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9-(2-ARYLOXYETHYL) DERIVATIVES OF ADENINE – A NEW CLASS OF NON-NUCLEOSIDIC ANTIVIRAL AGENTS

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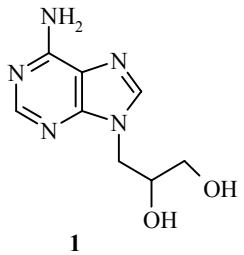
New 9-(aryloxyalkyl) derivatives of adenine have been prepared by alkylation of adenine with tosylates, bromides, and α-chloro ethers containing terminal aromatic fragments in anhydrous DMF in the presence of potassium carbonate. The compounds of the 9-(2-phenoxyethyl)adenine series appear to be highly reactive against cytomegaloviruses of mankind in vitro, while derivatives of 9-(2-benzyloxyethyl)adenine demonstrate anti-HIV-1 activity. Compounds with shorter or longer chains, and also compounds which do not have aromatic fragments at the ends of the chains, do not possess antiviral activity.

Keywords: adenine, $N_{(9)}$-alkylation, antiviral activity.

The problem of searching for effective media for the pharmacotherapy of virus infections has become all the greater in connection with the AIDS pandemic and the wide distribution of opportunistic herpes virus infections. At the present time the main direction remains the search for new antiviral agents among non-nucleosidic compounds, which, in contrast to their nucleoside analogs, do not require metabolic activation *in vivo* and are capable of direct interaction with the virus specific enzyme targets. Among adenine derivatives which show antiviral activity and are not nucleosides are the known 9-(*S*)-(2,3-dihydroxypropyl)adenine (**1**), which shows a wide range of antiviral activity [1], adenallene (**2**) which shows anti-HIV-1 activity *in vitro*, and 9-(allyloxymethyl)adenine (**3**), which we synthesized previously, and which inhibits the cytotoxic effect of HIV-1 in MT-4 lymphocyte culture in the concentration range 50-500 μg/ml [3].



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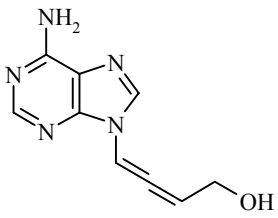

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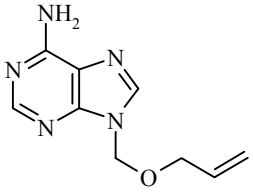

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Analysis of the chemical structures of non-nucleoside anti-HIV agents of various classes, including a number of analogues of emivirin (6-benzyl-1-ethoxymethyl-5-isopropyluracil) [4] and derivatives of S-alkyl-6-arylmethyl-2-thiouracil (S-DABO) [5], coupled with known information about the antiviral properties of other adenine compounds [6], permitted the prediction that 9-substituted derivatives of adenine containing an aromatic group at the end of an acyclic chain might be of considerable interest as potential antiviral substances. We had previously prepared 3-O-aryl ethers of 9-(*R,S*)-(2,3-dihydroxypropyl)adenine and its pyrimidine analogs as probable inhibitors of S-adenosyl-*L*-homocysteinylhydrolases [7,8], some of which (derivatives of adenine and cytosine) were active against HIV-1, HIV-2, herpes virus type 1, and Koksaki virus *in vitro* [9]. In a continuation of this study we have synthesized new 9-substituted derivatives of adenine containing aromatic nuclei (phenyl, naphthyl) groups at the end of an acyclic chain containing 1-5 carbon atoms and including an ether oxygen at various positions.

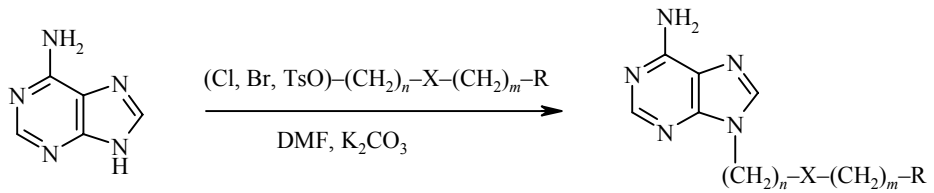
The synthesis of alkylating agents for the introduction of the aryl(oxy)alkyl substituents at $N_{(9)}$ adenine was carried out by three basic schemes.

