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Photochemical removal of the tosyl group from the 5′N position of 5′-aminopyrimidine nucleosides: synthetic applications

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ABSTRACT: The *p*-toluenesulfonyl (tosyl) group, an effective protector of the amine function of thymidine derivatives **2a** and **b**, has proven to be photoremovable. This photoreaction was successfully used in the synthesis of new 5′-amino analogs of 3′-azido-3′-deoxythymidine (AZT), **6a** and **b**. Selective photohydrolysis of 5′*N*-tosylamides **2a** and **b** was carried out by UV irradiation (>300 nm) in aqueous acetonitrile in the presence of 1,5-dimethoxynaphthalene as an electron donor. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 5′-aminopyrimidines; *p*-toluenesulfonyl photoremoval; 3′-azido-3′-deoxythymidine derivatives

INTRODUCTION

The discovery of significant antiviral activity of 5′-aminothymidine and 3′-aminothymidine has stimulated intense interest in the chemistry of nucleoside analogs with amino groups.[1] Thymidine derivatives with amino functions at the 5′- and 3′-positions have also attracted attention because of their use as precursors for the synthesis of various 2′,3′-dideoxynucleosides,[2,3] which have proved to be selective inhibitors of HIV-1 replication.

The *p*-toluenesulfonyl (tosyl) group has been recognized as a useful protector of amines because of the ease of its introduction and its stability under a wide variety of chemical conditions. The use of this group in synthesis is convenient. However, the strongly basic conditions[4] (e.g. sodium in ammonia, sodium butoxide and sodium naphthalenide) or the strongly acidic conditions (e.g. heating in 48% HBr) required for the detosylation step have limited its applicability. Hence the development of a mild and selective method for the removal of the tosyl group from the amino function of nucleoside derivatives would be welcome.

Umezawa *et al.*[5] have reported that on irradiation, in the presence of sodium borohydride, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-tosylates were readily cleaved to the corresponding tetrahydroisoquinolines in high yields. This process was explained by intramolecular electron transfer in the excited singlet state from the methoxy-substituted aromatic donor to the arylsulfonamide acceptor.[6] This idea was then extended to intermolecular sensitization by Hamada and co-workers.[7,8] They carried out photochemical hydrolysis of *N*-tosylphenethylamine derivatives and obtained detosylated phenethylamines via electron transfer from the excited electron-donating aromatic compounds (Scheme 1).

$$D \xrightarrow{h\nu} {}^1D^* \xrightarrow{A} D^{+\cdot}A^{-\cdot} \longrightarrow P + D$$

D: donor, A: acceptor, $D^{+\cdot}A^{-\cdot}$: radical ion pair, P: product

Scheme 1

In this paper, we present our results on the photochemical removal of tosyl group from the 5′N position of 5′-aminopyrimidine nucleosides and synthetic applications of this photoreaction.

RESULTS AND DISCUSSION

We have found that on irradiation at >300 nm in the presence of 1,5-dimethoxynaphthalene, the *N*-tosylates of 5′-aminopyrimidine nucleosides 1-[5-(*N*-methyl-*N*-tosyl)-3-*O*-mesyl-2,3,5-trideoxy-*β*-D-*threo*-pentafuranosyl]thymine (**2a**) and 1-[5-(*N*-ethyl-*N*-tosyl)-3-*O*-mesyl-2,3,5-trideoxy-*β*-D-*threo*-pentafuranosyl]thymine (**2b**) were readily cleaved to the corresponding 5-aminopyrimidine nucleosides **5a** and **5b** in high yields (Scheme 2). *N*-Tosylates of 5′-aminopyrimidine nucleosides **2a–c** were obtained by reaction of the corresponding compounds **1a–c**[9] with tosyl chloride and subsequently with mesyl chloride in anhydrous pyridine. The reaction of **2c** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in aceto-

