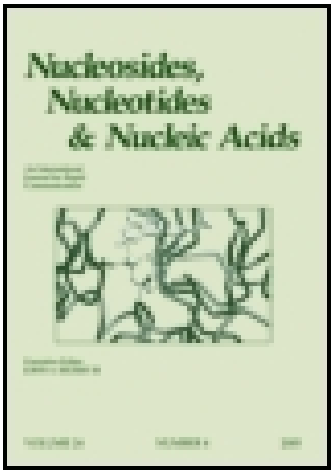


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

7-Deazainosine Derivatives: Synthesis and Characterization of 7- and 7,8-Substituted Pyrrolo [2,3-d]Pyrimidine Ribonucleosides

Nunzia Ciliberti [a] , Elisa Durini [a] , Stefano Manfredini [a] & Silvia Vertuani [a]

[a] Department of Pharmaceutical Sciences , University of Ferrara , Italy

Published online: 19 Jun 2008.

To cite this article: Nunzia Ciliberti , Elisa Durini , Stefano Manfredini & Silvia Vertuani (2008) 7-Deazainosine Derivatives: Synthesis and Characterization of 7- and 7,8-Substituted Pyrrolo [2,3-d]Pyrimidine Ribonucleosides, Nucleosides, Nucleotides and Nucleic Acids, 27:5, 525-533, DOI: 10.1080/15257770802089009

To link to this article: http://dx.doi.org/10.1080/15257770802089009

Nucleosides, Nucleotides and Nucleic Acids, 27:525–533, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802089009

Taylor & Francis
Taylor & Francis Group

7-DEAZAINOSINE DERIVATIVES: SYNTHESIS AND CHARACTERIZATION OF 7- AND 7,8-SUBSTITUTED PYRROLO [2,3-*d*]PYRIMIDINE RIBONUCLEOSIDES

Nunzia Ciliberti, Elisa Durini, Stefano Manfredini, and Silvia Vertuani

Department of Pharmaceutical Sciences, University of Ferrara, Italy

□ *The synthesis of model 7 deazapurine derivatives related to tubercidin and toyocamycin has been performed. Tubercidin derivatives were obtained by simple conversion of the amino group of the heterocyclic moiety of the starting 7-deazadenosine compounds, into a hydroxyl group. Preparation of toyocamycin derivatives was accomplished by treatment of the silylated 6-bromo-5-cyanopyrrolo[2,3-d]pyrimidin-4-one with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose. The glycosylation reaction afforded a mixture of 8-bromo 7-cyano 2′,3′,5′ tri-O-benzoyl 7-deazainosine and 6-bromo-5-cyano-3-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidin-4-one isomers: The structures were assigned on the basis of NMR spectroscopy studies. Next deprotection treatment gave the novel 7-deazainosine ribonucleosides.*

Kewords 7-Deazainosine derivatives; synthesis; RNA viruses

INTRODUCTION

A number of 7-deazapurine (pyrrolo[2,3-*d*]pyrimidine) ribonucleosides, such as tubercidin and toyocamycin occur naturally and exhibit a broad spectrum of biological activity (Figure 1).[1,2] The biological and pharmacological properties of these classes of compounds are at the bases of a large number of studies to investigate structure-activity relationships, synthesis, biochemical and physical properties, and incorporation into nucleic acids.[3–7] Among 7-deazapurine nucleosides, 7-deazadenosine-, and 7-deazaguanosine-derivatives have been extensively investigated with modifications on the heterocyclic[8] or glycosidic moiety,[9] but 7-deazainosines have been only marginally involved in these investigations. In view of the biological relevance of this class of compounds, we have investigated

Received 15 May 2007; accepted 18 March 2008.
Address correspondence to Stefano Manfredini, Università degli Studi di Ferrara, via Fossato di Mortara no. 19, 44100, Ferrara, Italy. E-mail: mv9@unife

