# 7-(1-CYANOBUT-3-EN-1-YL)-$N^6$-[(*N*,*N*-DIMETHYLAMINO)METHYLENE]-ADENINE AS A STARTING COMPOUND FOR THE SYNTHESIS OF α-BRANCHED ACYCLIC ANALOGUES OF $N^7$-ISOMER OF ADENOSINE

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7-(1-Cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine (**2**) was used as a multipurpose starting material for the synthesis of a series of α-branched acyclic analogues of $N^7$-isomer of adenosine by further reactions on allyl (hydroxylation) and/or cyano group (hydrolysis, methanolysis or tetrazole formation).

**Key words**: Nucleosides; Acyclic analogues; Purines; Nitriles; Antivirals.

Discovery of biological activity in the series of acyclic nucleoside analogues initiated a detailed investigation of the structure–activity relationship in this group[1]. Acyclic analogues are characterized by significant resistance against chemical and biological degradation as well as by the flexibility of the acyclic chain that enables the compound to adopt conformation suitable for interaction with an active enzyme site or with a receptor[2].

Although a broad spectrum of nucleoside analogues has been already studied[3], the $N^7$-isomers of nucleosides and their analogues were mostly obtained only as side products in $N^9$-alkylation reactions[4] or as a result of $N^7/N^9$-glycosyl transfer[5]. The first example of a naturally occurring $N^7$-isomer of purine nucleoside was 7-(α-D-ribofuranosyl)adenine isolated from pseudovitamin $B_{12}$ (ref.[6]); since then several syntheses of related compounds have been reported[7]. Recently we found that the alkylation of $N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[8] with certain halogeno derivatives leads selectively to $N^7$-substituted derivatives[9]. An active methylene moiety of thus prepared 7-cyanomethyl-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine (**1**) afforded on allylation in the presence of a deprotonating agent the title compound **2** with α-branched side chain[9a]. Such compound would be very difficult to prepare by standard alkylation reactions due to

the presence of an electron-withdrawing substituent in the α-position of the side chain[10].

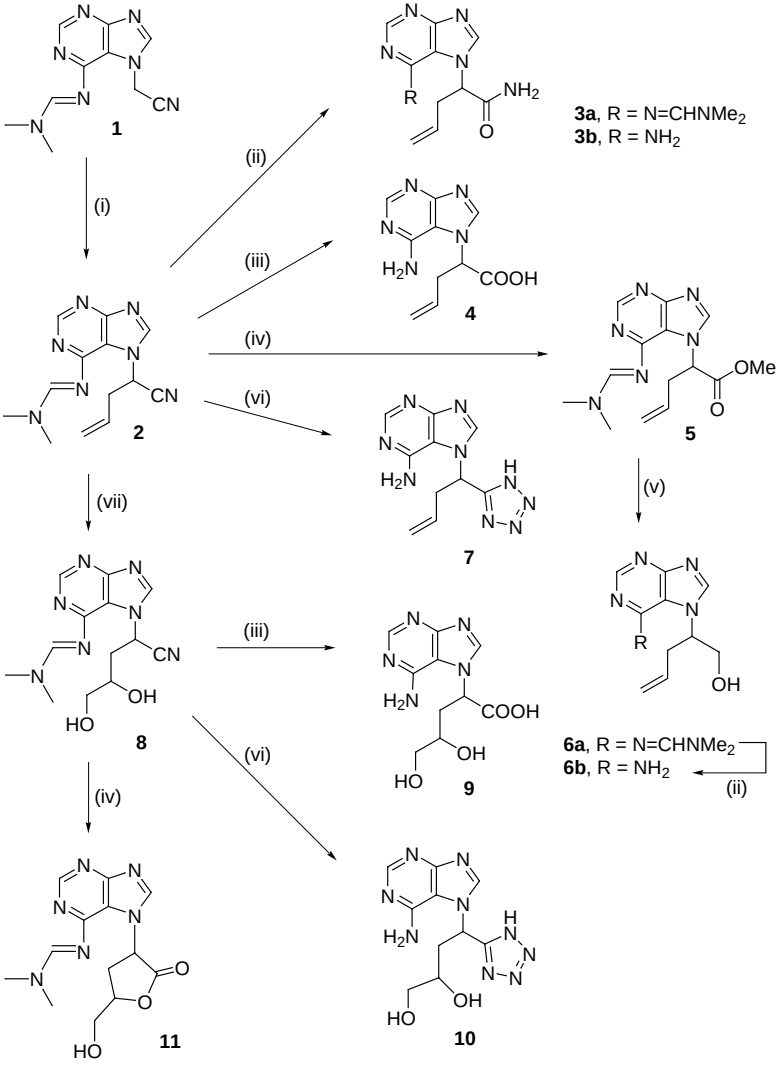
Since both the double bond and the cyano group in the side chain of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) can be easily modified, this derivative is a suitable precursor for the syntheses of $N^7$-isomers of acyclic nucleoside analogues bearing an α-branched side chain.