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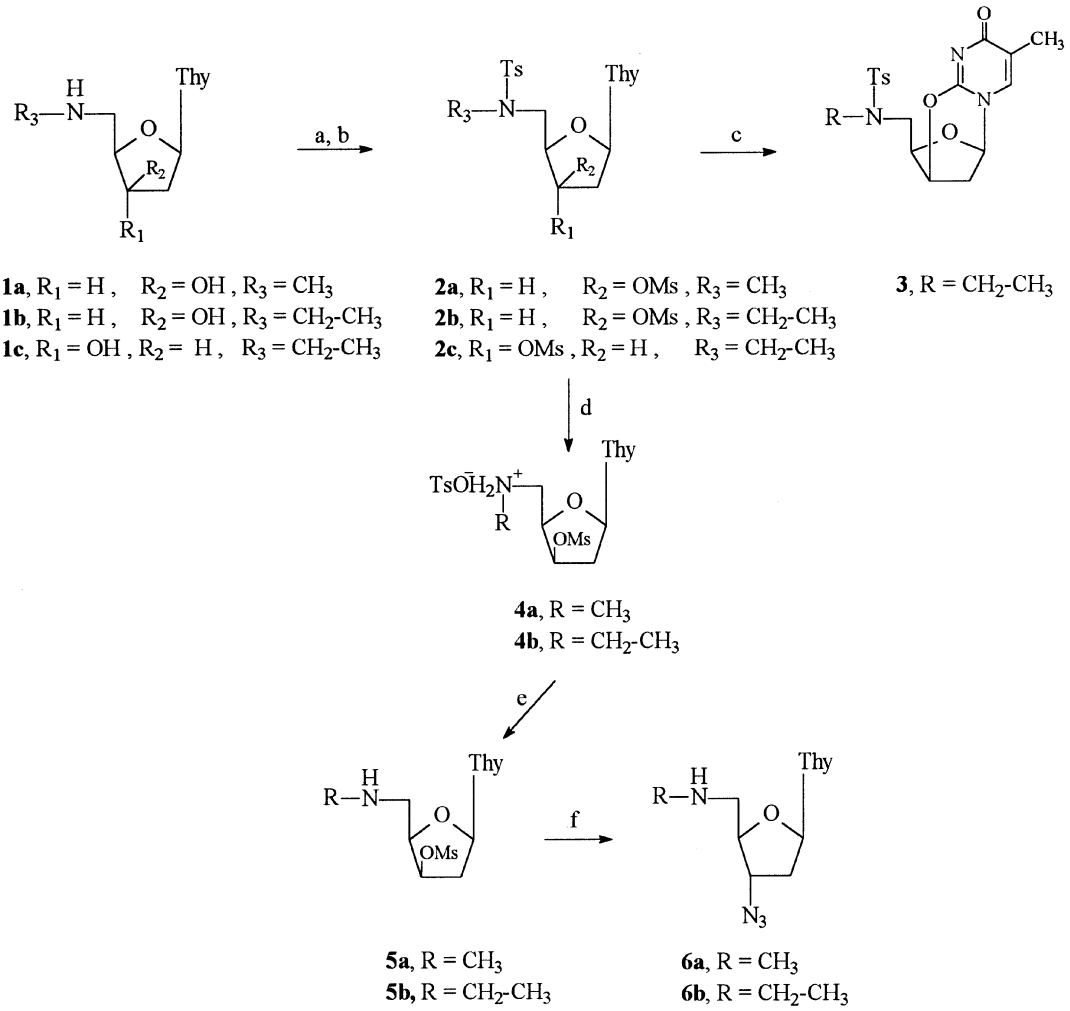

1a, R_1 = H , R_2 = OH , R_3 = CH_3
1b, R_1 = H , R_2 = OH , R_3 = CH_2-CH_3
1c, R_1 = OH , R_2 = H , R_3 = CH_2-CH_3

2a, R_1 = H , R_2 = OMs , R_3 = CH_3
2b, R_1 = H , R_2 = OMs , R_3 = CH_2-CH_3
2c, R_1 = OMs , R_2 = H , R_3 = CH_2-CH_3

3, R = CH_2-CH_3

4a, R = CH_3
4b, R = CH_2-CH_3

5a, R = CH_3
5b, R = CH_2-CH_3

6a, R = CH_3
6b, R = CH_2-CH_3

Scheme 2. (a) TsCl, Py, −5 °C, 12 h; (b) MsCl, Py, −5 °C, 12 h; (c) for **2c**, DBU, CH_3CN, 82 °C, 2 h; (d) for **2a** and **b**, $h\nu$ ($\lambda > 300$ nm), 1,5-dimethoxynapthalene, CH_3CN–H_2O (9:1, v/v); (e) Dowex 50Wx2; (f) NaN_3, DMF, 90 °C, 45min. Thy = thymin-1-yl; Ms = methanesulfonyl; Ts = *p*-toluenesulfonyl.