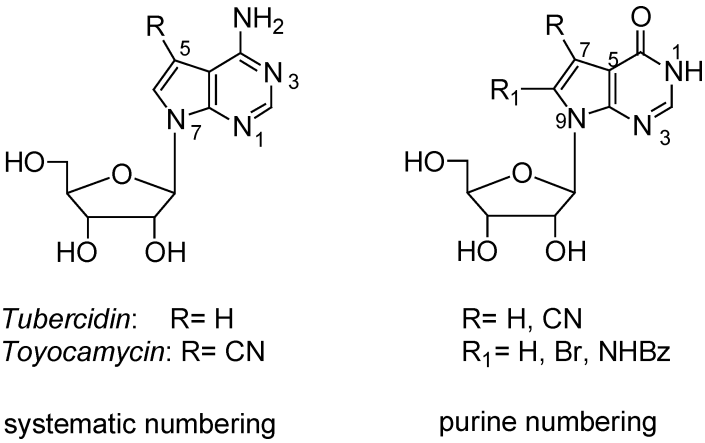


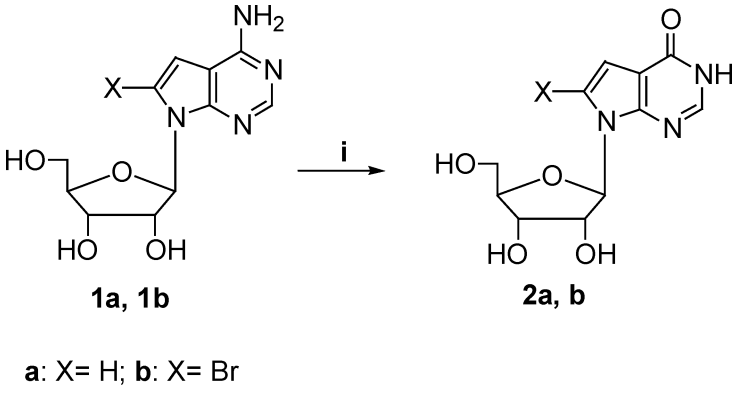
FIGURE 1 Several structures of natural and synthetic 7-deazapurines.

the synthesis of two representative 7- and 7,8-substituted 7-deazainosine derivatives (Figure 1).

RESULTS AND DISCUSSION

The synthesis of 7-deazainosine (**2a**) and 8-bromo-7-deazainosine (**2b**) was carried out starting from tubercidin (**1a**) or 8-bromo tubercidin (**1b**)[10] in the presence of acetic acid and $NaNO_2$ as described by Holmes et al.[11] (Scheme 1).

Preparation of toyocamycin derivatives was accomplished by glycosylation of the 6-bromo-5-cyanopyrrolo[2,3-d]pyrimidin-4-one[12] (**3**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). Activation of compound **3** was



SCHEME 1 (i) $NaNO_2$, AcOH, H_2O, 60°C, overnight.

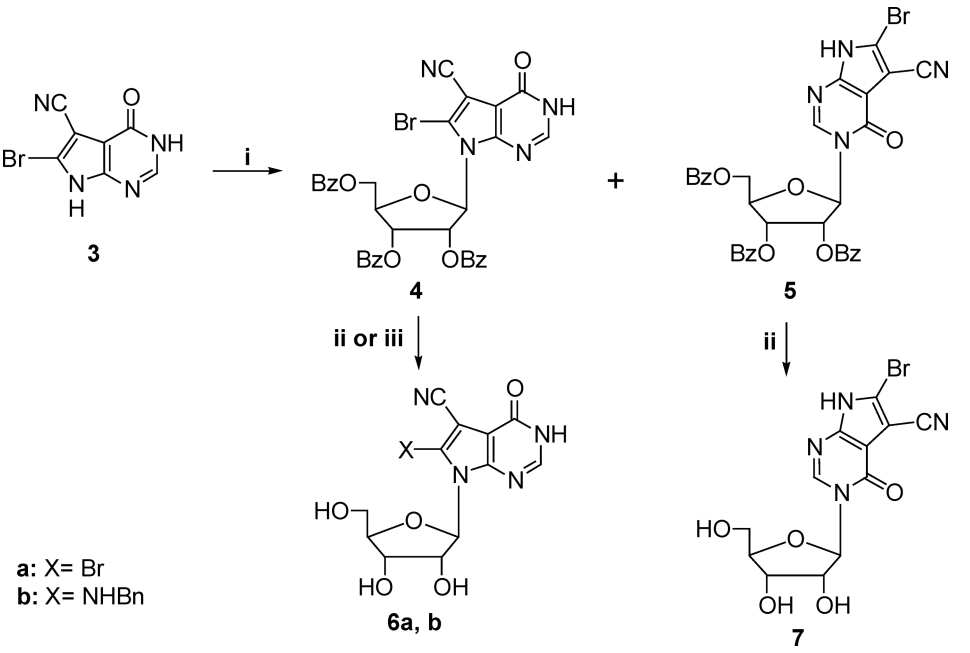
reached in situ by treatment with *N,O*-Bis(trimethylsilyl)acetamide (BSA) (Scheme 2).