The versatility of cyano group transformations was used in preparation of compounds **3**–**7** (Scheme 1). Conversion of starting cyano derivative **2** to amide **3a** proceeded under mild conditions; the $N^6$-unprotected amide **3b** was obtained as a minor product. Hydrolysis under more vigorous reaction conditions (reflux in aqueous NaOH/MeOH)[11] afforded carboxylic acid **4** with simultaneous cleavage of the dimethylaminomethylene group. Methyl ester **5** was prepared from cyano derivative **2** by reaction with sodium methoxide in methanol. The ester group was further reduced by sodium borohydride to give the hydroxymethyl derivative **6a** that was deprotected under basic conditions to compound **6b**. To extend the series of carboxylic acid derivatives, the tetrazole derivative **7** was prepared in a good yield by reaction of nitrile **2** with sodium azide in the presence of ammonium chloride. Tetrazole unit is not only comparable to carboxylic acid moiety, both in size and acidity, but is also metabolically more stable and therefore has been used as a carboxylic acid mimic in a wide number of compounds of biological interest[12].

Another possibility of modification of the title compound **2** consists in the transformation of the allyl moiety. Hydroxylation of the double bond with osmium tetroxide in a presence of hydrogen peroxide afforded diol **8**. Subsequent reactions of the cyano group afforded dihydroxycarboxylic acid **9** and its isosteric tetrazole analogue **10**. However, lactone **11** was isolated as a major product under the conditions analogous to those used for the preparation of ester **5**.

In conclusion, a series of α-branched acyclic analogues of $N^7$-isomer of adenosine was prepared divergently by functionalization of easily accessible precursor **2**. These compounds are difficult to synthesize by a direct alkylation of the purine base with secondary alkyl halides bearing an electron withdrawing group in α-position, since such substitution strongly favours elimination over nucleophilic substitution. Since $N^7$-isomers are usually prepared only as minor side products in the synthesis of $N^9$-substituted compounds, their biological activity[13] has not been thoroughly studied. Also their utilization in PNA synthesis could be of some interest.

The target α-branched derivatives **3**–**11** were prepared within the framework of our studies of structure–activity relationships in the series of acyclic nucleoside analogues. The cytostatic assays were performed by Dr I. Votruba at this Institute. None of the compounds exhibited significant




(i) 1. NaH/THF, 2. $CH_2$=$CHCH_2Br$; (ii) MeOH, aq. $NH_3$; (iii) 1. NaOH aq., MeOH, 2. Dowex 1; (iv) 0.1M NaOMe/MeOH; (v) $NaBH_4$/MeOH; (vi) 1. $NaN_3$, $NH_4Cl$, DMF, 2. $NH_3$/MeOH; (vii) *t*-BuOH/$H_2O_2$/$OsO_4$

SCHEME 1

cytostatic activity or cytotoxicity in L-1210 mouse leukemia cells. *In vitro* effects against the DNA viruses and retroviruses were examined at the Rega Institute for Medical Research (Prof. E. De Clercq, Head), Catholic University Leuven (Belgium); only compound **3a** had a weak effect ($IC_{50}$ ≈ 10–20 μg/ml) on varicella zooster virus[14].

## EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 2 kPa over $P_2O_5$. Melting points were determined on a Kofler block and are uncorrected. Analytical TLC were performed on Silufol $UV_{254}$ plates (Kavalier Votice, Czech Republic). Preparative TLC were carried out on 40 × 17 × 0.4 cm loose layer plates of silica gel containing a UV indicator. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB technique (ionisation by Xe, accelerating voltage 8 kV, glycerol matrix). Paper electrophoreses were performed on a Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate (TEAB) at pH 7.5; the electrophoretical mobilities are referenced to uridine 3′-phosphate. Dimethylformamide was distilled from $P_2O_5$ and stored over molecular sieves (4 A).

