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Original Scientific Paper

Synthesis, NMR and MS Study of Novel *N*-Sulfonylated Purine Derivatives

Biserka Žinić,[a,*] *Irena Krizmanić,*[b] *Dražen Vikić-Topić,*[a] *Dunja Srzić,*[a] *and Mladen Žinić*[a]

[a]*Ruđer Bošković Institute, P. O. Box 180, HR-10002 Zagreb, Croatia*

[b]*HERBOS Chem. Industry, Obrtnička 17, 44000 Sisak, Croatia*

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Tosylation and mesylation of adenine (**1**) at room temperature give regioselectively N^9-sulfonylated purines **2** and **5**. Excess of TsCl or MsCl at higher reaction temperatures leads to formation of unstable N^6,N^9-disulfonylated products **3** and **6**, which easily transform into the corresponding N^6-monosulfonylated product **4**. Two *N*-sulfonylated purine nucleoside derivatives **12** and **15** have also been prepared. 1D/2D NMR determined the site of sulfonylation and the spatial arrangement of the substituents. MS spectra showed unexpected rearrangement of protonated molecular ions that occurs upon the loss of SO_2.

Key words: synthesis, N^9-sulfonyl, N^6-sulfonyl, N^6, N^9-disulfonyl purine derivatives, NMR study, MS study.

INTRODUCTION

Modified nucleosides and nucleic acid bases have been the subject of many studies due to their potential activity as enzyme inhibitors resulting in antitumor[1] and antiviral[2] activity. Sulfonamide group R_1SO_2-NHR_2 is a common pharmacophore in various biologically active molecules, enzyme inhibitors and receptor antagonists.[3] Recently, we have reported the synthesis of a series of pyrimidine nucleic base derivatives possessing sulfonamide

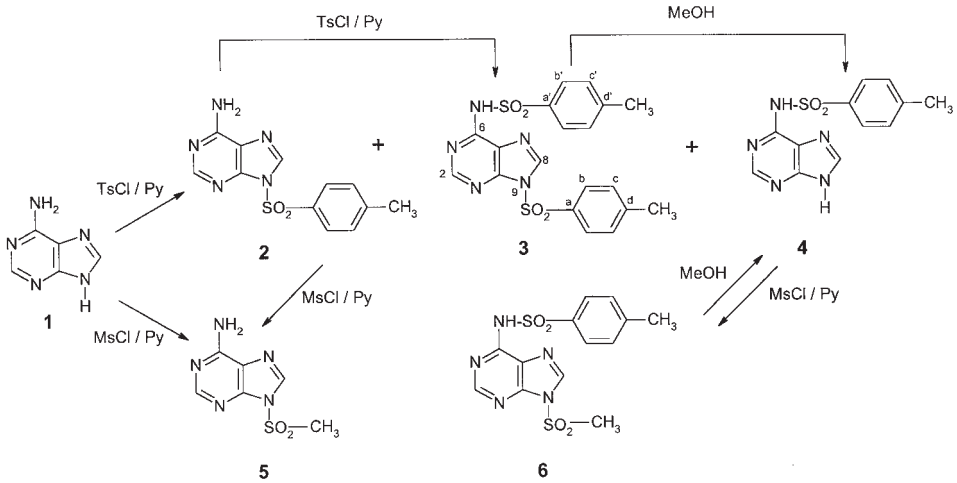
* Author to whom correspondence should be addressed.(E-mail: bzinic@rudjer.irb.hr)
Biserka Žinić was previously Biserka Kašnar.

pharmacophore, which showed promising *in vitro* antitumor activity.[4–6] These results directed our interest toward *N*-sulfonyl derivatives of purine nucleic bases as new candidates for compounds with antitumor activity. This type of compounds has received very limited attention in the literature. Martirosyan *et al.*[7] reported the preparation of N^9-tosyladenine in 81% yield and Zemlicka *et al*.[8] obtained the same compound (50% yield) in the reaction of adenallene with *p*-toluenesulfonyl chloride. It is known that the nucleoside adenosine exerts its physiological actions through activation of four distinct subtypes of cell surface receptors, recently classified as A_1, A_{2a}, A_{2b}, and A_3.[9] Structural modification at N^6 of adenosine leads to selective A_1 agonists[10,11] while modification at C-2 confers high potency and selectivity on A_{2a} receptors.[12] With respect to these observations, it also appeared of interest to investigate the approach to N^6- and C-2-aminosulfonyl derivatives of adenosine. In the present work, we report the synthesis and NMR and MS studies of novel N^9- and N^6-mono- and N^6, N^9-di-sulfonyladenine derivatives and the synthesis of two sulfonylated purine nucleoside derivatives.

RESULTS AND DISCUSSION

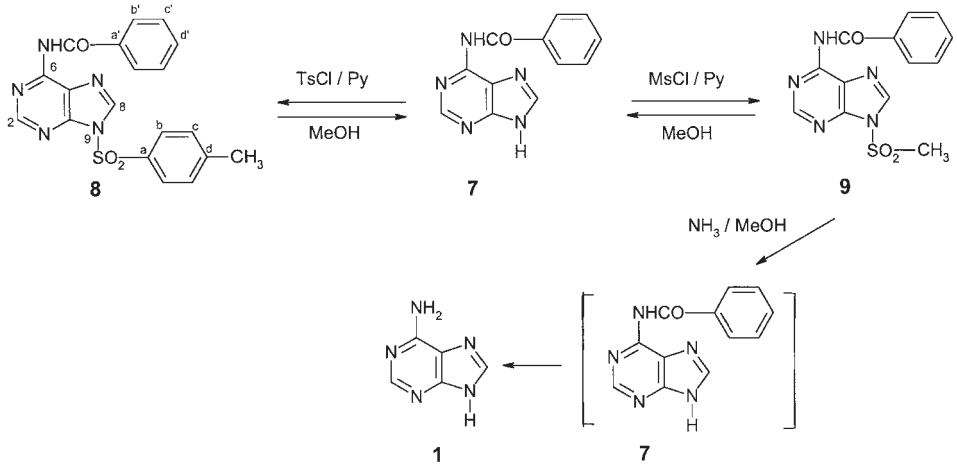
Synthesis

Following the Martirosyan procedure,[7] adenine (**1**) was reacted with 2 eq. of *p*-toluenesulfonyl chloride (TsCl) in pyridine (20 °C, 70 h). The N^9-(*p*-toluenesulfonyl)adenine (**2**) was isolated in 60% yield (Scheme 1). Reaction of adenine (**1**) with a large excess of TsCl (5 eq./ pyridine, 20 h) at 80 °C gave a mixture of unreacted **1** (26%), N^9-tosyladenine **2** (7%), N^6,N^9-bis(tosyl)adenine **3** (2–17%) and N^6-(tosyl)adenine **4** (3–12%). Formation of sulfonylated products in low yields despite a large excess of TsCl indicates their decomposition at elevated temperature. Prolonged reaction time (96 hours at 80 °C) gave only monosubstituted derivatives **2** (20% yield) and **4** (55% yield) as a consequence of the transformation of the initially formed bis-sulfonylated **3** into mono-sulfonylated **4**. The bis-sufonylated derivative **3** was also found to transform into **4** by alcoholysis (MeOH, EtOH) during the isolation procedure or by standing of alcohol solutions at room temperature. The attempted preparation of **3** in higher yield by reaction of **2** and TsCl gave a mixture of **3** (13% yield) and **4** (40% yield). Reaction of adenine (**1**) with 2–6 eq. of MsCl in pyridine, at room temperature, afforded only N^9-mesyladenine **5** in 90% yield; at higher reaction temperature, a considerable decomposition of **5** was observed. In the reaction of N^9-tosyladenine **2** with 6 eq. of MsCl, transsulfonylation was observed, giving **5** (33% yield) and adenine (**1**) (43% yield) instead of the expected N^6-mesyl-N^9-tosyl derivative or