For the glycosylation step different temperatures and reaction times were evaluated. When the reaction was carried out at temperatures higher than 80°C, the sugar decomposed providing very low reaction yield. Conducting careful and precise reaction condition control, we found that, within a temperature range of 70°C to 80°C and using a two-fold excess of BSA, the nucleobase was completely consumed in 24 hours. This protocol afforded a higher glycosylation yield of compound **4** (50%), along with a 25% yield of N^1 glycosylated derivative **5**.

Separation of compounds **4** and **5** required multiple purification steps and an accurate spectroscopic analysis was also required to distinguish and characterize the two isomers which have similar migration properties on silica gel. Structural assignments were based upon ^{1}H, ^{13}C (Table 1), HMQC, HMBC, and ^{1}H-^{1}H Roesy experiments.

In particular HMBC experiments showed that:

In the case of **4**, the H2 signal (^{1}H: $\delta = 8.00$ ppm) does not couple with anomeric C signal (^{13}C: $\delta = 89.0$ ppm) and the C2 signal (^{13}C: $\delta = 146.8$ ppm) does not couple with H1′ signal (^{1}H: $\delta = 6.41$–6.45 ppm);



SCHEME 2 (i) BSA, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, TMSOTf, CH_3CN, 80 °C; (ii) K_2CO_3, MeOH dry, CH_2Cl_2 dry, room temperature; (iii) benzylamine, dioxane, rfx, 3 days.

TABLE 1 ^{13}C chemical shift of the compounds 4 and 5[a]

	Chemical shifts, δ_{TMS} (ppm)											
	Base				Sugar				Others			
Compd[b]	C(2)	C(6)	C(5)	C(7)	C(8)	C(4)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	CN
4	146.8	155.3	108.8	c	118.8	147.7	89.0	73.2	69.7	78.7	62.4	113.2
5	147.5	154.7	107.7	89.1	162.2	148.2	91.0	73.8	69.9	78.6	62.9	113.8

[a]Measured in d^6 DMSO.
[b]Purine numbering.
[c]Not detected.

In the case of **5**, the H2 signal (^1H: $\delta = 8.47$ ppm) couples with anomeric C signal (^{13}C: $\delta = 91.0$ ppm) and the C2 signal (^{13}C: $\delta = 147.5$ ppm) couples with H1′ signal (^1H: $\delta = 6.34$ ppm).

Moreover NOE effects observed between the H1′ and H4′ in ^1H-^1H Roesy experiments, confirmed the β configuration of both obtained products (**4** and **5**).

The formation of the two stereoisomers **4** and **5** can be explicated by the different characteristics of the heterocyclic moiety in respect to purines. Indeed, the electrophilic glycosylation performed on the 7-deazapurines disrupts the aromatic character of the pyrrole ring making the N^9 position less sensitive to glycosylation, thus addressing the reaction to the pyrimidine moiety. However, the presence of an electron withdrawing substituent at C-7 facilitates the condensation of the N^9 heterocyclic with the benzoylated sugar. The result is the formation of a mixture of compounds of N^9 and N^1 glycosylation.

Finally compounds **4** and **5** were separately treated with K_2CO_3 in dry MeOH and CH_2Cl_2 affording the debenzoylated nucleosides **6a** and **7**. Treatment of compound **4** with benzylamine in refluxing dioxane afforded

TABLE 2 Antiviral evaluation of compounds **2a**, **2b**, **6a**, **6b,** and **7**

	MT-4	YFV		BVDV		DFV-2,WNV	
Compounds	[a]CC_{50}	[a]CC_{50}	[b]EC_{50}	[a]CC_{50}	[b]EC_{50}	[a]CC_{50}	[b]EC_{50}
2a	>100	>100	>100	>100	>100	>100	>100
2b	>100	>100	>100	>100	>100	>100	>100
6a	>100	>100	>100	>100	>100	>100	>100
6b	>100	>100	>100	>100	>100	>100	>100
7	>100	>100	>100	>100	>100	>100	>100

[a]Compound concentration (μM) required to reduce the viability of mock-infected cells by 50%, as determined by the MTT or plaque reduction method.
[b]Compound concentration (μM) required to achieve 50% protection from virus-induced cytopathogenicity, as determined by the MTT method.[13]

the hydroxyl deprotected nucleoside **6b** functionalized with benzylamine at the 8 position.