nitrile afforded the 2,3′-anhydro nucleoside **3**. Attempts at photochemical removal of the tosyl group from nucleosides **2a** and **b** and **3** were carried out using electron-donating aromatic compounds such as 2-methoxynaphthalene and 1,5-dimethoxynaphthalene. Irradiation of **2a** and **b** with Pyrex-filtered ultraviolet radiation (>300 nm) in aqueous acetonitrile solution in the presence of 1,5-dimethoxynaphthalene (which acts as an electron transfer photosensitizer) causes the selective removal of the tosyl group from the 5′N position and gives **4a** and **b** in about 78% yields. The 3′-*O*-*threo*-mesyl group in the products **4a** and **b** and **5a** and **b** remains intact. Toluenesulfonate salts **4a** and **b** were converted in to the free amino bases **5a** and **b** by passing them through Dowex 50Wx2 cation-exchange resin. The liberated *p*-toluenesulfonic acid and 1,5-dimethoxynaphthalene present in the reaction mixture were eluted with methanol – chloroform (2:1, v/v) and water and then **5a** and **b** were desorbed with 1 M ammonia solution. The formation of detosylated products **5a** and **b** was detected by HPLC using a photodiode array detector (PAD). The UV absorption spectra of **2a** and **b** show two characteristic bands at $\lambda_{max\ I}$ = 230 nm and $\lambda_{max\ II}$ = 266 nm. As a result of the photochemical removal of the tosyl group from the 5′N position of **2a** and **b**, the decay of the 230 nm band corresponding to the tosyl group was observed (Fig. 1).

When 2-methoxynaphthalene was used as an electron-donating compound, no reaction was observed. 2-Methoxynaphthalene was too weak as an electron donor to form an excited donor–acceptor pair with the tosyl ring, which can be explained by a value of the half-wave oxidation potential ($E_{1/2}^{ox}$ = 1.38 V) higher than that for 1,5-dimethoxynaphtalene ($E_{1/2}^{ox}$ = 1.28 V).[10] We also observed that UV irradiation of **3** (>300 nm) in aqueous acetonitrile in the presence of 1,5-dimethoxynaphthalene led to the removal of the tosyl group with simultaneous cleavage of the 2,3′-anhydro bond. This photoreaction

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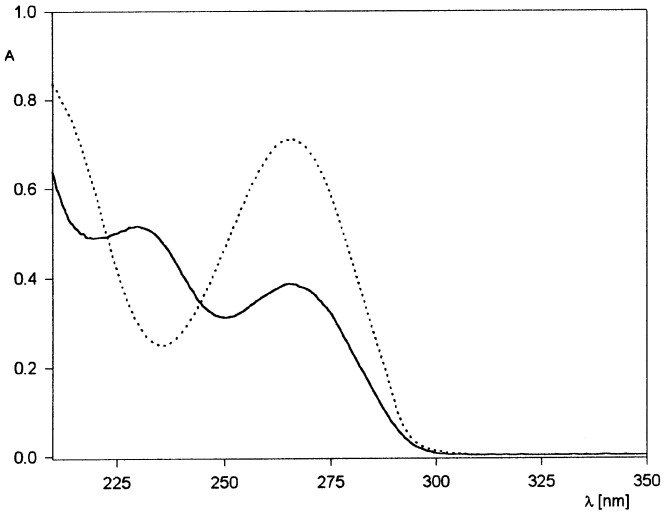

Figure 1. UV absorption spectra of 3′,5′-dideoxy-5′-(*N*-ethyl-*N*-tosyl)-3′-*O*-mesyl-*xylo*-thymidine ($c = 1.0 \times 10^{-4}$ mol dm^{-3}, solid line) and 3′,5′-dideoxy-5′-ethylamino-3′-*O*-mesyl-*xylo*-thymidine ($c = 9.9 \times 10^{-5}$ mol dm^{-3}, dotted line).

merits further investigation in order to identify the product formed.