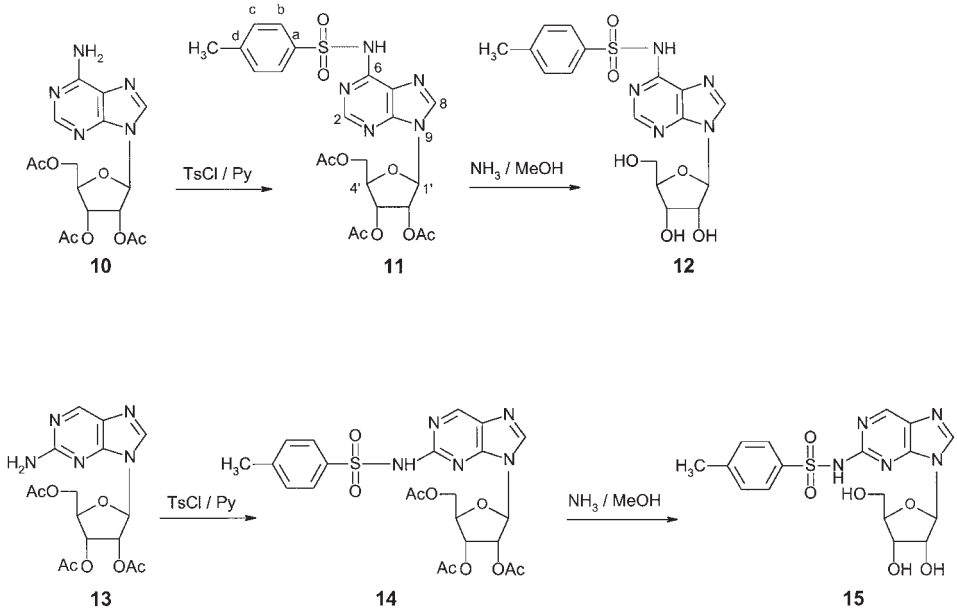
Scheme 1

N^6-mesyl derivative. However, the N^6-tosyl derivative **4** reacts with MsCl giving N^6-(*p*-toluenesulfonyl)-N^9-(methanesulfonyl)adenine (**6**); the ^{1}H NMR spectrum of the crude product corresponds to **6** countering the trace of pyridine. N^6,N^9-Disubstituted **6** also easily transforms into the N^6-tosyl derivative **4** by methanolysis at room temperature.



Scheme 2

The investigated tosylation and mesylation reactions of **1** reveal that at room temperature sulfonylation can be performed regioselectively at N-9 (**2**, 60% yield; **5**, 90% yield). However, excess of TsCl or MsCl at higher reaction temperatures leads to formation of unstable N^6,N^9-disulfonylated products **3** and **6** which easily transform into the corresponding N^6-monosulfonylated product **4**. Instability of the N^9-sulfonyl group is obvious from the observed transsulfonylation of **2** to **5** and fast alcoholysis of **3** and **6** at room temperature into the mono-sulfonylated product **4**. In contrast, N^6-sulfonylated products are more stable since no desulfonylation or removal by alcoholysis could be observed. It seems that the presence of the N^6-Ts increases the instability of N^9-sulfonyl group of **3** and **6** through strong electron withdrawing effects. In order to examine the influence of the N^6-acyl group on the yield of N^9-sulfonylation, N^6-benzoyladenine[13] (**7**) was prepared (Scheme 2). The reaction of **7** and TsCl gave N^6-benzoyl-N^9-(*p*-toluenesulfonyl)adenine (**8**) in 76% yield; with MsCl, N^6-benzoyl-N^9-(methanesulfonyl)adenine (**9**) was obtained in 94% yield. Thus, considerably higher yields of N^9-sulfonylated products could be obtained with the weaker electron withdrawing N^6-benzoyl group. However, both **8** and **9** are still very sensitive, giving starting compound **7** upon chromatographic purification on silica gel or



10 **11** **12**

13 **14** **15**

Scheme 3

upon recrystallization from alcohol. By ammonolysis (NH_3/MeOH) compound **9** transforms first into N^6-benzoyladenine (**7**) and then into debenzoylated **1**, as revealed by TLC monitoring of the reaction.

The synthetic route to *N*-sulfonylated nucleosides **12** and **15** is outlined in Scheme 3; the synthetic steps comprise protection of hydroxyl groups, sulfonylation of amino function and deprotection. Protected adenosine[14] **10** and 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-2-aminopurine (**13**) were treated with TsCl in pyridine to give 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-N^6-(*p*-toluenesulfonyl)adenosine (**11**) in 50% yield and 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-2-[*N*-(*p*-toluenesulfonyl)]aminopurine (**14**) in 47% yield. Deprotection of sulfonylated nucleosides **11** and **14** by methanolic ammonia afforded N^6-(*p*-toluenesulfonyl)adenosine (**12**) in 99% yield and 9-(ß-D-ribofuranosyl)-2-[*N*-(*p*-toluenesulfonyl)]aminopurine (**15**) in 98% yield.

NMR Spectra

In order to determine the positions of *N*-sulfonylation in **2**, **4** and **5**, we used the 1D and 2D NMR methods. Structures of the N^9-substituted compounds **2**, **5** and the N^6-substituted compound **4** were first deduced from their ^{1}H NMR spectra. The most striking difference refers to N-protons and purine skeleton hydrogen atoms, H-2 and H-8. In both spectra of N^9-sulfonylated **2** and **5**, two amino protons at C-6, readily exchangeable for deuterium by addition of D_2O, appear as singlets at 7.68 and 7.70 ppm, respectively. In **2** and **5**, H-2 is more shielded (8.23 and 8.29 ppm) than H-8 (8.62 and 8.41 ppm). The H-8 and H-2 assignments were confirmed by carbon-proton connectivity in the ^{1}H/^{13}C heteronuclear correlation spectra (HETCOR). Thus, signals at 138.43 and 154.64 ppm in the ^{13}C NMR spectra of N^9-tosyladenine **2** correspond to C-8 and C-2, respectively, with one-bond C-H coupling constants of 225 Hz ($^1J_{C\text{-}8,H}$) and 204 Hz ($^1J_{C\text{-}2,H}$), which is in agreement with literature data.[16] Additionally, in the NOESY spectrum of **2**, the assignment of H-8 was proved by its interaction with phenyl (Ph-b) protons (Figure 1).