BIOLOGICAL EVALUATION

The 7-deazainosine derivatives **2a**, **2b**, **6a**, **6b**, and **7** were evaluated for their *in vitro* inhibitory effect on the replication of different RNA viruses (Table 2). None of the tested compounds resulted endowed of the expected activity (EC_{50}>100 μM) or cytotoxicity (up to 100 μM).

CONCLUSION

In the present study we have reported the synthesis of 7 deazainosine derivatives. Preparation of tubercidin derivatives was performed by simple conversion of the amino group of **1a**,**b** into the corresponding hydroxyl group. These results highlight that the lack of a nitrogen at position 7 of the base (**1a**,**b**), independently of the presence of a substituent at position 8, does not affect the outcome of the reaction.

In contrast, the synthesis of the toyocamycin derivatives was accomplished with difficulty because of the different reactivity of the pyrrole of the heterocyclic base *versus* the imidazole ring present in purine nucleosides. Whereas imidazole nitrogens are easily attacked by electrophilic sugar cations, the free electron pair of the pyrrole nitrogen is rather inert, as its electron pair is part of the aromatic π system. As a result of the inertness of the pyrrole nitrogen, the silylation step becomes the determinant for the progress of the glycosylation reaction. In the present investigation we have highlighted that the TMSOTf-catalyzed glycosylation of 7-deazainosine strongly depends on the silylating reagent, on the reaction temperature and further on the characteristics of the heterocyclic moiety. The result has been the formation of a mixture of compounds of N^9 and N^1 glycosylation.

The nucleoside analogues **2a**, **2b**, **6a**, **6b**, and **7**, evaluated against different RNA viruses by they, did not exhibit any interesting activity. Further studies are currently in progress to investigate alternative modifications of the heterocyclic base.

EXPERIMENTAL

Preparation of 7-Deazainosine (2a) and 7-Deaza-8-Bromo-Inosine (2b)

General Procedure. To a solution of the selected derivative **1a** or **1b**[14] (1.8 mmol) in glacial AcOH (36.7 mL) aqueous $NaNO_2$ was added dropwise (1.29 g, 18.0 mmol/10.7 mL of H_2O) and the reaction was stirred at 60°C

for 12 hours. The solution was then concentrated in vacuo and the resulting residue was suspended in CH_2Cl_2 (100 mL). The suspended solid was filtered off from the mixture and the solvent evaporated to dryness. The crude material was purified by silica gel column chromatography (eluent: CH_2Cl_2/MeOH 98/2→95/5, v/v) to afford expected compounds **2a** or **2b**.

2a: yield 96%, white foam.

^{1}H NMR (DMSO-*d6*): δ (ppm) 3.49–3.63 (m, 2H, H5′, H5″); 3.85–3.90 (m, 1H, H4′); 4.05–4.12 (m, 1H, H3′); 4.29–4.35 (m, 1H, H2′); 5.04 (br s, 1H, OH2′); 5.22 (br s, 1H, OH3′); 5.41 (br s, 1H, OH5′); 6.01 (d, 1H, J = 6.0 Hz, H1′); 6.51 (d, 1H, J = 3.6 Hz, H7); 7.37 (d, 1H, J = 3.6 Hz, H8); 7.91 (s, 1H, H2); 11.90–12.10 (br s, 1H, NH).

MALDI-TOF MS: *m/z* 268.4 Da $[M+H]^+$; 290.23 Da $[M+Na]^+$; $C_{10}H_{12}N_4O_5$ Mol. Wt. 267.24.

2b: yield 63%, white foam.

^{1}H NMR (DMSO-*d6*): δ (ppm) 3.50–3.65 (ABX system, 2H, J_{AB} = 12.0 Hz, J_{AX} = 5.2 Hz, J_{BX} = 4.4 Hz, H5′, H5″); 3.84–3.90 (m, 1H, H4′); 4.14–4.18 (m, 1H, H3′); 4.90–5.04 (m, 1H, H2′); 5.88 (d, 1H, J = 6.0 Hz, H1′); 6.78 (s, 1H, H7); 7.98 (s, 1H, H2).