The reaction of **5a** and **b** with sodium azide in dimethylformamide at 90 °C provided the corresponding 5′-amino-3′-azido-3′,5′-dideoxythymidine derivatives **6a** and **b**.

Elemental analyses and spectral data (UV, IR and ^{1}H NMR) are consistent with the structures shown. The ^{1}H NMR spectra of **2a** and **b** and **5a** and **b** display a doublet of doublets at δ 6.13–6.27 ppm for H-1′. The presence of 3′-OMs at the 'up' position restricts rotation at C-5′, resulting in the H-5′ and H-5″ protons being displayed as multiplets with $\delta \approx 3.35$ ppm for **2a** and **b** and $\delta \approx 2.80$ ppm for **5a** and **b**. The signals for H-2′ and H-2″ are widely separated multiplets with $\delta \approx 2.50$ and 2.80 ppm for **2a** and **b** and with $\delta \approx 2.25$ and 2.60 ppm for **5a** and **b**, which indicates a *cis* configuration of H-1′ and H-3′.[11,12] The ^{1}H NMR spectra of **6a** and **b**, in contrast, display a doublet at $\delta \approx 2.80$ ppm for H-5′ and H-5″, a pseudo-triplet at $\delta \approx 6.10$ ppm for H-1′ and closely spaced multiplets at δ 2.21–2.50 ppm for H-2′ and H-2″.

In conclusion, we have demonstrated that the tosyl group can be selectively removed by a photochemical method from the 5′-amino function of thymidine derivatives **2a** and **b**. The 3′-*O*-*threo*-mesyl group in the products **5a** and **b** remains intact, which permits nucleophilic substitution by the azide to obtain new 5′-amino derivatives of 3′-azido-3′-deoxythymidine (AZT), **6a** and **b**.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Microanalyses were obtained on an Perkin-Elmer model 240 elemental analyzer. UV spectra were recorded on a Specord M40 instrument (Carl Zeiss, Jena, Germany). IR spectra were recorded on a Perkin-Elmer Model 180 infrared spectrophotometer. ^{1}H NMR spectra were determined on Varian-Gemini 300 MHz spectrometer.

Column chromatography was performed on a Merck silica gel 60 H (5–40 μm) column. Analytical HPLC was carried out on a Waters Nova-Pak C_{18} reverse phase column (3.9 × 50 mm, 4 μm particle size), with water – methanol (55:45) as the eluent at a flow-rate of 1 ml min^{-1} and detection at 265 nm with a Waters Model 966 photodiode array detector.

Irradiations at >300 nm were carried out in a cylindrical reactor using an immersed, water-cooled, 400 W high-pressure mercury lamp (Polamp, Poland), with a cylindrical Pyrex light filter in an argon atmosphere.

*Preparation of compounds **2a** and **b**.* To a solution of **1a–c** (0.5 g) in anhydrous pyridine (30 ml) at −5 °C, tosyl chloride (1.2 equiv.) was added and the reaction mixture was stirred at −5 °C for 12 h. Mesyl chloride (1.2 equiv.) was added to the reaction mixture, which was stirred at −5 °C for a further 12 h. Subsequently the mixture was poured into cold water (50 ml) and the solution was extracted with chloroform (3 × 15 ml). The combined organic extracts were washed with aqueous $NaHCO_3$ and then with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Products **2a** and **b** were crystallized from ethanol and dried *in vacuo* over phosphorus pentoxide. Compounds **2a** and **b** were obtained in 88% yield.

2a: m.p. 101–103 °C (EtOH). UV (CH_3OH):λ_{max} 230, 267 nm. ^{1}H NMR ($CDCl_3$):δ 1.94 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.43 (s, 3H, tosyl CH_3), 2.48 (dd, 1H, J = 2.7, 15.9 Hz, H-2′), 2.81 (m, 1H, H-2″), 2.99 (s, 3H, mesyl CH_3), 3.26 (s, 3H, 5′*N*-CH_3), 3.30 (m, 2H, H-5′, H-5″), 4.30 (m, 1H, H-4′), 5.32 (m, 1H, H-3′), 6.21 (dd, 1H, H-1′), 7.32 (d, 2H, J = 8.2 Hz, *meta* Hs of tosyl), 7.45 (d, 1H, J = 1.1 Hz, H-6), 7.68 (d, 2H, J = 8.3 Hz, *ortho* Hs of tosyl). Analysis: calculated for $C_{19}H_{25}N_3O_8S_2$, C 46.81, H 5.17, N 8.62; found, C 46.70, H 5.30, N 8.70%.