Commercial aliphatic-aromatic alcohols (benzyl, 2-phenylethyl, or 3-phenylpropyl) and also butylcellosolve, 2-benzoyloxyethanol, and 2-(1-adamantyloxy)ethanol , obtained by the addition of ethylene glycol to 1,3-dehydroadamantane[10] were converted into the α-chloro ethers by the Anry reaction [11] or the tosylates which were used directly for the synthesis of the required compounds **6-11**, **13**, and **14**.

Reactive halides of the benzyl (benzyl chloride, α-chloromethylnaphthalene, 1-bromo-1-phenylethane, and diphenylbromomethane) of allyl types (allyl bromide) in an anhydrous glycol (ethylene glycol, 1,3-propylene glycol or 1,4-butylene glycol) at a temperature of about 80°C in the presence of potassium hydroxide and dibenzo-18-crown-6 (molar ratio halide–glycol–alkali–coronand 1:5-10:1;0.05) readily formed the corresponding ω-aryl(allyl)oxyalkanols, which were then converted into the tosylates used in the synthesis of compounds **12**, **18-21**, **24**, and **26**.

Finally, compounds of the phenol type (phenol, α- and β-naphthol) were alkylated with an excess of 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, or 1,5-dibromopentane by refluxing in the presence of 30% aqueous potassium hydroxide and dibenzo-18-crown-6 (molar ratio of phenol–dibromoalkane–alkali–coronand 1:3-5:1:0.05) which gave ω-aryloxyalkyl bromides – the synthons for obtaining the final compounds **15-17**, **23**, **25**, and **27**.

Alkylated adenine bases were synthesized *via* the ω-aryl(oxy)alkyl bromides (method A) or the tosylates of the ω-aryl(oxy)alkanols (method B) in anhydrous DMF in the presence of potassium carbonate at 110-120°C by the method which we developed for the alkylation of adenine with arylglycidyl ethers [7, 8]. Alkylation of adenine with benzyl chloride and α-chloromethylnaphthalene was carried out analogously, but the reaction mixture was refluxed for 1 h more (method C) which allowed the preparation of the previously described [12] 9-benzyladenine (**4**) and also 9-(α-naphthylmethyl)adenine (**5**). The reaction of adenine with α-chloro ethers to give compounds **8-10** was carried out in DMF in the presence of potassium carbonate at room temperature (method D). For the synthesis of 9-(2-hydroxyethyl)adenine (**11**), removal of the benzoyl group from the product of alkyation of adenine with the tosylate of 2-benzyloxyethanol was carried out at room temperature with a methanolic ammonia solution without isolation of the 9-(2-benzoyloxyethyl)adenine.