MALDI-TOF MS: *m/z* 347.13 Da $[M+H]^+$; 347.12 Da $[M+Na]^+$; $C_{11}H_{12}BrN_3O_5$ Mol. Wt. 346.13.

6-Bromo-5-Cyanopyrrol[2,3-*d*]Pyrimidin-4-one (3)[15]

^{1}H NMR (DMSO-*d6*): δ (ppm) 7.99 (d, 1H, J = 3.2 Hz, H2); 12.39 (br s, 1H, NH); 13.85 (br s, 1H, NH1). ^{13}C NMR (DMSO-*d6*): δ (ppm) 108.4, 113.9, 114.0, 115.3, 146.1, 149.0, 155.7

8-Bromo 7-Cyano 2′,3′,5′ Tri-*O*-Benzoyl 7-Deazainosine (4) and 6-Bromo-5-Cyano-3-(2′,3′,5′ Tri-*O*-Benzoyl-β-D-Ribofuranosyl) Pyrrolo[2,3-*d*]Pyrimidin-4-one (5)

N,O-Bis(trimethylsilyl)acetamide (BSA) (1.02 mL, 4.2 mmol) was added to a stirred suspension of **3** (500 mg, 2.1 mmol) in dry acetonitrile (20 mL) at room temperature and under argon atmosphere. After 15 minutes, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.05 g, 2.1 mmol) was added along with trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.135 mL, 6.3 mmol). The mixture was stirred at room temperature for 10 min, during which time the suspension became a clear yellow solution. This latter was then heated to 80°C for 3 hours under argon atmosphere and then cooled, diluted with ethyl acetate (20 mL) and poured into aqueous sodium bicarbonate (20 mL, sat.) at room temperature. The aqueous layer was separated and the organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography

(eluent: $CHCl_3$/AcOEt 100/0→95/5, v/v) to afford 700 mg of **4** and 350 mg of **5**.

4: yield 50%, white foam.

^{1}H NMR (DMSO-*d6*): δ (ppm) 4.60 (dd, part of ABX system, 1H, J_{AB} = 12.2 Hz, J_{AX} = 4.8 Hz, H5′); 4.79 (part of ABX system, 1H, J_{AB} = 12.2 Hz, J_{BX} = 3.2 Hz, H5″); 4.85–4.90 (m, part of ABX system, 1H, H4′); 6.25–6.30 (m, 1H, H3′); 6.41–6.45 (m, 2H, H2′, H1′); 7.42–7.92 (m, 15H, benzoyl); 8.00 (d, 1H, J = 2.8 Hz; H2); 12.75 (br s, 1H, NH).

MALDI-TOF MS: *m/z* 684.5 Da $[M+H]^+$; 706.45 Da $[M+Na]^+$; 722.56 Da $[M+K]^+$. $C_{33}H_{23}BrN_4O_8$ Mol. Wt. 683.46

5: yield 25%, white foam.

^{1}H NMR (DMSO-*d6*): δ (ppm) 4.61–4.74 (part of ABX system, 2H, J_{AB} = 12.4 Hz, J_{AX} = 4.8 Hz, J_{BX} = 3,2 Hz, H5′, H5″); 4.75–4.85 (m, part of ABX system, 1H, H4′); 6.12 (dd, 1H, $J_{2'3'}$ = 6.4 Hz, $J_{2'1'}$ = 2.8 Hz; H2′); 6.14–6.20 (m, 1H, H3′); 6.34 (d, 1H, J = 2.8 Hz, H1′); 7.41–8.20 (m, 15H, benzoyl); 8.47 (s, 1H, H2); 14.12 (br s, 1H, 9-NH).

MALDI-TOF MS: *m/z* 684.5 Da $[M+H]^+$; 706.45 Da $[M+Na]^+$; 722.56 Da $[M+K]^+$. $C_{33}H_{23}BrN_4O_8$ Mol. Wt. 683.46

Preparation of 8-Bromo-7-Cyano-7-Deazainosine (6a) and 6-Bromo-5-Cyano-3-(β-D-Ribofuranosyl)Pyrrolo[2,3-*d*]Pyrimidin-4-one (7)

General Procedure. Compound **4** or **5** (5.1 mmol) was dissolved in a mixture of dry CH_2Cl_2 (7 mL) and dry MeOH (18 mL) and to this solution K_2CO_3 (70 mg, 5.1 mmol) was added. The solution, stirred overnight at room temperature, was then concentrated *in vacuo* to give a residue which was purified by column chromatography (eluent: CH_2Cl_2/MeOH 90/10, v/v) affording the desired compound **6a** or **7**.