Contrary to **2** and **5**, in the N^6-substituted compound **4**, the H-8 (8.30 ppm) and H-2 (8.37 ppm) signals changed positions and the H-2 signal decreased in intensity. In the ^{1}H NMR spectra of N^6-tosyladenine **4**, two broadened one-proton singlets at 13.60 and 12.80 ppm, both exchangeable with D_2O, were observed. No splitting between these N-protons was observed in 1D spectra, while COSY and NOESY spectra showed no cross-peaks. Therefore, the observed signals for *N*-protons are not due to the chemically non-equivalent geminal N-protons but to protons at two different N-atoms in **4**.

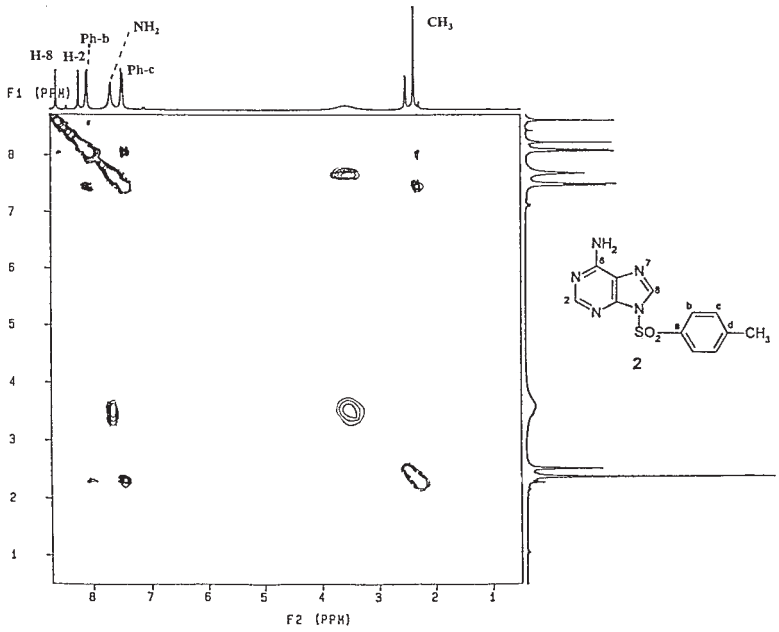


Figure 1. NOESY spectrum of N^9-(*p*-toluenesulfonyl)adenine (**2**).

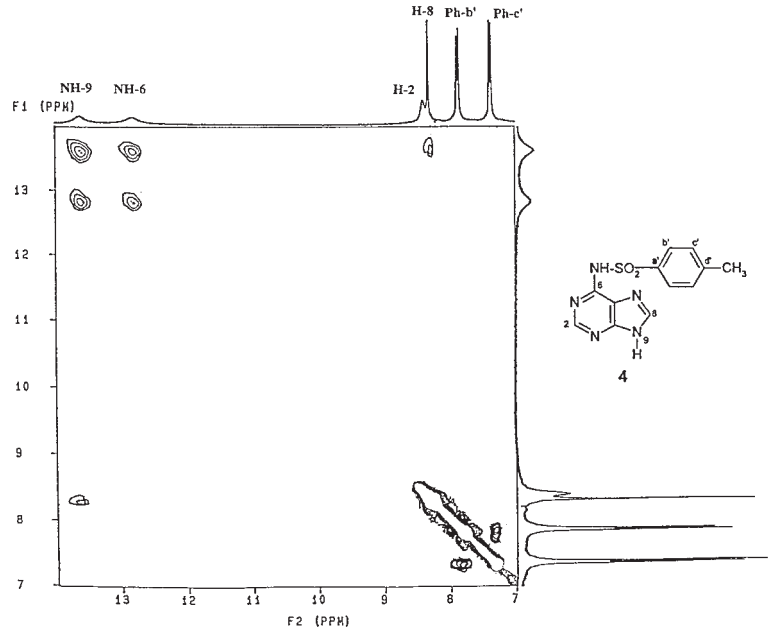


Figure 2. NOESY spectrum of N^6-(*p*-toluenesulfonyl)adenine (**4**).

The NH-6 and NH-9 signals were identified by interaction of NH-9 with H-8, which can be shown in part of the NOESY spectrum (Figure 2).

It has to be emphasized that the N^7-substituted product was disregarded, since in the hypothetical N^7-substituted molecule two broad signals for non-equivalent geminal NH_2 protons, displaying cross-peaks in COSY and NOESY spectra, should be observed.

Mass Spectra

The 70 eV EI mass spectra at 100 μs and 1 s time delay of N^9-monosulfonylated products **2** and **5**, N^6-monosulfonylated products **4** and **11**, and N^6,N^9-disulfonylated products **3**, **8** and **9** are shown in the Experimental section (Table II).

Analysis of the mass spectra shows the characteristic behavior of these compounds under electron impact: a) under the 1 s time delay conditions the formation of stable $[M+H]^+$ species is strongly preferred and fragment ions of low abundance are detected in their mass spectra, and b) these compounds show evidence of skeletal rearrangement of molecular ions by the appearance of $[M\text{-}SO_2]^+$ and $[M\text{-}SO_2H]^+$ ions. Their compositions are checked by high resolution measurements for compounds **2** and **4** (Table I).

TABLE I

High-resolution mass measurement data for $[M\text{-}SO_2]^+$ of compounds **2** and **4**

compound	*m*/*z*	measured value	calculated value	elemental composition
2	225	225.093369	225.100896	$C_{12}H_{11}N_5$
4	225	225.089105	225.100896	$C_{12}H_{11}N_5$

CONCLUSIONS

N^9-Tosyl purine **2** and N^9-mesyl purine **5** have been prepared regioselectively by tosylation and mesylation reactions of **1** at room temperature (**2**, 60% yield; **5**, 90% yield). Excess of TsCl or MsCl at higher reaction temperatures leads to formation of unstable N^6,N^9-disulfonylated products **3** and **6**, which easily transform into the corresponding N^6-monosulfonylated product **4**. 1D/2D NMR determined the site of sulfonylation and the

spatial arrangement of the substituents. Two *N*-sulfonylated purine nucleoside derivatives, N^6-(*p*-toluenesulfonyl)adenosine (**12**) and 9-(ß-D-ribofuranosyl)-2-[*N*-(*p*-toluenesulfonyl)]aminopurine (**15**) have also been prepared in satisfactory yields. MS spectra showed unexpected rearrangement of protonated molecular ions that occurs upon the loss of SO_2.