4–27

TABLE 1. Characteristics of Compounds **4-27**

Compound	*n*	*m*	X	R	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
						C	H	N			
1	2	3	4	5	6	7	8	9	10	11	12
4	0	0	CH_2	Ph	$C_{12}H_{11}N_5$	63.90 / 63.99	4.87 / 4.92	31.12 / 31.09	226-228	0.22	68 (C)
5	0	0	CH_2	α-Naphthyl	$C_{16}H_{13}N_5$	70.01 / 69.80	4.83 / 4.76	25.10 / 25.44	273-275	0.23	70 (C)
6	1	0	CH_2	Ph	$C_{13}H_{13}N_5$	65.31 / 65.25	5.40 / 5.48	29.43 / 29.27	177-179	0.20	64 (B)
7	2	0	CH_2	Ph	$C_{14}H_{15}N_5$	66.43 / 66.38	6.08 / 5.97	27.50 / 27.65	184-187	0.40	53 (B)
8	1	1	O	Ph	$C_{13}H_{13}N_5O$	61.30 / 61.16	5.05 / 5.13	27.24 / 27.43	224-227	0.23	48 (D)
9	1	2	O	Ph	$C_{14}H_{15}N_5O$	62.40 / 62.44	5.72 / 5.61	25.80 / 26.01	195-198	0.24	54 (D)
10	1	3	O	Ph	$C_{15}H_{17}N_5O$	63.72 / 63.59	6.13 / 6.05	24.58 / 24.72	173-176	0.27	48 (D)
11	2	0	O	H	$C_7H_9N_5O$	47.12 / 46.92	5.16 / 5.06	38.88 / 39.09	241-243	0.05	67 (B)
12	2	0	O	$CH_2CH{=}CH_2$	$C_{10}H_{13}N_5O$	54.85 / 54.78	5.90 / 5.98	32.14 / 31.94	145-148	0.29	57 (B)
13	2	0	O	Bu	$C_{11}H_{17}N_5O$	56.03 / 56.15	7.31 / 7.28	29.63 / 29.77	112–114	0.33	41 (B)
14	2	0	O	1-Adamantyl	$C_{17}H_{23}N_5O$	65.30 / 65.14	7.51 / 7.40	22.14 / 22.35	254-256	0.24	53 (B)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
15	2	0	O	Ph	$C_{13}H_{13}N_5O$	61.31 61.16	5.20 5.13	27.29 27.43	216-218	0.33	58 (A)
16	2	0	O	α-Naphthyl	$C_{17}H_{15}N_5O$	66.93 66.87	4.80 4.95	23.12 22.94	237-239	0.29	66 (A)
17	2	0	O	β-Naphthyl	$C_{17}H_{15}N_5O$	66.99 66.87	4.82 4.95	22.77 22.94	252-255	0.20	72 (A)
18	2	1	O	Ph	$C_{14}H_{15}N_5O$	62.51 62.44	5.80 5.61	25.79 26.01	162-163	0.35	48 (B)
19	2	1	O	α-Naphthyl	$C_{18}H_{17}N_5O$	67.91 67.70	5.43 5.37	21.80 21.93	212-214	0.37	49 (B)
20	2	0	O	CH(Me)Ph	$C_{15}H_{17}N_5O$	63.70 63.59	6.11 6.05	24.55 24.72	145-147	0.35	35 (B)
21	2	0	O	$CHPh_2$	$C_{20}H_{19}N_5O$	69.40 69.55	5.63 5.54	20.14 20.28	187-189	0.37	46 (B)
22	2	3	O	Ph	$C_{16}H_{19}N_5O$	64.53 64.63	6.40 6.44	23.68 23.55	166-168	0.54	49 (B)
23	3	0	O	Ph	$C_{14}H_{15}N_5O$	62.56 62.44	5.43 5.61	25.92 26.01	175-177	0.26	59 (A)
24	3	1	O	Ph	$C_{15}H_{17}N_5O$	63.70 63.59	6.12 6.05	24.60 24.72	124-126	0.51	45 (B)
25	4	0	O	Ph	$C_{15}H_{17}N_5O$	63.77 63.59	6.09 6.05	24.55 24.72	197-200	0.49	79 (A)
26	4	1	O	Ph	$C_{16}H_{19}N_5O$	64.50 64.63	6.58 6.44	23.60 23.55	143-145	0.60	51 (B)
27	5	0	O	Ph	$C_{16}H_{19}N_5O$	64.78 64.63	6.50 6.44	23.47 23.55	169-171	0.56	55 (A)

The $N_{(9)}$-substituted derivatives of adenine (Table 1) were readily obtained with equimolar ratios of adenine and the alkylating agents in the conditions described (Table 1).