6a: yield 95%, white foam.

^{1}H NMR (DMSO-*d6*): δ (ppm) 3.47–3.70 (m, 2H, H5′, H5″); 3.85–3.92 (m, 1H, H4′); 4.15–4.22 (m, 1H, H3′); 4.92–5.01 (m, 2H, H2′, OH5′); 5.26 (d, 1H, J = 5.2 Hz, OH3′); 5.51 (d, 1H, J = 6.0 Hz, OH2′); 5.93 (d, 1H, J = 6.4 Hz, H1′); 8.13 (s, 1H, H2); 12.74 (br s, 1H, NH).

MALDI-TOF MS: *m/z* 372.15 Da $[M+H]^+$; 394.13 Da $[M+Na]^+$; 410.24 Da $[M+K]^+$. $C_{12}H_{11}BrN_4O_5$ Mol. Wt. 371.14

7: yield 65%, white solid, m.p. 130–132°C.

^{1}H NMR (DMSO-*d6*): δ (ppm) 3.80–4.10 (m, 3H, H4′, H5′, H5″); 4.25–4.28 (m, 1H, H3′); 4.35–4.45 (m, 1H, H2′); 4.47, 4.58, 4.80 (br s, 3H, OH2′, OH3′, OH5′); 6.10 (d, 1H, J = 4.0 Hz, H1′); 8.40 (s, 1H, H2); 14.15 (br s, 1H, NH).

MALDI-TOF MS: *m/z* 372.15 Da $[M+H]^+$; 394.13 Da $[M+Na]^+$; 410.24 Da $[M+K]^+$. $C_{12}H_{11}BrN_4O_5$ Mol. Wt. 371.14

8-Benzylamino-7-Cyano-7-Deazainosine (6b)

To a solution of **4** (684 mg, 1 mmol) in dry dioxane (14 mL) an excess of benzylamine (3.3 mL, 30 mmol) was added and the solution was heated at 80°C. After 48 hours the mixture was concentrated in vacuo and co-evaporated with toluene (2 × 30 mL) and ethanol (2 × 30 mL). The crude product was purified by silica gel column chromatography (eluent: CH_2Cl_2/MeOH 95/5→80/20, v/v). The appropriate fractions were concentrated to afford compound **6b** as a white solid (yield 60%, m.p. 120–125°C).

^{1}H NMR (DMSO-*d6*): δ (ppm) 3.62–3.80 (m, 2H, H5′, H5″); 4.00–4.09 (m, 1H, H4′); 4.10–4.16 (m, 1H, H3′); 4.52–4.60 (m, 1H, H2′); 4.66 (d, 2H, J = 6.8 Hz, N-CH_2); 5.20–5.50 (br s, 2H, OH3′, OH5′); 5.95 (br s, 1H, OH2′); 6.19 (d, 1H, J = 8.0 Hz, H1′); 7.20–7.40 (m, 5H, Ph); 7.85 (s, 1H, H2); 7.92 (t, 1H, J = 6.8 Hz, NH).

MALDI-TOF MS: *m/z* 398.4 Da $[M+H]^+$; 420.37 Da $[M+Na]^+$. $C_{19}H_{19}N_5O_5$ Mol. Wt. 397.38