2b: m.p. 104–105 °C (CH_3OH). UV (CH_3OH):λ_{max} 230, 266 nm. ^{1}H NMR ($CDCl_3$):λ 1.11 (t, 3H, J = 7.1 Hz, 5′ *N*-C-CH_3), 1.96 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.44 (s, 3H, tosyl CH_3), 2.51 (dd, 1H, J = 3.1, 16.2 Hz, H-2′), 2.83 (m, 1H, H-2″), 3.15 (s, 3H, mesyl CH_3), 3.21 (m, 2H, 5′ *N*-CH_2), 3.35 (m, 2H, H-5′, H-5″), 4.22 (m, 1H, H-4′), 5.27 (m, 1H, H-3′), 6.27 (dd, 1H, J = 3.0, 8.3 Hz, H-1′), 7.33 (d, 2H, J = 8.0 Hz, *meta* Hs of tosyl), 7.45 (d, 1H, J = 1.2 Hz, H-6), 7.70 (d, 2H, J = 8.2 Hz, *ortho* Hs of tosyl), 8.88 (s, 1H, 3*N*-H). Analysis: calculated for $C_{20}H_{27}N_3O_8S_2$, C 47.89, H 5.43, N 8.38; found, C 48.10, H 5.21, N 8.28%.

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Preparation of compound ***3****.* The crude product **2c** (0.3 g, 0.06 mmol) was dissolved in acetonitrile (15 ml), then DBU was added (0.11 ml, 0.117 g) and the reaction mixture was refluxed for 2 h. The solvent was evaporated under reduced pressure. The residue was recrystallized from acetonitrile and dried *in vacuo* over phosphorus pentoxide to afford product **3** in 75% yield.

3: m.p. 202–204 °C (CH_3CN). UV (CH_3OH):λ_{max} 234 nm. ^{1}H NMR (DMSO-d_6): δ 0.95 (t, 3H, J = 7.0 Hz, 5′ *N*-C-CH_3), 1.76 (d, 3H, J = 1.0 Hz, 5-CH_3), 2.39 (s, 3H, tosyl CH_3), 2.60 (dd, 1H, H-2′), 3.06–3.31 (m, 4H, 5′*N*-CH_2, H-2″, H-5′), 3.45 (dd, 1H, J = 4.5, 15.1 Hz, H-5″), 4.41 (m, 1H, H-4′), 5.31 (s, 1H, H-3′), 5.82 (d, 1H, J = 3.5 Hz, H-1′), 7.41 (d, 2H, J = 8.5 Hz, *ortho* Hs of tosyl). Analysis: calculated for $C_{19}H_{23}N_3O_5S$, C 56.28, H 5.72, N 10.36; found, C 56.44, H 5.87, N 10.51%.

Preparation of compounds ***5a*** *and* ***b*** *by irradiation of compounds* ***2a*** *and* ***b*** *in the presence of 1,5-dimethoxynaphthalene.* A solution of **2** (0.3 g) and 1,5-dimethoxynaphthalene (0.6 mmol) in aqueous acetonitrile [200 ml of CH_3CN–H_2O (9:10, v/v)] was irradiated for 4 h. After removal of the solvents, the residue was dissolved in methanol – water (75:25, v/v) and the solution was applied to a column (2 × 5 cm) of Dowex 50Wx2 (H^+) (50–100 mesh). The column was eluted with methanol – chloroform (3:1, v/v) (200 ml) and then with water (300 ml) in order to remove *p*-toluenesulfonic acid and 1,5-dimethoxynaphthalene. Finally, the amino nucleosides **5a** and **b** were eluted with 1 M ammonia solution in nearly quantitative yield. The fractions containing **5** were combined and evaporated under reduced pressure. The residue as a solid foam was dried *in vacuo* over phosphorus pentoxide to afford product **5** in 78% yield.