The antiviral properties of compounds **4-27** *in vitro* with respect to a wide range of DNA and RNA containing viruses were studied at the Rega Institute for Medical Research (Catholic University, Louvain, Belgium). The greatest effects of the new 9-(aryloxyalkyl) derivatives of adenine were demonstrated against the human cytomegaloviruses (CMV) and HIV-1 (Table 2). Structure-activity analysis indicated that the most powerful effects were shown by adenine derivatives in which the heterocyclic base and the aromatic unit were separated by 3 or 4 atoms. Compounds with longer or shorter chains were less active.

The oxygen atom played a very important role in the composition of the chain: its presence was responsible for the antiviral properties with respect to both viruses. Shift of the oxygen atom from the γ-position in the acyclic relative to atom $N_{(9)}$ of adenine to the β- or δ-position led to practically complete loss in activity (cf. compounds **7**,**8**, and **15**; **9**, **18**, and **23**). Replacement of the aromatic phenyl nucleus in the active compound **15** by the unsaturated allyl group in compound **12**, or the saturated butyl group (compound **13**), or the bulky non-aromatic 1-adamantyl group (compound **14**), like the complete separation of the substituent with an oxygen atom (compound 11) led to considerable weakening (by 6 to 150 times) or complete extinction of anti-cytomegalovirus (CMV) activity. In contrast, substitution of the phenyl group in compound **15** by the α-naphthyl (compound **16**) or β-naphthyl groups (compound **17**) increased the anti-viral effect against CMV by

TABLE 2. Anti-virus Activity of the Synthesized Compounds *in vitro**

Com-pound	Anti-CMV activity (AD-169 strain)		Anti-HIV-1 activity (IIIB strain)	
	EC_{50}, μmol / l	CC_{50}, μmol / l	EC_{50}, μg/ml	CC_{50}, μg/ml
4	>200	>200	167	>250
5	50	>200	>50	~250
6	>50	140	>250	>250
7	>50	200	>50	89.3
8	>200	>200	65.0	>250
9	>200	>200	43.8	104
10	>20	>20	25.0	127
11	20	>200	>250	>250
12	>50	>200	>250	>250
13	2	>200	>250	~250
14	50	200	>50	71.6
15	0.32	48	>50	156
16	0.005	9	>10	27.6
17	0.05	>200	>50	~250
18	0.2	>200	18.3	~250
19	0.8	>200	3.33	~250
20	>20	>20	0.50	~100
21	>20	165	1.07	191
22	2	>20	>20	25.1
23	5	>200	65.0	131
24	>50	>200	>50	212
25	20	>200	>50	95.5
26	2	121	~35	79.1
27	2	>200	>10	22.5

* EC_{50} is the effective concentration which produces a 50% reduction in the cytopathic effect of the virus on the cells; CC_{50} is the cytotoxic concentration which decreases the survival rate of non-infected cells by 50%.

TABLE 3. Effectiveness of the Anti-CMV Effect of the Synthesized Compounds *in vitro*

Compound	Antivirus activity, EC_{50}, μmol/l		Cytotoxicity, CC_{50}, μmol/l	Selectivity index, $SI = CC_{50} / EC_{50}$	
	AD-169 strain	Davis strain		AD-169 strain	Davis strain
15	0.32	0.37	48	150	130
16	0.005	0.005	9	1800	1800
17	0.05	0.04	>200	>4000	>5000
18	0.2	0.4	>200	>1000	>500
19	0.8	2.7	>200	>250	>75
Gantsiklovir	6.3	5.9	>150	>24	>25
Cilofovir	0.5	0.5	>150	>300	>300

65 and 6 times respectively. In summary the antiviral effects *in vitro* of the analogues of 9-(2-phenoxyethyl)adenine **15-17** and 9-(2-benzyloxyethyl)adenine **18** and **19** considerably exceed the activity of ganciklovir [13] and cidofovir [14] which are currently in clinical use as anti-CMV agents (Table 3).