REFERENCES

1. Suhadolnik, R.J. In *Pyrrolopyrimidine Nucleosides in Nucleoside Antibiotics*. Wiley Interscience, New York, 1970, pp. 298–353 (and references therein).
2. Kasai, H.; Ohashi, Z.; Harada, F.; Nishimura, S.; Oppenheimer, N.J.; Crain, P.F.; Liehr, J.G.; von Minden, D.L.; McCloskey, J.A. Structure of modified nucleoside-Q isolated from Escherichia-Coli transfer ribonucleic-acid–7-(4,5-cis- dihydroxy-1-cyclopenten-3-ylaminomethyl)-7-deazaguanosine. *Biochemistry* **1975**, 14, 4198–4208.
3. Revankar, G.R.; Robins, R.K. In *Pyrrolo[2,3-d]pyrimidine (7-Deazapurine) Nucleosides in Chemistry of Nucleosides and Nucleotides*, ed. L.B. Townsend, Plenum Press, New York, 1991, pp. 200–247 (and references therein).
4. Seela, F.; Peng, X.; Li, H. Base-pairing, tautomerism, and mismatch discrimination of 7-halogenated 7-deaza-2′–deoxyisoguanosine: Oligonucleotides duplexes with parallel and antiparallel chain orientation. *J. Am. Chem. Soc.* 2005, 127, 7739–7751.
5. Li, H.; Peng, X.; Seela, F. Fluorescence quenching of parallel-stranded DNA bound ethidium bromide: the effect of 7-deaza-2′- deoxyisoguanosine and 7-halogenated derivatives. *Bioorg. Med. Chem. Lett.* **2004**, 14, 6031–6034.
6. a) Saito, Y.; Kato, K.; Umezawa, K. Synthesis and structure-activity relationship of ribofuranosyl echiguanine analogs as inhibitors of phosphatidylinositol 4-kinase. *Tetrahedron* **1998**, 54, 4251–4266. b) Tolman, R.L.; Robins, R.K.; Townsend, L.B. Pyrrolo[2,3-d]pyrimidine nucleoside antibiotics. Total synthesis and structure of toyocamicin, unamycin B, vengicide, antibiotic E-212, and sangivamycin (BA-90912). *J. Am. Chem. Soc.* **1968**, 90, 524–526.
7. a) Watanabe, S.; Ueda, T. Nucleosides and nucleotides. 41. Thiocyanation of tubercidin and its derivatization to 6-propyl-derivative and 6-cyano derivative. *Nucleosides & Nucleotides* 1982, 1, 191–203; b) Watanabe, S.; Ueda, T. Conversion of tubercidin to toyocamicin-some properties of tubercidin derivatives nucleosides and nucleotides. 47. **1983**, *Nucleosides Nucleotides 2*, 113–125.
8. Seela, F.; Peng, X. 7-functionalized 7-deazapurine ribonucleosides related to 2-aminoadenosine, guanosine, and xanthosine: Glycosylation of pyrrolo[2,3-d]pyrimidines with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose. *J. Org. Chem.* **2006**, 71, 81–90.
9. Peng, X.; Seela, F. Halogenated 7-deazapurine nucleosides: stereoselective synthesis and conformation of 2′-deoxy-2′-fluoro-beta-D-arabinonucleosides. *Org. Biomolecular Chem.* **2004**, 2, 2838–2846.
10. Bergstrom, D.E.; Brattesani, A.J. Halogenation of tubercidin by N-halosuccinimides. A direct route to a 5-bromotubercidin, a reversible inhibitor of RNA synthesis in eukaryotic cells. *Nucleic Acids Res.* **1980**, 8, 6213–6219.

11. Holmes, R.E., Robins R.K. Purine Nucleosides. VII. Direct Bromination of Adenosine, Deoxyadenosine, Guanosine, and Related Purine Nucleosides. *J. Am. Chem. Soc.* **1964**, 86, 1242–1245.
12. Porcari, A.R., and Townsend, L.B. An improved total synthesis of triciribine: a tricyclic nucleoside with antineoplastic and antiviral proprieties. *Nucleosides Nucleotides Nucleic Acids* **2004**, 23, 31–39.
13. Manfredini, S.; Angusti, A.; Veronese, A.C.; Durini, E.; Vertuani, S.; Nalin, F.; Solaroli, N.; Pricl, S.; Ferrone, M.; Mura, M.; Piano, M.A.; Poddessu, B.; Cadeddu, A., La Colla, P.; Loddo, R. Hindered nucleoside analogs as antiflaviviridae agents. *Pure Appl. Chem.* **2004**, 76, 1007–1015.
14. Bergstrom, D.E.; Brattesani, A.J. Halogenation of tubercidin by N-halosuccinimides. A direct route to a 5-bromotubercidin, a reversible inhibitor of RNA synthesis in eukaryotic cells. *Nucleic Acids Research* **1980**, 8, 6213–6219.
15. Tolman, R.L.; Robins, R.K.; Townsend, L.B. Pyrrolopyrimidine nucleosides. III. The total synthesis of toyocamycin, sangivamycin, tubercidin, and related derivatives. *J. Am. Chem. Soc.* **1969**, 91, 2102–2108.