5a: UV (CH_3OH):λ_{max} 266 nm. ^{1}H NMR (DMSO-d_6):δ 1.81 (s, 3H, 5-CH_3), 2.23 (dd, 1H, J = 2.6, 16.0 Hz, H-2′), 2.32 (s, 3H, 5′*N*-CH_3), 2.57 (m, 1H, H-2″), 2.80 (m, 2H, H-5′, H-5″), 3.15 (s, 3H, mesyl CH_3), 4.12 (m, 1H, H-4′), 5.28 (m, 1H, H-3′), 6.18 (dd, 1H, H-1′), 7.38 (s, 1H, H-6). Analysis: calculated for $C_{12}H_{19}N_3O_6S$, C 43.23, H 5.75, N 12.61; found, C 43.34, H 5.91, N 12.78.

5b: UV (CH_3OH):λ_{max} 266 nm. ^{1}H NMR (DMSO-d_6):δ 1.01 (t, 3H, J = 8.5 Hz, 5′*N*-C-CH_3), 1.78 (s, 3H, 5-CH_3), 2.25 (dd, 1H, J = 2.4, 15.8 Hz, H-2′), 2.55–2.63 (m, 3H, 5′*N*-CH_2, H-2″), 2.84 (m, 2H, H-5′, H-5″), 3.28 (s, 3H, mesyl CH_3), 4.08 (m, 1H, H-4′), 5.23 (m, 1H, H-3′), 6.13 (dd, 1H, J = 2.7, 8.0 Hz, H-1′), 7.40 (s, 1H, H-6). Analysis: calculated for $C_{13}H_{21}N_3O_6S$, C 44.95, H 6.09, N 12.10; found, C 45.10, H 6.15, N 12.22%.

Preparation of compounds ***6a*** *and* ***b*** *from* ***5a*** *and* ***b****.* To a solution of **5** (0.10 g) in dimethylformamide (8 ml) was added sodium azide (2 equiv.) and the reaction mixture was stirred at 90 °C for 45 min. The cooled reaction mixture was evaporated under reduced pressure and the crude product was applied to a silica gel column (15 g) and chromatographed using chloroform–methanol (80–50:1, v/v) as eluent. The fractions containing **6** were combined and evaporated under reduced pressure. The solid foam obtained was dried over phosphorus pentoxide to afford product **6** in 89% yield.

6a: UV (CH_3OH):λ_{max} 266 nm. ^{1}H NMR (DMSO-d_6):δ 1.80 (s, 3H, 5-CH_3), 2.28 (m, 2H, H-2′, H-2″), 2.34 (s, 3H, 5′*N*-CH_3), 2.79 (d, 2H, J = 5.1 Hz, H-5′, H-5″), 3.84 (m, 1H, H-4′), 4.39 (m, 1H, H-3′), 6.12 (t, 1H, J = 6.4 Hz, H-1′), 7.68 (s, 1H, H-6). IR (KBr):ν_{max} 2100 cm^{-1} (N_3). Analysis: calculated for $C_{11}H_{16}N_6O_3$, C 47.13, H 5.76, N 29.99; found, C 47.27, H 5.83, N 30.12%.

6b: UV (CH_3OH):λ_{max} 265 nm. ^{1}H NMR (DMSO-d_6):δ 1.02 (t, 3H, J = 7.1 Hz, 5′*N*-C-CH_3), 1.79 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.21–2.50 (m, 2H, H-2′, H-2″) 2.57 (q, 2H, J = 7.1 Hz, 5′*N*-CH_2), 2.75 (d, 2H, J = 5.3 Hz, H-5′, H-5″), 3.81 (q, 1H, H-4′), 4.38 (m, 1H, H-3′), 6.07 (t, 1H, J = 6.6 Hz, H-1′), 7.66 (d, 1H, J = 1.1 Hz, H-6). IR (KBr):ν_{max} 2100 cm^{-1} (N_3). Analysis: calculated for $C_{12}H_{18}N_6O_3$, C 48.97, H 6.16, N 28.56; found, C 48.81, H 6.28, N 28.70%.

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