF (30 ml). The further treatment and isolation were carried out as described for method A.

Alkylation of hypoxanthine with α,ω-chlorohydrin *O*-acetyl derivatives (method E). 1,8-Diazabicyclo[5.4.0]undec-7-ene (30 mmol) and then an *O*-acetyl-α,ω-chlorohydrin (30 mmol) were added to a suspension of hypoxanthine (20 mmol) in anhydrous DMF (30 ml), and the reaction mixture was heated for 15–20 h at 80–100°C. The further treatment and isolation were performed as described for method A. The acetyl group was removed by treatment with 5 M ammonia in methanol.

***N*^{9}-(δ-Ethoxycarbonyl-*n*-butyl)adenine (Ia)**, R_f 0.29 (1); ^{1}H NMR ($CDCl_3$): 1.23 (3 H, t, $J_{1'',2''}$ 7.10, H2''), 1.68 (2 H, m, H3'), 1.95 (2 H, m, H2'), 2.36 (2 H, t, $J_{3',4'}$ 7.1, H4'), 4.12 (2 H, q, H1''), 4.23 (2 H, t, $J_{1',2'}$ 7.1, H1'), 6.45 (2 H, s, NH_2), 7.82 (1 H, s, H2), and 8.36 (1 H, s, H8); MS: *m*/*z* 264 [M^+], calc. 263 ($C_{12}H_{17}N_5O_2$).

***N*^{9}-(ω-Ethoxycarbonyl-*n*-hexyl)adenine (Id)**, R_f 0.33 (1); ^{1}H NMR ($CDCl_3$): 1.25 (3 H, t, $J_{1'',2''}$ 7.10, H2''), 1.37 (4 H, m, H3'–H4'), 1.62 (2 H, m, H5'), 1.90 (2 H, m, H2'), 2.27 (2 H, t, $J_{5',6'}$ 7.10, H6'), 4.12 (2 H, q, H1''), 4.20 (2 H, t, $J_{1',2'}$ 7.3, H1'), 6.50 (2 H, s, NH_2), 7.82 (1 H, s, H2), and 8.37 (1 H, s, H8); MS: *m*/*z* 292 [M^+], calc. 291 ($C_{14}H_{21}N_5O_2$).

***N*^{9}-(ω-Ethoxycarbonyl-*n*-octyl)adenine (Ig)**, R_f 0.37 (1); ^{1}H NMR ($CDCl_3$): 1.22 (3 H, t, $J_{1'',2''}$ 7.10, H2''), 1.37 (8 H, m, H3'–H6'), 1.65 (2 H, m, H7'), 1.95 (2 H, m, H2'), 2.30 (2 H, t, $J_{7',8'}$ 7.10, H8'), 4.10 (2 H, q, H1''), 4.20 (2 H, t, $J_{1',2'}$ 7.10, H1'), 6.50 (2 H, s, NH_2), 7.82 (1 H, s, H2), and 8.35 (1 H, s, H8); MS: *m*/*z* 320 [M^+], calc. 319 ($C_{16}H_{25}N_5O_2$).

***N*^{9}-(δ-Ethoxycarbonyl-*n*-butyl)hypoxanthine (IIa)**, R_f 0.22 (1); ^{1}H NMR ($CDCl_3$): 1.25 (3 H, t, $J_{1'',2''}$ 7.30, H2''), 1.67 (2 H, m, H3'), 1.97 (2 H, m, H2'), 2.38 (2 H, t, $J_{3',4'}$ 7.10, H4'), 4.13 (2 H, q, H1''), 4.23 (2 H, t, $J_{1',2'}$ 7.10, H1'), 7.87 (1 H, s, H2), 8.28 (1 H, s, H8), and 13.20 (1 H, s, OH); MS: *m*/*z* 265 [M^+], calc. 264 ($C_{12}H_{16}N_4O_3$).

***N*^{9}-(ω-Ethoxycarbonyl-*n*-hexyl)hypoxanthine (IId)**, R_f 0.27 (1); ^{1}H NMR ($CDCl_3$): 1.25 (3 H, t, $J_{1'',2''}$ 7.10, H2''), 1.37 (4 H, m, H3'–H4'), 1.63 (2 H, m, H5'), 1.92 (2 H, m, H2'), 2.28 (2 H, t, $J_{5',6'}$ 7.30, H6'), 4.12 (2 H, q, H1''), 4.20 (2 H, t, $J_{1',2'}$ 7.10, H1'), 7.83 (1 H, s, H2), 8.27 (1 H, s, H8), and 13.20 (1 H, s, OH); MS: *m*/*z* 293 [M^+], calc. 292 ($C_{14}H_{20}N_4O_3$).