$^1H$ and $^{13}C$ NMR spectra were measured on a Varian UNITY 500 or 200 spectrometer ($^1H$ at 499.88 or 200.04 MHz; $^{13}C$ at 125.71 MHz) at room temperature (≈293K) in DMSO-$d_6$ referenced to the solvent signal (2.5 ppm for $^1H$ and 39.7 ppm for $^{13}C$ NMR).

### 2-{$N^6$-[(*N*,*N*-Dimethylamino)methylene]adenin-7-yl}pent-4-en amide (**3a**) and 2-(Adenin-7-yl)pent-4-en amide (**3b**)

A solution of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) (0.51 g, 1.9 mmol) in a mixture of methanol, concentrated aqueous ammonia and water (2 : 2 : 1, 20 ml) was stirred at room temperature for 24 h and the mixture was taken down. The mixture was separated by column chromatography on silica gel (10–20% of methanol in chloroform) to give **3a** as a major product in the yield 0.26 g (48%) and the minor product **3b** in the yield 0.06 g (13.5%).

**3a**: M.p. 222–225 °C. $^1H$ NMR: 8.89 s, 1 H (NCH); 8.47 s, 1 H and 8.40 s, 1 H (H-2 and H-8); 7.64 brs and 7.33 brs, 2 × 1 H ($NH_2$); 6.03 m, 1 H (H-1′); 5.67 m, 1 H (H-3′); 5.03 brd, 1 H, $J$(4′,3′) = 17.1 (H-4′*trans*); 4.93 brd, 1 H, $J$(4′,3′) = 10.3 (H-4′*cis*); 3.20 s and 3.14 s, 2 × 3 H ($NCH_3$); 3.01 m, 2 H (H-2′). For $C_{13}H_{17}N_7O$ (287.3) calculated: 54.34% C, 5.96% H, 34.12% N; found: 54.18% C, 5.92% H, 32.50% N. FAB MS, *m/z* (rel.%): 288 (100) [M + H].

**3b**: M.p. 230–232 °C. $^1H$ NMR: 8.31 s, 1 H and 8.19 s, 1 H (H-2 and H-8); 7.96 brs and 7.72 brs, 2 × 1 H ($NH_2$); 7.12 brs, 2 H ($NH_2$); 5.63 ddt, 1 H, $J$(2′,3′) = 6.3, $J$(4′a,3′) = 17.1, $J$(4′b,3′) = 10.3 (H-3′); 5.27 dd, 1 H, $J$(1′,2′) = 7.1 and 9.5 (H-1′); 4.99 dq, 1 H, $J$(4a′,2′) = $J_{gem}$ = 1.7, $J$(4′a,3′) = 17.1 (H-4′a); 4.96 ddt, 1 H, $J$(4′b,2′) = 1.0, $J_{gem}$ = 1.7, $J$(4′b,3′) = 10.3 (H-4′b); 2.87 m, 2 H (H-2′). For $C_{10}H_{12}N_6O$ (232.2) calculated: 51.72% C, 5.21% H, 36.19% N; found: 51.57% C, 5.42% H, 35.83% N. FAB MS, *m/z* (rel.%): 233 (100) [M + H].

2-(Adenin-7-yl)pent-4-enoic Acid (**4**)