In contrast to the derivatives of 9-(2-phenoxyethyl)adenine **15-17**, the derivatives of 9-(2-benzyloxyethyl)adenine **18-21** show antiviral activity against HIV-1 as well as CMV virus. An increase in the size of the aromatic substituent and branching in the chain at the α-position of the benzyl radical also considerably increase the antiviral activity of the substance, which reaches its maximum with compound **20** (inhibitory concentration EC_{50} = 0.50 μg/ml, selectivity index $SI > 200$).

We have therefore a new class of non-nucleosidic inhibitors of virus reproduction which have high activity against human CMV and at the same time show anti-HIV-1 activity *in vitro*. On the basis of the structure-activity ratios in the compounds obtained, further deliberately directed search for new highly active compounds for the complex medical treatment of AIDS and opportunistic CMV infection.

EXPERIMENTAL

^{1}H NMR spectra of 1:1 DMSO-d_6–acetone-d_6 solutions with MDS as internal standard were recorded with a Tesla BS-567A (100 MHz). Interpretation of the spectra was carried out using the decision programme ACD/HNMR Pro 3.0 (Advanced Chemistry Development, Canada). Electron impact mass spectra were recorded with a Varian MAT-111 machine with direct inlet of the sample into the ion source, energy of ionizing electrons 70 eV). TLC was carried out Silufol UV-254 strips with 10:1 chloroform–methanol as eluent, and development with iodine vapor. Melting points were measured in glass capillaries with a Mel-Temp 3.0 apparatus (Laboratory Devices,Inc, U.S.A.).

9-(1-Naphthylmethyl)adenine (5). A mixture of adenine (2.0 g, 14.8 mmol) and anhydrous potassium carbonate (3.0 g, 21.7 mmol) in DMF (50 ml) was stirred for 30 min at 105-110°C, α-chloromethylnaphthalene (2.7 g, 15.2 mmol) was added, stirring was continues at the same temperature for 2 h, and the mixture was refluxed for 1 h. The hot reaction mixture was filtered, the filtrate was evaporated in vacuum, cooled, and the solid residue was washed with water (25 ml), dried in air, and recrystallized from glacial acetic acid (25 ml) to give compound **5** (2.85 g) as a white crystalline substance. ^{1}H NMR spectrum, δ, ppm: 5.75 (2H, s, CH_2); 6.97-7.90 (7H, m, naphthyl); 7.07 (2H, br. s, NH_2); 7.99 (1H, s, 8-H); 8.11 (1H, s, 2-H). Mass spectrum, *m/z* 275 [M^+].

9-(2-Hydroxyethyl)adenine (11). A mixture of adenine (2.0 g, 14.8 mmol) and anhydrous potassium carbonate (3.0 g, 21.7 mmol) in DMF (50 ml) was stirred for 30 min at 105-110°C, a solution of 2-benzoylethyl tosylate (4.6 g, 15.0 mmol) in DMF (10 ml) was added, and the mixture was stirred at the same temperature for 2 h. The hot reaction mixture was filtered, the filtrate was evaporated in vacuum, cooled, dissolved in methanol (50 ml), saturated with gaseous ammonia, and stirred for 1 d at room temperature in a sealed vessel. The reaction mixture was evaporated to dryness in vacuum (~100°C), cooled, washed with ether (3 × 10 ml), and recrystallized from DMF (20 ml) to give compound **11** (1.75 g) as light-yellow crystals. ^{1}H NMR spectrum, δ, ppm: 3.58-3.81 (2H, m, CH_2O); 4.01-4.25 (2H, m, NCH_2); 4.96 (1H, br. s, OH); 7.19 (2H, br. s, NH_2); 7.99 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum: *m/z* 179 [M^+].