***N*^{9}-(ω-Ethoxycarbonyl-*n*-octyl)hypoxanthine (IIg)**, R_f 0.29 (1); ^{1}H NMR ($CDCl_3$): 1.22 (3 H, t, $J_{1'',2''}$ 7.30, H2''), 1.35 (8 H, m, H3'–H6'), 1.62 (2 H, m, H7'), 1.95 (2 H, m, H2'), 2.25 (2 H, t, $J_{7',8'}$ 7.10, H8'), 4.10 (2 H, q, H1''), 4.22 (2 H, t, $J_{1',2'}$ 7.10, H1'), 7.83 (1 H, s, H2), 8.20 (1 H, s, H8), and 13.15 (1 H, s, OH); MS: *m*/*z* 321 [M^+], calc. 320 ($C_{16}H_{24}N_4O_3$).

***N*^{9}-(δ-Hydroxycarbonyl-*n*-butyl)adenine (Ib)**, R_f 0.31 (3); ^{1}H NMR (DMSO-d_6): 1.50 (2 H, m, H3'), 1.85 (2 H, m, H2'), 2.20 (2 H, t, $J_{3',4'}$ 7.30, H4'), 4.20 (2 H, t, $J_{1',2'}$ 7.30, H1'), 6.85 (2 H, s, NH_2), 8.05 (1 H, s, H2 or H8), and 8.15 (1 H, s, H8 or H2); MS: *m*/*z* 236 [M^+], calc. 235 ($C_{10}H_{13}N_5O_2$).

***N*⁹-(ω-Hydroxycarbonyl-*n*-hexyl)adenine (Ie)**, R_f 0.39 (3); ^{1}H NMR (DMSO-d_6): 1.30 (4 H, m, H3'–H4'), 1.52 (2 H, m, H5'), 1.90 (2 H, m, H2'), 2.15 (2 H, t, $J_{5',6'}$ 7.30, H6'), 4.20 (2 H, t, $J_{1',2'}$ 7.30, H1'), 6.85 (2 H, s, NH_2), 8.08 (1 H, s, H2 or H8), and 8.15 (1 H, s, H8 or H2); MS: *m*/*z* 264 [M^+], calc. 263 ($C_{12}H_{17}N_5O_2$).

***N*⁹-(ω-Hydroxycarbonyl-*n*-octyl)adenine (Ih)**, R_f 0.54 (3); ^{1}H NMR (DMSO-d_6, 50°C): 1.22 (8 H, m, H3'–H6'), 1.45 (2 H, m, H7'), 1.80 (2 H, m, H2'), 2.18 (2 H, t, $J_{7',8'}$ 7.20, H8'), 4.12 (2 H, t, $J_{1',2'}$ 7.30, H1'), 6.80 (2 H, s, NH_2), 8.08 (1 H, s, H8 or H2), and 8.12 (1 H, s, H2 or H8); MS: *m*/*z* 292 [M^+], calc. 291 ($C_{14}H_{21}N_5O_2$).

***N*⁹-(δ-Hydroxycarbonyl-*n*-butyl)hypoxanthine (IIb)**, R_f 0.22 (4); ^{1}H NMR (DMSO-d_6): 1.65 (2 H, m, H3'), 1.95 (2 H, m, H2'), 2.15 (2 H, t, $J_{3',4'}$ 7.20, H4'), 4.15 (2 H, t, $J_{1',2'}$ 7.20, H1'), 8.05 (1 H, s, H2), and 8.45 (1 H, s, H8); MS: *m*/*z* 237 [M^+], calc. 236 ($C_{10}H_{12}N_4O_3$).

***N*⁹-(ω-Hydroxycarbonyl-*n*-hexyl)hypoxanthine (IIe)**, R_f 0.56 (3); ^{1}H NMR (DMSO-d_6): 1.25 (4 H, m, H3'–H4'), 1.50 (2 H, m, H5'), 1.88 (2 H, m, H2'), 2.18 (2 H, t, $J_{5',6'}$ 7.15, H6'), 4.20 (2 H, t, $J_{1',2'}$ 7.15, H1'), 8.05 (1 H, s, H2), and 8.60 (1 H, s, H8); MS: *m*/*z* 265 [M^+], calc. 264 ($C_{12}H_{16}N_4O_3$).

***N*⁹-(ω-Hydroxycarbonyl-*n*-octyl)hypoxanthine (IIh)**, R_f 0.58 (3); ^{1}H NMR (DMSO-d_6): 1.25 (8 H, m, H3'–H6'), 1.45 (2 H, m, H7'), 1.85 (2 H, m, H2'), 2.15 (2 H, t, $J_{7',8'}$ 7.15, H8'), 4.20 (2 H, t, $J_{1',2'}$ 7.15, H1'), 8.05 (1 H, s, H2), and 8.60 (1 H, s, H8); MS: *m*/*z* 293 [M^+], calc. 292 ($C_{14}H_{20}N_4O_3$).