A solution of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) (0.3 g, 1.11 mmol) in a mixture of methanol (14.5 ml) and 25% aqueous sodium hydroxide (3.5 ml) was refluxed for 4.5 h and then stirred at room temperature overnight. Methanol was evaporated and the resulting aqueous solution was applied onto a column of Dowex 1 (acetate form). The column was washed with water and product was eluted with 1 M acetic acid. The product-containing fractions were taken down and codistilled with water to give white solid. Yield: 0.25 g (96%), m.p. 134–137 °C. $^1$H NMR: 12.40 brs, 1 H (COOH); 8.44 s, 1 H and 8.20 s, 1 H (H-2 and H-8); 7.01 brs, 2 H ($NH_2$); 5.63 ddt, 1 H, *J*(2′,3′) = 6.2, *J*(4′*trans*,3′) = 17.2, *J*(4′*cis*,3′) = 10.3 (H-3′); 5.61 dd, 1 H, *J*(1′,2′) = 5.8 and 9.2 (H-1′); 5.05 dm, 1 H, *J*(4′*trans*,3′) = 17.2 (H-4′*trans*); 4.97 dm, 1 H, *J*(4′*cis*,3′) = 10.3 (H-4′*cis*); 3.02 m, 1 H (H-2′a); 2.98 m, 1 H (H-2′b). $^{13}$C NMR: 171.32 (COOH); 159.21 (C-4); 151.98 (C-2); 151.65 (C-6); 145.60 (C-8); 133.25 (C-3′); 119.11 (C-5); 111.66 (C-4′); 58.62 (C-1′); 35.82 (C-2′). For $C_{10}H_{11}N_5O_2$ (233.2) calculated: 51.50% C, 4.75% H, 30.03% N; found: 51.25% C, 4.40% H, 29.88% N. FAB MS, *m/z* (rel.%): 234 (100) [M + H].

Methyl 2-(Adenin-7-yl)pent-4-enoate (**5**)

A solution of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) (1.12 g, 4.16 mmol) in a mixture of methanol (40 ml) and 1 M sodium methanolate in methanol (4.5 ml) was stirred at room temperature for 5 h, pH of the reaction mixture was adjusted to 6–7 by addition of acetic acid and the solvent was evaporated. The residue was codistilled with water and partitioned between water and chloroform. The organic layer was taken down and the crude product was crystallized from ethanol–light petroleum. Yield: 0.80 g (64%), m.p. 173–175 °C. $^1$H NMR: 8.88 s, 1 H (NCH); 8.38 s, 2 H (H-2 and H-8); 5.91 m, 1 H (H-1′); 5.68 m, 1 H (H-3′); 4.93 brd, 1 H (H-4′a); 4.87 brd, 1 H (H-4′b); 3.62 s, 3 H ($OCH_3$); 3.20 s and 3.08 s, 2 × 3 H ($NCH_3$); 3.12 m, 2 H (H-2′). For $C_{14}H_{18}N_6O_2$ (302.3) calculated: 55.62% C, 6.00% H, 27.80% N; found: 55.84% C, 6.10% H, 28.16% N. FAB MS, *m/z* (rel.%): 303 (100) [M + H].

2-{$N^6$-[(*N*,*N*-Dimethylamino)methylene]adenine-7-yl}pent-4-en-1-ol (**6a**)

To a solution of methyl 2-(adenin-7-yl)pent-4-enoate (**5**) (0.8 g, 2.65 mmol) in methanol (30 ml), $NaBH_4$ (0.15 g, 3.96 mmol) was added at –10 °C. After stirring at room temperature for 4 h, the solvent was evaporated and the residue was partitioned between water and chloroform. The organic layer was dried over magnesium sulfate, filtered, the solvent was evaporated and the residue was subjected to preparative TLC (17% methanol in chloroform) to give pure product **6a** as a white solid. Yield: 0.3 g (41%), m.p. 146–149 °C. $^1$H NMR: 8.91 s, 1 H (NCH); 8.43 s and 8.49 s, 2 × 1 H (H-2 and H-8); 5.72 ddt, 1 H, *J*(3′,2′) = 6.7, *J*(3′,4′*cis*) = 10.1, *J*(3′,4′*trans*) = 16.8 (H-3′); 5.34 m, 1 H (H-1′); 5.04 t, 1 H, *J* = 5.3 (OH); 4.98 d, 1 H, *J*(4′,3′) = 16.8 (H-4′*trans*); 4.92 d, 1 H, *J*(4′,3′) = 10.1 (H-4′*cis*); 3.85 dm, 2 H ($CH_2OH$); 3.21 s and 3.10 s, 2 × 3 H ($CH_3$); 2.51 m, 2 H (H-2′). For $C_{13}H_{18}N_6O \cdot 1/3\ H_2O$ (280.3) calculated: 55.70% C, 6.71% H, 29.98% N; found: 55.88% C, 6.44% H, 29.98% N. FAB MS, *m/z* (rel.%): 275 (100) [M + H].