9-[2-(Phenoxy)ethyl]adenine (15). A mixture of adenine (2.0 g, 14.8 mmol) and anhydrous potassium carbonate (3.0 g, 21.7 mmol) in DMF (50 ml) was stirred for 30 min at 105-110°C, a solution of 1-bromo-2-phenoxyethane (3.0 g, 14.9 mmol) in DMF (10 ml) was added and the mixture was stirred at the same temperature for 2 h. The hot solution was filtered, the filtrate evaporated in vacuum, cooled, and the solid residue was washed with water (25 ml), dried in the air, and recrystallized from 95% ethanol to give compound **15** (2.20 g) as white crystals. ^{1}H NMR spectrum, δ, ppm: 4.20-4.57 (4H, m, CH_2CH_2); 6.67-7.23 (7H, m, phenyl, NH_2); 8.03 (1H, s, 8-H); 8.09 (1H, s, 2-H). Mass spectrum, *m/z* 255 [M^+].

Compounds 4, 6-10, 12-14, and **16-27** were made analogously.

9-Benzyladenine (4). ^{1}H NMR spectrum, δ, ppm: 5.43 (2H, s, CH_2); 6.95-7.25 (7H, m, phenyl, NH_2); 8.12 (1H, s, 8-H); 8.28 (1H, s, 2-H). Mass spectrum, *m/z* 225 [M^+].

9-(2-Phenylethyl)adenine (6). ^{1}H NMR spectrum, δ, ppm: 3.39 (4H, m, CH_2CH_2); 7.0 (2H, br. s, NH_2); 7.12 (5H, m, phenyl); 8.02, 1H, s, 8-H); 8.11 (1H, s, 2-H). Mass spectrum, *m/z* 239 [M^+].

9-(3-Phenylpropyl)adenine (7). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.91-2.66 (4H, m, CH_2CH_2); 4.12 (2H, t, J = 7, NCH_2); 7.04 (2H, br. s, NH_2); 7.08 (5H, s, phenyl); 8.00 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum, *m/z* 253 [M^+].

9-(Benzyloxymethyl)adenine (8). ^{1}H NMR spectrum, δ, ppm: 4.51 (2H, s, CH_2); 5.57 (2H, s, NCH_2); 6.98 (2H, br. s, NH_2); 7.19 (5H, s, phenyl); 8.07 (1H, s, 8-H); 8.12 (1H, s, 2-H). Mass spectrum, *m/z* 255 [M^+].

9-(2-Phenylethoxymethyl)adenine (9). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (2H, t, J = 6, CH_2); 4.12 (2H, t, J = 6, OCH_2); 5.52 (2H, s, NCH_2O); 7.01 (2H, br. s, NH_2); 7.08 (5H, s, phenyl); 7.98, 1H, s, 8-H); 8.11 (1H, s, 2-H). Mass spectrum, *m/z* 269 [M^+].

9-(3-Phenylpropoxymethyl)adenine (10). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39-1.83 (2H, m, CH_2); 2.57 (2H, J = 6, CH_2); 3.48 (2H, J = 6, OCH_2); 5.45 (2H, s, NCH_2O); 7.02 (2H, br. s, NCH_2); 7.14 (5H, s, phenyl); 8.01 (1H, s, 8-H); 8.08 (1H, s, 2-H). Mass spectrum, *m/z* 283 [M^+].

9-(2-Allyloxyethyl)adenine (12). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (2H, t, J = 6, CH_2O); 3.84 (2H, dd, J = 5, J = 1, OCH_2); 4.26 (2H, t, J = 6, NCH_2); 4.85-5.17 (2H, m, $=CH_2$); 5.44-5.90 (1H, m, -CH=); 6.88 (2H, br. s, NH_2); 7.92 (1H, s, 8-H); 8.05 (1H, s, 2-H). Mass spectrum, *m/z* 210 [M^+].

9-(2-Butoxyethyl)adenine, (13). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.75 (3H, t, J = 6, CH_3); 1.02-1.65 (4H, m, CH_2CH_2); 3.29 (2H, t, J = 5, OCH_2); 3.63 (2H, t, J = 5, OCH_2); 4.26 (2H, t, J = 5, NCH_2); 6.90 (2H, br. s, NH_2); 7.98 (1H, s, 8-H); 8.12 (1H, s, 2-H). Mass spectrum, *m/z* 235 [M^+].