EXPERIMENTAL

General

Solvents were distilled from appropriate drying agents shortly before use. TLC was carried out on Merck precoated glass plates or DC-plastikfolien Kieselgel 60 F_{254} and preparative thick layer (2 mm) chromatography on Merck 60 F_{254}. Flash column chromatography was performed on silica gel Merck 0.040–0.063 mm. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. UV Spectra [λ_{max}/nm, log ε/dm^3 mol^{-1} cm^{-1}] were taken on a Philips PU8700 UV/VIS spectrophotometer. IR Spectra were obtained for KBr pellets on a Perkin-Elmer 297 spectrophotometer.

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 75.46 MHz for the ^{13}C nucleus. The samples were dissolved in DMSO-d_6 or $CDCl_3$ and measured at 20 °C in 5 mm NMR tubes. Sample concentrations were 0.1 M for ^{1}H and 0.2 M for ^{13}C measurements. Chemical shifts (δ/ppm) are referred to TMS. Digital resolution was 0.3 Hz per point in ^{1}H and 0.5 Hz per point in ^{13}C NMR one-dimensional spectra. The applied techniques were standard ^{1}H and ^{13}C with broadband proton decoupling, ^{13}C gated decoupling, COSY, NOESY and HETCOR. For proton decoupling, the Waltz-16 modulation was used. The COSY spectra were recorded in the magnitude mode with 1024 points in F2 dimension and 256 increments in F1 dimension, zero-filled to 1024 points. Increments were measured with 16 scans, 4500 Hz spectral width and a relaxation delay of 0.8 s. The corresponding digital resolution was 8.9 Hz per point and 17.6 Hz per point in F2 and F1 dimensions, respectively. The NOESY spectra were recorded in a phase-sensitive mode and at mixing times of 0.45–0.80 s. All other measurement parameters were as for the COSY spectra. The HETCOR spectra were recorded with 2048 points in F2 dimension and 256 increments in F1 dimension zero-filled to 512 points. Each increment was recorded by 96 scans with a relaxation delay of 1.0 s. Spectral widths were 19000 Hz in F2 and 4500 Hz in F1 dimensions, and the corresponding digital resolutions were 18.6 Hz per point and 17.6 Hz per point, respectively.

All mass spectrometric investigations were performed using a Fourier transform mass spectrometer ThermoQuest FT/MS 2001 DD (Madison, WI, USA) equipped with a 3 T superconducting magnet. Following the electron impact (EI) ion formation at 70 eV, a time delay of 100 μs or 1 s was employed for relaxation of the initial cyclotron and axial motions by collision with background neutrals. The samples were introduced by direct insertion.

*Reactions of adenine (**1**) with* p-*toluenesulfonyl chloride (TsCl)*

1) Adenine (**1**) (135 mg, 1.00 mmol) was suspended in anhydrous pyridine (5 mL) and TsCl (380 mg, 2.00 mmol) was added. After stirring at room temperature for 70

hours, the solvent was evaporated under reduced pressure. Ethanol was added to the residual yellow solid and the resulting white solid was filtered off. Recrystallization from ethanol yielded N^9-(*p*-toluenesulfonyl)adenine (**2**)[7] 170 mg (60%); m.p. = 206–207 °C (lit. m.p. = 206–207 °C); R_f = 0.57 (CH_2Cl_2/MeOH 9:1).

Additional data for N^9-(p-*toluenesulfonyl)adenine (**2**):* UV (MeOH) λ_{max}/nm: 254.9 (shoulder), 237.1 and 205.5; log ε/ dm^3 mol^{-1} cm^{-1}: 4.14, 4.25 and 4.38; IR (KBr) ν_{max}/cm^{-1}: 3310 (m), 3160 (m), 3040 (w), 2920 (w), 1680 (s), 1670 (m), 1600 (s), 1570 (m), 1480 (m), 1385 (m), 1290 (m, doublet), 1190 (s), 1180 (s), 1160–1150 (s, doublet); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.62 (s, 1H, H-8), 8.23 (s, 1H, H-2), 8.09 (d, 2H, J = 8.1 Hz, Ph-b), 7.68 (s, 2H, NH_2), 7.49 (d, 2H, J = 8.1 Hz, Ph-c), 2.37 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 156.59 (s, C-6), 154.64 (d, C-2), 148.65 (s, Ph-a), 146.94 (s, C-4), 138.43 (d, C-8), 133.83 (s, Ph-d), 130.55 (d, Ph-c), 128.31 (d, Ph-b), 119.02 (s, C-5), 21.22 (q, CH_3).

2) Adenine (**1**) (135 mg, 1.00 mmol) was suspended in anhydrous pyridine (8 mL) and TsCl (950 mg, 5.00 mmol) was added. After stirring at 80 °C for 20 hours, the resulting yellow solution was evaporated under reduced pressure. The residue was treated with methanol and the resulting solid was filtered off, yielding 75 mg (17%) of N^6, N^9-bis(*p*-toluenesulfonyl)adenine (**3**). The filtrate was evaporated and purified by preparative chromatography (CH_2Cl_2/MeOH 20:1) yielding N^9-(*p*-toluenesulfonyl)adenine (**2**) 20 mg (7%), adenine (**1**) 35 mg (26%) and N^6-(*p*-toluenesulfonyl)adenine (**4**) 9 mg (3%).

N^6,N^9-*Bis(*p-*toluenesulfonyl)adenine* (**3**): m.p. = 245 °C; R_f = 0.73 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 269.6 (shoulder), 233.5 and 203.2; log ε/ dm^3 mol^{-1} cm^{-1}: 3.99, 4.06 and 4.30; IR (KBr) ν_{max}/cm^{-1}: 3460–3400 (br, w), 3120 (w), 3080 (w), 2960–2920 (w), 2820 (w), 1640 (s, doublet), 1590 (s, doublet), 1490 (w), 1435 (m), 1390 (s), 1315 (s), 1295 (m), 1195 (s), 1180 (s), 1170 (s), 1155 (s). ^{1}H NMR (DMSO-d_6) δ/ppm: 12.70 (brs, 1H, NH), 8.77 (s, 1H, H-8), 8.40 (s, 1H, H-2), 8.03 (d, 2H, J = 8.0 Hz, Ph-b), 7.82 (d, 2H, J = 8.0 Hz, Ph-b'), 7.45 (d, 2H, J = 8.3 Hz, Ph-c), 7.30 (d, 2H, J = 7.7 Hz, Ph-c'), 2.33 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ / ppm: 156.00 (s, C-6), 152.55 (d, C-2), 151.52 (s, C-4 or Ph-a), 148.51 (s, Ph-a or C-4), 147.09 (d, C-8 or Ph-d or Ph-d'), 141.86 (s, Ph-a'), 139.29 (s, Ph-d or Ph-d' or C-8), 133.65 (s, Ph-d or Ph-d' or C-8), 130.62 (d, Ph-c), 129.08 (d, Ph-c'), 128.31 (d, Ph-b), 127.18 (d, Ph-b'), 123.26 (s, C-5), 21.25 (q, CH_3), 20.99 (q, CH_3).