2-(Adenine-7-yl)pent-4-en-1-ol (**6b**)

Aqueous ammonium hydroxide (25%, 15 ml) was added to a solution of 2-{$N^6$-[(*N*,*N*-dimethylamino)methylene]adenin-7-yl}pent-4-en-1-ol (**6a**) (0.2 g, 0.73 mmol) in methanol (15 ml) and the mixture was stirred at room temperature for 2 days. Methanol was evaporated and the resulting aqueous solution was applied onto a column of Dowex 50 ($H^+$ form). The column was washed with water and the product was eluted with 2.5% aqueous ammonium hydroxide. The product-containing fractions were taken down and purified by column chromatography on silica gel (20% methanol in chloroform) to afford product **6b** as a yellow foam. Yield: 0.12 g (75%). $^1$H NMR: 8.91 s, 1 H (NCH); 8.38 s and 8.17 s, 2 × 1 H (H-2 and H-8); 6.90 s, 2 H ($NH_2$); 5.72 ddt, 1 H, *J*(3′,2′) = 6.5, *J*(3′,4′*cis*) = 10.6, *J*(3′,4′*trans*) = 17.0 (H-3′); 5.30 brt, 1 H (OH); 5.05 dd, 1 H, *J*(4′,3′) = 17.0 (H-4′*trans*); 4.96 dd, 1 H, *J*(4′,3′) = 10.6 (H-4′*cis*); 4.82 m, 1 H (H-1′); 3.73 t, 2 H ($CH_2OH$); 2.71 m, 2 H (H-2′). For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.66% C, 6.23% H, 31.59% N. FAB MS, *m/z* (rel.%): 220 (100) [M + H].

7-[1-(Tetrazol-5-yl)but-3-en-1-yl]adenine (**7**)

$NaN_3$ (0.2 g, 3.14 mmol) and $NH_4Cl$ (0.17 g, 3.14 mmol) were added to a solution of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) (0.58 g, 2.15 mmol) in dimethylformamide (8 ml). After stirring at 125 °C for 3 h, water (5 ml) was added, the solvent was evaporated and the residue codistilled with water. The aqueous solution was applied onto a column of Dowex 50X8 ($H^+$ form). The column was washed with water and the product was eluted with 3% aqueous ammonia. The product-containing fraction was taken down to give the title compound as a foam. Yield: 0.4 g (72%). $^1$H NMR: 8.40 s, 1 H and 8.13 s, 1 H (H-2 and H-8); 7.89 brs, 1 H (NH); 7.18 brs, 2 H ($NH_2$); 6.09 dd (H-1′); 5.62 m, 1 H (H-3′); 4.95 m, 1 H (H-4′a); 4.86 m, 1 H (H-4′b); 3.029 m, 2 H (H-2′). FAB MS, *m/z* (rel.%): 258 (100) [M + H].

4,5-Dihydroxy-2-{$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine-7-yl}pentanenitrile (**8**)

A solution of $OsO_4$ (0.5% solution in *tert*-butanol, 0.18 ml) in a mixture of *tert*-butanol and 30% aqueous hydrogen peroxide (5 : 1, 45 ml) was added to a solution of 7-(1-cyanobut-3-en-1-yl)-$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine[9a] (**2**) (3.8 g, 14.1 mmol) in a mixture of *tert*-butanol and chloroform (2 : 1, 30 ml), the reaction mixture was stirred at room temperature for 17 h and taken down. The chromatography of the residue on a column of silica gel (5–20% methanol in chloroform) gave the recovered starting material (0.58 g, 15%) and compound **8** as a white solid. Yield: 1.97 g (46%), m.p. 248–252 °C, mixture of diastereomers 1 : 1. $^1$H NMR: A: 8.96 s, 1 H (NCH); 8.67 s and 8.48 s, 2 × 1 H (H-2 and H-8); 6.59 m, 1 H (H-1′); 5.16 d, 1 H, *J*(3′,OH) = 5.1 (3′-OH); 4.78 t, 1 H, *J*(4′,OH) = 5.4 (4′-OH); 3.71 m, 1 H (H-3′); 3.40 dt, 1 H, *J*(4′,OH) = *J*(4′,3′) = 5.4, $J_{gem}$ = 11.0 (H-4′a); 3.27 dt, 1 H, *J*(4′,OH) = *J*(4′,3′) = 5.4, $J_{gem}$ = 11.0 (H-4′b); 3.23 s and 3.17 s, 2 × 3 H ($NCH_3$); 2.90 m and 2.00 m, 2 × 1 H (H-2′). B: 8.96 s, 1 H (NCH); 8.54 s and 8.485 s, 2 × 1 H (H-2 and H-8); 6.42 m, 1 H (H-1′); 5.00 d, 1 H, *J*(3′,OH) = 5.1 (3′-OH); 4.63 t, 1 H, *J*(4′,OH) = 5.4 (4′-OH); 3.28 m, 1 H (H-3′); 3.24 s and 3.19 s, 2 × 3 H ($NCH_3$); 3.20 m, 2 H (H-4′); 2.90 m and 2.21 m, 2 × 1 H (H-2′). For $C_{13}H_{17}N_7O_2$ (303.3) calculated: 51.48% C, 5.65% H, 32.32% N; found: 51.26% C, 5.66% H, 32.11% N. FAB MS, *m/z* (rel.%): 304 (100) [M + H].