9-[2-(1-Adamantyloxy)ethyl]adenine (14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44-2.10 (15H, m, adamantyl); 3.61 (2H, t, J = 6, OCH_2); 4.24 (2H, t, J = 6, NCH_2); 6.90 (2H, br. s, NH_2); 7.94 (1H, s, 8-H); 8.08 (1H, s, 2-H) Mass spectrum, *m/z* 313 [M^+].

9-[2-(1-Naphthyloxy)ethyl]adenine (16). ^{1}H NMR spectrum, δ, ppm: 4.34-4.71 (4H, m, NCH_2CH_2O); 6.76-7.97 (9H, m, naphthyl, NH_2); 7.94 (1H, s, 8-H); 8.17 (1H, s, 2-H). Mass spectrum, *m/z* 305 [M^+].

9-[2-(2-Naphthyloxy)ethyl]adenine (17). ^{1}H NMR spectrum, δ, ppm: 4.27-4.63 (4H, m, NCH_2CH_2O); 6.89-7.85 (9H, m, naphthyl, NH_2); 8.04 (1H, s, 8-H); 8.11 (1H, s, 2-H). Mass spectrum, *m/z* 305 [M^+].

9-(2-Benzyloxyethyl)adenine (18). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.43 (2H, t, *J* = 6, OCH_2); 4.31 (2H, t, *J* = 6, NCH_2); 6.97 (2H, br. s, NH_2); 7.10 (5H, s, phenyl); 8.03 (1H, s, 8-H); 8.10 (1H, s, 2-H). Mass spectrum: *m/z* 269 [M^+].

9-[2-(1-Naphthylmethoxy)ethyl]adenine (19): ^{1}H NMR spectrum, δ, ppm: 3.73-3.98 (2H, m, OCH_2); 4.23-4.42 (2H, m, NCH_2); 4.86 (2H, s, OCH_2); 6.98 (2H, br. s, NH_2); 7.18-7.88 (7H, m, naphthyl); 7.93 (1H, s, 8-H); 8.02 (1H, s, 2-H). Mass spectrum, *m/z* 319 [M^+].

9-[2-(1-Phenylethoxy)ethyl]adenine (20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58 (3H, s, CH_3); 3.73 (2H, t, *J* = 6, OCH_2); 4.21-4.40 (3H, m, NCH_2, CH); 7.00 (2H, br. s, NH_2); 7.09 (5H, s , phenyl); 8.03 (1H, s, 8-H); 8.12 (1H, s, 2-H). Mass spectrum, *m/z* 283 [M^+].

9-[2-(Diphenylmethoxy)ethyl]adenine (21). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.69 (2H, t, *J* = 6, OCH_2); 4.36 (2H, t, *J* = 6, NCH_2); 5.37 (1H, s, CH); 7.01 (2H, br. s,NH_2); 7.11 (10H, s, phenyl); 8.03 (1H, s, 8-H); 8.13 (1H, s, 2-H). Mass spectrum, *m/z* 318 [M - HCN]$^+$.

9-[2-(3-Phenylpropoxy)ethyl]adenine (22). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47-1.82 (2H, m , CH_2); 2.52 (2H, *J* = 6 , CH_2); 3.19-3.70 (4H, m, CH_2OCH_2); 4.23 (2H, t, *J* = 6, NCH_2); 6.95 (2H, br. s, NH_2); 7.12 (5H, s, phenyl); 8.02 (1H, s, 8-H); 8.08 (1H, s, 2-H). Mass spectrum, *m/z* 297 [M^+].

9-(3-Phenoxypropyl)adenine (23). ^{1}H NMR spectrum, δ, ppm): 1.70-1.95 (2H, m, CH_2); 3.45-3.80 (4H, m, NCH_2CH_2O); 6.62-7.30 (7H, m, phenyl, NH_2); 7.95 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum, *m/z* 269 [M^+].