3) Adenine (**1**) (135 mg, 1.00 mmol) was suspended in anhydrous pyridine (8 mL) and TsCl (950 mg, 5.00 mmol) was added. After stirring at 80 °C for 96 hours, the resulting dark yellow solution was evaporated under reduced pressure. The residue was purified by preparative chromatography on a funnel (CH_2Cl_2/MeOH 25:1) yielding N^9-(*p*-toluenesulfonyl)adenine (**2**) 58 mg (20%) and N^6-(*p*-toluenesulfonyl)adenine (**4**) 160 mg, (55%).

N^6-(p-*toluenesulfonyl)adenine (**4**):* m.p. = 305 °C; R_f = 0.31 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 291.1 and 208.0 (shoulder); log ε/ dm^3 mol^{-1} cm^{-1}: 4.60 and 4.61; IR (KBr) ν_{max}/cm^{-1}: 3500–3400 (br, w), 3140 (w), 3060–2940 (br, w), 2820 (w), 1630 (s), 1620 (m), 1595 (s), 1500 (m), 1450 (m), 1365 (s), 1350 (s), 1280 (m), 1170 (s); ^{1}H NMR (DMSO-d_6) δ/ppm: 13.60 (brs, 1H, NH-9), 12.80 (brs, 1H, NH-6), 8.37 (brs, 1H, H-2), 8.30 (s, 1H, H-8), 7.85 (d, 2H, J = 8.1 Hz, Ph-b'), 7.36 (d, 2H, J = 8.1 Hz, Ph-c'), 2.36 (s, 3H, CH_3); ^{13}C NMR (300 MHz), (DMSO-d_6) δ / ppm: 145.80 (very broad signal, C-2), 144.50 (very broad signal C-8), 142.72 (s, Ph-a'), 140.34 (s, Ph-d'), 129.69 (d, Ph-c'), 126.36 (d, Ph-b'), 21.02 (q, CH_3). Signals for C-6, C-4, and C-5 are missing.

^{13}C NMR (600 MHz), (DMSO-d_6) δ/ppm: 156.70 (very broad signal, C-6), 145.90 (very broad signal, C-2), 144.34 (very broad signals C-8+C-4), 142.30 (s, Ph-a'), 140.04 (s, Ph-d'), 129.29 (d, Ph-c'), 126.01 (d, Ph-b'), 113.93 (very broad signal, C-5), 20.80 (q, CH_3).

Anal. calcd. for $C_{12}H_{11}N_5O_2S_1$ (M_r = 289.32): C 49.82, H 3.83, N 24.21%; found: C 49.79, H 3.34, N 24.41%.

Reaction of N^9*-(*p*-toluenesulfonyl)adenine (**2**) with* p*-toluenesulfonyl chloride (TsCl)*

N^9-Tosyladenine **2** (140 mg, 0.48 mmol) was dissolved in anhydrous pyridine (5 mL) and TsCl (185 mg, 0.97 mmol) was added. The solution was stirred at 20 °C for three days and treated with another amount of TsCl (185 mg, 0.97 mmol). The reaction mixture was stirred at 80 °C for three more days. The reaction mixture contained derivatives **3**, **4** and decomposition products, as seen from the TLC plate (CH_2Cl_2/MeOH 15:1). From this mixture, N^6,N^9-bis(*p*-toluenesulfonyl)adenine (**3**) 28 mg (13%) and N^6-(*p*-toluenesulfonyl)adenine (**4**) 56 mg (40%) were isolated by preparative chromatography (CH_2Cl_2/MeOH 15:1).

Reaction of N^9*-(*p*-toluenesulfonyl)adenine (**2**) with methanesulfonyl chloride (MsCl)*

N^9-Tosyladenine **2** (200 mg, 0.69 mmol) was dissolved in anhydrous pyridine (7 mL) and MsCl (0.11 mL, 1.38 mmol) was added. The solution was stirred at 80 °C for three hours and during that time another two portions of MsCl (2 × 0.11 mL) were added. The dark brown solution was evaporated to dryness and the residue was purified by preparative chromatography (CH_2Cl_2/MeOH 9:1), yielding N^9-(methanesulfonyl)adenine (**5**) 48 mg (33%), and adenine (**1**) 40 mg (43%).

N^9*-(methanesulfonyl)adenine (**5**)*

Adenine (**1**) (200 mg, 1.54 mmol) was suspended in anhydrous pyridine (8 mL) and MsCl (0.24 mL, 3.08 mmol) was added into the reaction mixture at 0 °C. After stirring at room temperature for 48 hours, the solvent was evaporated. The residue was treated with ethanol and the resulting white solid was filtered off. Recrystallization from ethanol yielded N^9-(methanesulfonyl)adenine (**5**) 296 mg (90%) as white crystals: m.p. = 228–230 °C; R_f = 0.37 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 256.1 (shoulder) and 207.6; log ε/ dm^3 mol^{-1} cm^{-1}: 3.80 and 3.88; IR (KBr) ν_{max}/cm^{-1}: 3300 (m), 3140 (m), 3040 (w), 3000 (w), 2920 (w), 1670 (s), 1610 (m), 1570 (m), 1470 (m), 1350 (s), 1330 (m), 1275 (m), 1185 (s), 1160 (s), 1145 (s); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.41 (s, 1H, H-8), 8.29 (s, 1H, H-2), 7.70 (s, 2H, NH_2), 3.78 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ/ppm: 156.58 (s, C-6), 154.45 (d, C-2), 148.76 (s, C-4), 137.89 (d, C-8), 119.02 (s, C-5), 41.99 (q, CH_3).

Anal. calcd. for $C_6H_7N_5O_2S_1$ (M_r = 213.22): C 33.80, H 3.31, N 32.85%; found: C 33.93, H 3.52, N 32.80%.

N^6-(p-*toluenesulfonyl)*-N^9-*(methanesulfonyl)adenine* (***6***)

A mixture of *N*^{6}-(*p*-toluenesulfonyl)adenine (**4**) (100 mg, 0.35 mmol) and MsCl (0.054 mL, 0.69 mmol) in anhydrous pyridine (4 mL) was stirred at room temperature for 24 hours. The solvent was evaporated and the mixture was treated with dichloromethane and hexane. The resulting solid was filtered off, yielding the starting material **4** (60 mg). Another crystallization of the mother liquor (adding hexane) yielded product **6** (*ca*. 40 mg, 32%) mixed with pyridine which stabilized the product: R_f = 0.50 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.88 (d, 2H, J = 6.0 Hz, Py's H-2 and H-6), 8.52 (m, 1H, Py's H-4), 8.34 (s, 1H, H-8), 8.26 (s, 1H, H-2), 8.01 (t, 2H, J = 6.5 Hz, Py's H-3 and H-5), 7.82 (d, 2H, J = 7.3 Hz, Ph-b), 7.33 (d, 2H, J = 7.9 Hz, Ph-c), 3.60 (brs, NH+H_2O), 2.32 (s, 3H, CH_3), 2.30 (s, 3H, CH_3).