2-(Adenin-7-yl)-4,5-dihydroxypentanoic Acid (**9**)

A solution of 4,5-dihydroxy-2-{$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine-7-yl}pentanenitrile (**8**) (0.34 g, 1.12 mmol) in a mixture of methanol (15 ml) and 25% aqueous sodium hydroxide (3.6 ml) was refluxed for 4 h and then stirred at room temperature overnight. Methanol was evaporated and the resulting aqueous solution was applied onto a column of Dowex 1 (acetate form). The column was washed with water and the product was eluted with 1 M acetic acid. The product-containing fractions were taken down and codistilled with water to afford a colourless foam which was purified by preparative HPLC. Yield: 0.14 g (47%) of hygroscopic compound **9** as a 1 : 1 mixture of diastereomers, $E_{UP}$ = 0.53. $^1$H NMR: 8.37 s, 8.365 s, 8.20 s and 8.19 s, 4 × 1 H (H-2 and H-8); 7.12 brs and 7.00 brs, 2 × 2 H ($NH_2$); 5.94 dd, 1 H, *J* = 9.0 and 12.0; 5.80 t, 1 H, *J* = 10.1 (3′-OH); 5.40 m and 5.36 m, 2 × 1 H (H-1′); 4.82 m, 1 H and 4.66 dd, 1 H, *J* = 3.0 and 5.5 (4′-OH); 3.76 dd, 1 H, *J* = 3.0 and 12.4; 3.65 dd, 1 H, *J* = 5.1 and 12.3 (H-3′); 3.28 ddd, 2 H, *J* = 5.0, 5.0 and 11.0; 3.25 ddd, 2 H, *J* = 5.4, 5.4 and 11.0 (H-4′); 1.99 m, 2.13 m, 2.35 m and 2.45 m, 4 × 1 H (H-2′). FAB MS, *m/z* (rel.%): 268 (100) [M + H].

4-(Adenin-7-yl)-4-(tetrazol-5-yl)butane-1,2-diol (**10**)

$NaN_3$ (0.13 g, 2.0 mmol) and $NH_4Cl$ (0.10 g, 2.0 mmol) were added to a solution of 4,5-dihydroxy-2-{$N^6$-[(*N*,*N*-dimethylamino)methylene]adenine-7-yl}pentanenitrile (**8**) (0.40 g, 1.3 mmol) in dimethylformamide (7 ml). The mixture was stirred at 125 °C for 2 h and then at room temperature overnight. Water (5 ml) was added to the mixture, the solvent was evaporated and the residue codistilled with water. Aqueous solution of the residue was applied onto a column of Dowex 50X8 ($H^+$ form), the column was washed with water and the product was eluted with 3% aqueous ammonia. The product-containing fraction was taken down to afford crude product as a foam, which was further purified by preparative HPLC. Yield: 0.16 g (42%) of hygroscopic compound **10** as a mixture of diastereomers 1 : 1, $E_{UP}$ = 0.45. $^1$H NMR: 8.46 s, 8.45 s, 8.235 s and 8.23 s, 4 × 1 H (H-2 and H-8); 7.90 brs and 7.72 brs, 2 × 2 H ($NH_2$); 6.28 dd, 1 H, *J*(1′,2′a) = 3.4, *J*(1′,2′b) = 10.5 (H-1′-A); 6.26 dd, 1 H, *J*(1′,2′a) = 6.1, *J*(1′,2′b) = 9.0 (H-1′-B); 5.30 br (OH); 2.79 ddd, 1 H, *J* = 3.4, 9.0 and 13.7 (H-2′a-A); 2.73 ddd, 1 H, *J* = 2.4, 11.5 and 14.4 (H-2′a-B); 2.17 m, 1 H (H-2′b-B); 2.14 ddd, 1 H, *J* = 6.1, 8.5 and 13.7 (H-2′b-A); 3.23 m, 2 H (H-3′); 3.30 m, 4 H (H-4′). FAB MS, *m/z* (rel.%): 292 (100) [M + H].