9-(3-Benzyloxypropyl)adenine (24). ^{1}H NMR spectrum, δ, ppm : 1.68-1.95 (2H, m, CH_2); 3.44-3.76 (4H, m, NCH_2CH_2O); 4.42 (2H, s, OCH_2); 6.90 (2H, br.s, NH_2); 7.12 (5H, s, phenyl); 7.93 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum, *m/z* 283 [M^+].

9-(4-Phenoxybutyl)adenine (25). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52-2.06 (4H, m, CH_2CH_2); 3.89 (2H, t, *J* = 6, OCH_3); 4.14 (2H, t, *J* = 6, NCH_2); 6.65-7.22 (7H, m, phenyl, NH_2); 7.98 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum, *m/z* 283 [M^+].

9-(4-Benzyloxybutyl)adenine (26). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38-2.06 (4H, m, CH_2CH_2); 3.37 (2H, t, *J* = 6, OCH_2); 4.08 (2H, t, NCH_2); 4.32 (2H, s, OCH_2); 6.82 (2H, br.s, NH_2); 7.14 (5H, s, phenyl); 7.91 (1H, s, 8-H); 8.04 (1H, s, 2-H). Mass spectrum, *m/z* 297 [M^+].

9-(5-Phenoxypentyl)adenine (27). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10-2.03 (6H, m, $CH_2CH_2CH_2$); 3.82 (2H, t, *J* = 6, OCH_2); 4.08 (2H, t, *J* = 6, NCH_2); 6.62-7.20 (7H, m, phenyl, NH_2); 7.91 (1H, s, 8-H); 8.02 (1H, s, 2-H). Mass spectrum, *m/z* 297 [M^+].

REFERENCES

1. E. De Clercq, J. Deschamps, P. De Somer, and A. Holy, *Science***, 200**, 563 (1978).
2. S. Hayashi, S. Phadtaro, J. Zemlicka, M. Matsukara, H. Mitsuya, and S. Broder, *Proc. Nat. Acad. Sci. USA,* **85,** 6127 (1988).
3. A. A. Ozerov, *Thesis for Doctor of Chem. Sci.*, Volgograd, 1994.
4. H. Tanaka, H. Takashima, M. Ubasawa. K. Sekiya, N. Inoue, M. Baba, S.Shigeta, R. T. Walker, E. De Clercq, and T. Miyasaka, *J. Med. Chem.,* **38,** 2860 (1995).
5. A. Mai, M. Artico, G. Sbardella, S. Massa, A. G. Loi, E. Tramontano, P. Seano, and P. La Colla, *J. Med. Chem.,* **38**, 3258 (1995).
6. J. Balzarini and E. De Clercq, *J. Biol. Chem.,* **266,** 8686 (1991).
7. T. P. Ozerova, A. K. Brel', and M. S. Novikov, *Vestn. Volgograd. Med. Akad.,* **54**, No. 4, 36 (1998).
8. A. A. Ozerov, M. S. Novikov, and A. K. Brel', *Khim. Geterotsikl. Soedin.,* 82 (1999).
9. T. P. Ozerova, *Thesis for Candidate of Chem. Sci,* Volgograd, 2000.
10. V. I. No, G. M. Butov, and V. M. Mokhov, *Zh. Org. Khim.,* **35**, 149 (1999).

11. Yu. V. Pokonova, *Chemistry and Technology of Halo Ethers* [in Russian], Leningrad State University, Leningrad, 1982.
12. Z. Sun and R. S. Hosmane, *Synth. Commun.,* **31**, 549 (2001).
13. D. H. Shepp, P. S. Dandliker, P. de Miranda, T. C. Burnette, D. M. Cederberg, L. E. Kirk, and J. D. Meyers, *Ann. Intern. Med.,* **103**, 368 (1985).
14. R. Snoek, I. Sakuma, E. De Clercq, I. Rosenberg, and A. Holy, *Antimicrob. Agents Chemother.,* **32**, 1839 (1988).