N^6-*benzoyladenine*[13] (***7***)

Additional data: ^{1}H NMR (DMSO-d_6) δ/ppm: 12.46 (brs, 1H, NH-9), 11.53 (brs, 1H, NH-6), 8.76 (brs, 1H, H-2), 8.54 (s, 1H, H-8), 8.13 (d, 2H, J = 8.1 Hz, Ph-b'), 7.67 (m, 1H, Ph-d'), 7.57 (m, 2H, Ph-c'). The NH-6 signal was identified by interaction with the Ph-b' protons in the NOESY spectrum, and the NH-9 signal was identified by interaction with the Ph-c' proton in the LR-COSY spectrum. ^{13}C NMR (DMSO-d_6) δ/ppm: 166.91 (s, C=O), 162.0 (broad signal, C-6), 151.50 (d, C-2), 146.29 (brs, C-8), 145.50 (broad signal, C-4), 133.13 (s, Ph-a'), 132.99 (d, Ph-d'), 128.88 (d, Ph-b' or Ph-c'), 128.78 (d, Ph-b' or Ph-c'), 115.00 (broad signal, C-5).

N^6-*Benzoyl*-N^9-*(*p-*toluenesulfonyl)adenine* (***8***)

A mixture of *N*^{6}-benzoyladenine[13] (**7**) (200 mg, 0.84 mmol) and TsCl (192 mg, 1.00 mmol) in anhydrous pyridine (5 mL) was stirred at –5 °C to +5 °C. Another amount of TsCl (127 mg, 0.67 mmol) was added after 20 min and the solution was stirred at 5 °C for 45 minutes. The residue was treated with dichloromethane (5 mL) and extracted with water. The organic layer was dried over Na_2SO_4, evaporated to one half of the volume without heating, and treated with hexane. The resulting white solid was filtered off, yielding *N*^{6}-benzoyl-*N*^{9}-(*p*-toluenesulfonyl)adenine (**8**) 250 mg (76%): m.p. = 160 °C; R_f = 0.78 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 277.4, 235.2, 206.3 and 204.9; log ε/ dm^3 mol^{-1} cm^{-1}: 4.41, 4.48, 4.60 and 4.61; IR (KBr) ν_{max}/cm^{-1}: 3185 (w), 3140 (w), 3090 (w), 3040 (w), 2910 (w), 1990–1850 (br, vw), 1690 (w-m), 1594 (m), 1568 (m), 1490 (s), 1380–1365 (m, doublet), 1235 (br, m), 1190 (m), 1175 (s), 1140 (s). ^{1}H NMR ($CDCl_3$) δ/ppm: 9.00 (brs, 1H, NH-6), 8.87 (s, 1H, H-2), 8.48 (s, 1H, H-8), 8.18 (d, 2H, J = 7.9 Hz, Ph-b), 8.00 (d, 2H, J = 7.7 Hz, Ph-c), 7.62 (m, 1H, Ph-d'), 7.52 (m, 2H, Ph-c'), 7.40 (d, 2H, J = 7.9 Hz, Ph-b'), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ/ppm: 164.60 (s, C=O), 153.88 (d, C-2), 150.55 (s, C-6), 149.99 (s, C-4), 147.03 (s, Ph-a), 140.15 (s, Ph-d), 133.22 (s, Ph-a'), 132.86 (d, C-8), 130.09 (d, Ph-c), 128.68 (d, Ph-c'), 128.49 (d, Ph-b'), 127.76 (d, Ph-b), 125.74 (d, Ph-d'), 123.38 (s, C-5), 21.64 (q, CH_3).

N^6-*Benzoyl*-N^9-*(methanesulfonyl)adenine* (***9***)

A mixture of *N*^{6}-benzoyladenine[13] (**7**) (200 mg, 0.84 mmol) and MsCl (0.13 mL, 1.68 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature. Another amount of MsCl (0.13 mL) was added after one hour. The suspension was stirred at

room temperature for 2.5 hours and the solvent was evaporated. The resulting solid was treated with ethanol, filtered off, to give 250 mg (94%) of N^6-benzoyl-N^9-(methanesulfonyl)adenine (**9**) (Any recrystallization leads to decomposition of product **9** to the starting material **7**): m.p. = 171 °C; $R_{f=}$ 0.58 (CH_2Cl_2/MeOH 9:1). UV (MeOH) λ_{max}/nm: 277.9, 228.9, 205.5, 196.4 and 192.8; log ε/ dm^3 mol^{-1} cm^{-1}: 4.17, 3.95, 4.23, 3.86 and 3.85; IR (KBr) ν_{max}/cm^{-1}: 3305 (m), 3280 (m), 3090 (m), 3010 (m), 2920 (w), 1955 (vw), 1805 (vw), 1690 (s), 1600 (s), 1580 (s), 1500–1480 (s, doublet), 1370 (s), 1340 (m), 1270 (s), 1250 (s), 1185 (s), 1160 (s); ^{1}H NMR (DMSO-d_6) δ/ppm: 11.50 (brs, 1H, NH-6), 8.94 (s, 1H, H-2), 8.74 (s, 1H, H-8), 8.07 (d, 2H, J = 7.4 Hz, Ph-b'), 7.68 (m, 1H, Ph-d'), 7.58 (m, 2H, Ph-c'), 3.89 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 170.20 (s, C=O), 166.76 (s, C-6), 156.10 (s, C-4), 151.87 (d, C-2), 144.70 (s, Ph-a'), 133.50 (d, Ph-d'), 133.22 (d, C-8), 128.73 (d, Ph-c'), 128.71 (d, Ph-b'), 114.29 (s, C-5), 40.10 (q, CH_3).

*9-(2,3,5-Tri-*O*-acetyl-ß-D-ribofuranosyl)-*N^6*-(*p*-toluenesulfonyl)adenosine (**11**)*