2-{$N^6$-[(*N*,*N*-Dimethylamino)methylene]adenin-7-yl}-4-(hydroxymethyl)buteno-4-lactone (**11**)

A 1 M solution of sodium methanolate in methanol (3.2 ml) was added to a solution of 4,5-dihydroxy-2-{$N^6$-[(*N*,*N*-dimethylamino)methylene]adenin-7-yl}pentanenitrile (**8**) (0.4 g, 1.32 mmol) in methanol (30 ml) and the mixture was stirred at room temperature for 4.5 h. Afterwards, pH of the reaction mixture was adjusted to 6–7 by addition of acetic acid and the solvent was evaporated. The residue was codistilled with water and subjected to preparative TLC ($H_2O$–ethanol–acetone–ethyl acetate 1 : 1 : 1 : 4). Yield: 0.15 g (37%), mixture of diastereomers. $^1$H NMR: A: 8.88 s, 1 H (NCH); 8.57 s, 1 H (H-8); 8.45 s, 1 H (H-2); 6.24 dd, 1 H, *J*(1′,2′a) = 12.0, *J*(1′,2′b) = 9.6 (H-1′); 5.41 t, 1 H, *J*(4′,OH) = 5.1 (OH); 4.81 ddd, 1 H, *J*(3′,4′) = 2.7, *J*(3′,2′a) = 9.4, *J*(3′,2′b) = 0.9 (H-3′); 3.76 ddd, 1 H, *J*(4′a,3′) = 2.6, *J*(4′a,OH) = 5.1, $J_{gem}$ = 12.2 (H-4′a); 3.62 ddd, 1 H, *J*(4′b,3′) = 2.8, *J*(4′b,OH) = 5.1, $J_{gem}$ = 12.2 (H-4′b); 3.21 s

and 3.11 s, 2 × 3 H ($NCH_3$); 2.99 dt, 1 H, *J*(2′a,3′) = 9.4, *J*(2′a,1′) = $J_{gem}$ = 12.0 (H-2′a); 2.70 ddd, 1 H, *J*(2′b,3′) = 0.9, *J*(2′b,1′) = 9.6, $J_{gem}$ = 12.0 (H-2′b). B: 8.88 s, 1 H (NCH); 8.44 s, 1 H (H-8); 8.45 s, 1 H (H-2); 6.30 dd, 1 H, *J*(1′,2′a) = 8.8, *J*(1′,2′b) = 12.2 (H-1′); 5.19 t, 1 H, *J*(4′,OH) = 5.6 (OH); 4.69 dddd, 1 H, *J*(3′,4′a) = 3.7, *J*(3′,4′b) = 5.7, *J*(3′,2′a) = 12.2, *J*(3′,2′b) = 10.4 (H-3′); 3.68 ddd, 1 H, *J*(4′a,3′) = 3.7, *J*(4′a,OH) = 5.6, $J_{gem}$ = 12.2 (H-4′a); 3.63 dt, 1 H, *J*(4′b,3′) = *J*(4′b,OH) = 5.6, $J_{gem}$ = 12.2 (H-4′b); 3.21 s and 3.13 s, 2 × 3 H ($NCH_3$); 2.78 ddd, 1 H, *J*(2′a,3′) = 12.2, *J*(2′a,1′) = 8.8, $J_{gem}$ = 11.8 (H-2′a); 2.37 ddd, 1 H, *J*(2′b,3′) = 10.4, *J*(2′b,1′) = 12.2, $J_{gem}$ = 11.8 (H-2′b). For $C_{13}H_{16}N_6O_3$ (304.3) calculated: 51.31% C, 5.30% H, 27.62% N; found: 51.55% C, 5.21% H, 27.28% N. FAB MS, *m/z* (rel.%): 305 (100) [M + H].

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