***N*⁹-(ω-Hydroxy-*n*-amyl)adenine (Ic)**, R_f 0.18 (2); ^{1}H NMR (DMSO-d_6): 1.25 (2 H, m, H3'), 1.45 (2 H, m, H4'), 1.80 (2 H, m, H2'), 3.40 (2 H, t, $J_{4',5'}$ 6.55, H5'), 4.00 (1 H, s, OH), 4.13 (2 H, t, $J_{1',2'}$ 7.15, H1'), 6.80 (2 H, s, NH_2), 8.10 (1 H, s, H2 or H8), and 8.15 (1 H, s, H8 or H2); MS: *m*/*z* 222 [M^+], calc. 221 ($C_{10}H_{15}N_5O$).

***N*⁹-(ω-Hydroxy-*n*-heptyl)adenine (If)**, R_f 0.38 (2); ^{1}H NMR (DMSO-d_6, 50°C): 1.28 (6 H, m, H3'–H5'), 1.38 (2 H, m, H6'), 1.62 (2 H, m, H2'), 3.37 (2 H, t, $J_{6',7'}$ 6.55, H7'), 4.00 (1 H, s, OH), 4.12 (2 H, t, $J_{1',2'}$ 7.15, H1'), 6.77 (2 H, s, NH_2), 8.08 (1 H, s, H2 or H8), and 8.15 (1 H, s, H8 or H2); MS: *m*/*z* 250 [M^+], calc. 249 ($C_{12}H_{19}N_5O$).

***N*⁹-(ω-Hydroxy-*n*-nonyl)adenine (Ii)**, R_f 0.40 (2); ^{1}H NMR (DMSO-d_6): 1.25 (10 H, m, H3'–H7'), 1.48 (2 H, m, H8'), 1.80 (2 H, m, H2'), 3.37 (2 H, t, $J_{8',9'}$ 6.55, H9'), 3.98 (1 H, s, OH), 4.13 (2 H, t, $J_{1',2'}$ 7.15, H1'), 6.80 (2 H, s, NH_2), 8.08 (1 H, s, H2 or H8), and 8.15 (1 H, s, H8 or H2); MS: *m*/*z* 278 [M^+], calc. 277 ($C_{14}H_{23}N_5O$).

***N*⁹-(ω-Hydroxy-*n*-amyl)hypoxanthine (IIc)**, R_f 0.40 (3); ^{1}H NMR (DMSO-d_6, 50°C): 1.22 (2 H, m, H3'), 1.40 (2 H, m, H4'), 1.75 (2 H, m, H2'), 3.40 (2 H, t, $J_{4',5'}$ 6.55, H5'), 4.00 (1 H, s, OH), 4.20 (2 H, t, $J_{1',2'}$ 7.15, H1'), 7.85 (1 H, s, H2), 8.05 (1 H, s, H8), and 12.00 (1 H, s, NH); MS: *m*/*z* 223 [M^+], calc. 222 ($C_{10}H_{14}N_4O_2$).

***N*⁹-(ω-Hydroxy-*n*-heptyl)hypoxanthine (IIf)**, R_f 0.25 (2); ^{1}H NMR (DMSO-d_6, 50°C): 1.26 (6 H, m, H3'–H5'), 1.38 (2 H, m, H6'), 1.78 (2 H, m, H2'), 3.40 (2 H, t, $J_{6',7'}$ 6.55, H7'), 4.00 (1 H, s, OH), 4.17 (2 H, t, $J_{1',2'}$ 7.15, H1'), 7.85 (1 H, s, H2), 8.05 (1 H, s, H8), and 12.00 (1 H, s, NH); MS: *m*/*z* 251 [M^+], calc. 250 ($C_{12}H_{18}N_4O_2$).

***N*⁹-(ω-Hydroxy-*n*-nonyl)hypoxanthine (IIi)**, R_f 0.32 (2); ^{1}H NMR (DMSO-d_6, 50°C): 1.20 (10 H, m, H3'–H7'), 1.40 (2 H, m, H8'), 1.80 (2 H, m, H2'), 3.40 (2 H, t, $J_{8',9'}$ 6.55, H9'), 3.95 (1 H, s, OH), 4.20 (2 H, t, $J_{1',2'}$ 7.15, H1'), 7.85 (1 H, s, H2), 8.00 (1 H, s, H8), and 12.05 (1 H, s, NH); MS: *m*/*z* 279 [M^+], calc. 278 ($C_{14}H_{22}N_4O_2$).

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