A mixture of 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)adenosine[14] (**10**) (100 mg, 0.25 mmol) and TsCl (171 mg, 0.88 mmol) in anhydrous pyridine (11 mL) was stirred at 80 °C for 4 days. During this time, three portions of TsCl (3 × 171 mg) were added (total amount of TsCl was 684 mg, 3.50 mmol). The dark yellow solution was evaporated and the residue was purified by preparative chromatography on a funnel (CH_2Cl_2/MeOH 30:1), yielding 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-N^6-(*p*-toluenesulfonyl)adenosine (**11**) 68 mg (50%): m.p. = 113 °C; R_f = 0.60 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 274.4 (shoulder), 202.3 (shoulder) and 192.1; log ε/ dm^3 mol^{-1} cm^{-1}: 3.63, 3.51 and 3.37; IR (KBr) ν_{max}/cm^{-1}: 3500–3400 (br, w), 3230 (w), 3120 (w), 2960–2940 (br, w), 1750 (s), 1630 (s), 1580–1560 (br, s), 1440 (m), 1370 (s), 1250–1200 (br, s), 1140 (s), 1080 (s), 1040 (br, s), 920 (m); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.49 (s, 1H, H-2), 8.33 (s, 1H, H-8), 7.86 (d, 2H, J = 8.1 Hz, Ph-b), 7.34 (d, 2H, J = 8.1 Hz, Ph-c), 6.22 (d, 1H, J = 5.3 Hz H-1',), 5.94 (t, 1H, J = 5.6 Hz, H-2'), 5.57 (t, 1H, J = 5.2 Hz, H-3'), 4.39 (m, 2H, H-4'+H-5'$_a$), 4.25 (m, 1H, H-5'$_b$), 3.35 (brs, NH-6+H_2O), 2.35 (s, 3H, CH_3-Ts), 2.11 (s, 3H, CH_3-Ac), 2.02 (s, 3H, CH_3-Ac), 2.01(s, 3H, CH_3-Ac); ^{13}C NMR (DMSO-d_6) δ/ppm: 170.39 (s, C=O), 169.79 (s, C=O), 169.60 (s, C=O), 150.60 (s, C-6), 149.50 (d, C-2), 149.00 (s, C-4), 142.37 (s, Ph-a), 140.96 (d, C-8), 140.42 (s, Ph-d), 129.36 (d, Ph-c), 126.92 (d, Ph-b), 123.33 (s, C-5), 85.84 (d, C-1'), 79.78 (d, C-4'), 72.25 (d, C-2'), 70.17 (d, C-3'), 62.94 (t, C-5'), 21.02 (q, CH_3-Ts), 20.55 (q, CH_3-Ac), 20.44 (q, CH_3-Ac), 20.25 (q, CH_3-Ac).

Anal. calcd. for $C_{23}H_{25}N_5O_9S_1$ (M_r = 547.53): C 50.45, H 4.60, N 12.79%; found: C 50.52, H 4.69, N 12.58%.

*N^6-(p-Toluenesulfonyl)adenosine (**12**)*

Nucleoside **11** (90 mg, 0.16 mmol) was dissolved in methanolic ammonia (10 mL) and stirred at room temperature overnight. The solvent was evaporated and the residue recrystallized from methanol to give 82 mg (99%) of product **12** as white crystals: m.p. = 104–106 °C; R_f = 0.59 (CH_2Cl_2/MeOH 3:1); UV (MeOH) λ_{max}/nm: 286.6 (shoulder), 222.5 and 192.0; log ε/ dm^3 mol^{-1} cm^{-1}: 3.23, 3.43 and 3.31; IR (KBr) ν_{max}/cm^{-1}: 3600–3200 (br, s), 2960 (s), 1630 (s), 1590 (s), 1560 (s), 1450 (m), 1400 (m), 1360 (m), 1260 (s), 1150–1010 (br, s), 800 (s); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.29 (s, 1H, H-2), 8.09 (s, 1H, H-8), 7.78 (d, 2H, J = 8.1 Hz, Ph-b), 7.24 (d, 2H, J = 8.1 Hz, Ph-c),

6.71 (brs, 1H, NH-6), 5.83 (d, 1H, J = 5.9 Hz, H-1'), 5.45 (brs, 2H, OH-5'+OH-2'), 5.19 (brs, 1H, OH-3'), 4.52 (t, 1H, J = 5.5 Hz, H-2'), 4.12 (dd, 1H, J_1 = 3.3 Hz, J_2 = 4.8 Hz, H-3'), 3.96 (d, 1H, J = 3.1 Hz, H-4'), 3.60 (m, 2H, H-5'), 2.29 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm: 149.91 (C-6+C-2), 149.06 (s, C-4), 142.20 (s, Ph-a), 140.77 (d, C-8), 140.20 (s, Ph-d), 128.78 (d, Ph-c), 126.98 (d, Ph-b), 124.07 (s, C-5), 88.10 (d, C-1'), 85.98 (d, C-4'), 73.75 (d, C-2'), 70.71 (d, C-3'), 61.70 (t, C-5'), 20.96 (q, CH_3).

Anal. calcd. for $C_{17}H_{19}N_5O_6S_1$ (M_r = 421.42): C 48.45, H 4.54, N 16.62%; found: C 48.54, H 4.67, N 16.48%.

*9-(2,3,5-Tri-*O*-acetyl-ß-D-ribofuranosyl)-2-[*N*-(p-toluenesulfonyl)] aminopurine (**14**)*

A mixture of 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-2-aminopurine[15] (**13**) (100 mg, 0.25 mmol) and TsCl (171 mg, 0.88 mmol) in anhydrous pyridine (11 mL) was stirred at 80 °C for 23 hours. During that time, one more portion of TsCl (171 mg) was added (total amount of TsCl was 342 mg, 1.75 mmol). The brown solution was evaporated and the residue was purified by preparative chromatography (CH_2Cl_2/MeOH 9:1) to give 65 mg (47%) of 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2-*p*-toluenesulfonylaminopurine (**14**) as a white solid: m.p. = 104 °C, R_f = 0.54 (CH_2Cl_2/MeOH 9:1); UV (MeOH) λ_{max}/nm: 286.9 (shoulder), 250.2, 235.0 and 216.9; log ε/ dm^3 mol^{-1} cm^{-1}: 3.60, 3.63, 3.83 and 4.09; IR (KBr) ν_{max}/cm^{-1}: 3460–3320 (br, m), 3040 (m), 2910–2840 (br, m), 1740 (s), 1600 (br, m), 1500 (w), 1400 (s), 1350 (m), 1240 (br, s), 1160 (s), 1075 (m), 1040 (br, m); ^{1}H NMR ($CDCl_3$) δ/ppm: 11.80 (brs, 1H, NH-2), 8.85 (s, 1H, H-6), 8.54 (s, 1H, H-8), 7.87 (d, 2H, J = 8.0 Hz, Ph-b), 7.33 (d, 2H, J = 8.0 Hz, Ph-c), 6.13 (d, 1H, J = 5.7 Hz, H-1'), 5.81 (t, 1H, J = 5.8 Hz, H-2'), 5.54 (t, 1H, J = 5.2 Hz, H-3'), 4.37 (m, 2H, H-4'+H-5'$_a$), 4.23 (m, 1H, H-5'$_b$), 2.31 (s, 3H, CH_3-Ts), 2,14 (s, 3H, CH_3-Ac), 1.99 (s, 6H, 2CH_3-Ac); ^{13}C NMR (DMSO-d_6) δ/ppm: 170.23 (s, C=O), 169.55 (s, C=O), 169.36 (s, C=O), 153.17 (s, C-2), 151.94 (s, C-4), 149.44 (d, C-6), 144.11 (d, C-8), 143.21 (s, Ph-a), 137.96 (s, Ph-d), 130.11 (s, C-5), 129.36 (d, Ph-c), 127.69 (d, Ph-b), 85.26 (d, C-1'), 79.87 (d, C-4'), 72.07 (d, C-2'), 70.34 (d, C-3'), 63.31 (t, C-5'), 21.15 (q, CH_3-Ts), 20.65 (q, CH_3-Ac), 20.57 (q, CH_3-Ac), 20.28 (q, CH_3-Ac).

Anal. calcd. for $C_{23}H_{25}N_5O_9S_1$ (M_r = 547.53): C 50.45, H 4.60, N 12.79%; found: C 50.57, H 4.72, N 12.68%.

*9-(ß-D-Ribofuranosyl)-2-[*N*-(p-toluenesulfonyl)]aminopurine (**15**)*

Nucleoside **14** (70 mg, 0.13 mmol) was dissolved in methanolic ammonia (10 mL) and stirred at room temperature for three days. The solvent was evaporated and the residue was purified by preparative chromatography (CH_2Cl_2/MeOH 3:1), yielding 9-(ß-D-ribofuranosyl)-2-[*N*-(*p*-toluenesulfonyl)]aminopurine (**15**) 52 mg (98%): m.p. = 92-94 °C, R_f = 0.52 (CH_2Cl_2/MeOH 3:1); UV (MeOH) λ_{max}/nm: 313.4, 257.6, 225.8 and 201.7; log ε/ dm^3 mol^{-1} cm^{-1}: 3.65, 3.91, 4.29 and 4.20; IR (KBr) ν_{max}/cm^{-1}: 3500–3200 (br, s), 2940–2820 (br, m), 1650 (br, m), 1600–1570 (br, m), 1500 (m), 1390–1320 (br, m), 1245 (s), 1180–1000 (br, s), 780 (s); ^{1}H NMR (DMSO-d_6) δ/ppm: 8.78 (s, 1H, H-6), 8.54 (s, 1H, H-8), 7.89 (d, 2H, J = 7.9 Hz, Ph-b), 7.32 (d, 2H, J = 7.7 Hz, Ph-c), 6.70 (brs, 1H, NH-2), 5.87 (d, 1H, J = 5.3 Hz H-1'), 5.60–5.31 (br, 2H, OH-5'+OH-2'), 5.30–5.18 (br, 1H, OH-3'), 4.49 (t, 1H, J = 4.9 H-2', Hz), 4.15 (brs, 1H, H-3'), 3.95 (d, 1H, J = 3.3 Hz, H-4'), 3.59 (m, H-5'+H_2O), 2.30 (s, 3H, CH_3-Ts); ^{13}C NMR (DMSO-d_6) δ/ppm: 153.95 (s, C-2), 152.32 (s, C-4), 148.97 (d, C-6), 144.00 (d,

C-8). 142.70 (s, Ph-a), 138.50 (s, Ph-d), 129.66 (s, C-5), 129.20 (d, Ph-c), 127.96 (d, Ph-b), 87.01 (d, C-1'), 85.60 (d, C-4'), 73.67 (d, C-2'), 70.41 (d, C-3'), 61.39 (t, C-5'), 21.18 (q, CH_3-Ts).

Anal. calcd. for $C_{17}H_{19}N_5O_6S_1$ (M_r = 421.42): C 48.45, H 4.54, N 16.62%; found: C 48.63, H 4.69, N 16.38%. MS (EI) exact mass calcd for $C_{17}H_{19}N_5O_6S_1+H^+$ *m/e* 422.112883, found 422.119945.

Mass spectra:

TABLE II

The 70 eV EI mass spectra of **2-5**, **8**, **9**, and **11** at 100 μs and 1 s time delay

compound	time delay 100 μs			time delay 1 s		
	M^+ (%)	$[M+H]^+$ (%)	fragment ions (%)	M^+ (%)	$[M+H]^+$ (%)	fragment ions (%)
2	289 (22)	290 (0)	272 (3) 262 (2) $[M-HCN]^+$ 225 (100) $[M-SO_2]^+$ 224 (17) $[M-SO_2H]^+$ 209 (4) 198 (9) 183 (24) 170 (3) 155 (6)	289 (3)	290 (100)	226 (32) $[M+H-SO_2]^+$ other ions of low intensity
3	443 (0)	444 (0)	378 (72) $[M-SO_2H]^+$ 262 (5) 224 (100) $[M-SO_2PhMe-SO_2]^+$ 155 (17) 149 (21)	443 (0)	444 (100)	379 (12) $[M+H-SO_2]^+$ 378 (48) 329 (7) 290 (8) 224 (9) 222 (8) 140 (15)
4	289 (2)	290 (0)	262 (2) $[M-HCN]^+$ 225 (20) $[M-SO_2]^+$ 224 (100)$[M-SO_2H]^+$ 202 (10) 149 (18)	289 (0)	290 (100)	224 (31) 202 (7)
5	213 (100)	214 (20)	148 (3) $[M-SO_2H]^+$ 135 (14)	213 (0)	214 (100)	

TABLE II (cont.)

com-pound	time delay 100 μs M^+ (%)	100 μs $[M+H]^+$ (%)	100 μs fragment ions (%)	1 s M^+ (%)	1 s $[M+H]^+$ (%)	1 s fragment ions (%)
8	393 (6)	394 (0)	378 (55)	393 (0)	394 (100)	364 (21)
			364 (50)			344 (15)
			331 (30)			240 (45)
			329 (30) $[M-SO_2]^+$			
			274 (40)			
			272 (33)			
			262 (32)			
			213 (100)			
			210 (42)			
			155 (33)			
			149 (27)			
			135 (99)			
9	317 (0)	318 (0)	288 (27)	317 (0)	318 (37)	279 (23)
			202 (28)			240 (100)
			149 (100)			225 (17)
						205 (19)
						203 (17)
						202 (34)
11					548 (100)	428 (12)
						290 (16)
						274 (7)
						258 (14)
						224 (18)

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SAŽETAK

Sinteza, te NMR i MS studija novih *N*-Sulfonil-derivata purina

Biserka Žinić, Irena Krizmanić, Dražen Vikić-Topić, Dunja Srzić i Mladen Žinić

Tosiliranje i meziliranje adenina (**1**) na sobnoj temperaturi regioselektivno daje N^9-sulfonilpurine **2** i **5**. Suvišak TsCl ili MsCl, te povišena temperatura reakcije vode do nestabilnih N^6,N^9-disulfonil-produkata **3** i **6**, koji se lagano transformiraju u odgovarajući N^6-monosulfonil-produkt **4**. Također su sintetizirani *N*-sulfonil-derivati purinskih nukleozida **12** i **15**. Mjesta sulfoniliranja kao i prostorni raspored supstituenata utvrđeni su s pomoću 1D i 2D NMR spektroskopije. MS spektri pokazuju neočekivanu pregradnju protoniranih molekulnih iona do koje dolazi zbog gubitka SO_2.