SYNTHESIS OF 2',3'-DIDEOXY-D-ERYTHRO-HEX-2'-ENOPYRANOSYL NUCLEOSIDES FROM 5-AMINOURACILS AND 3,4,6-TRI-*O*-ACETYL-D-GLUCAL

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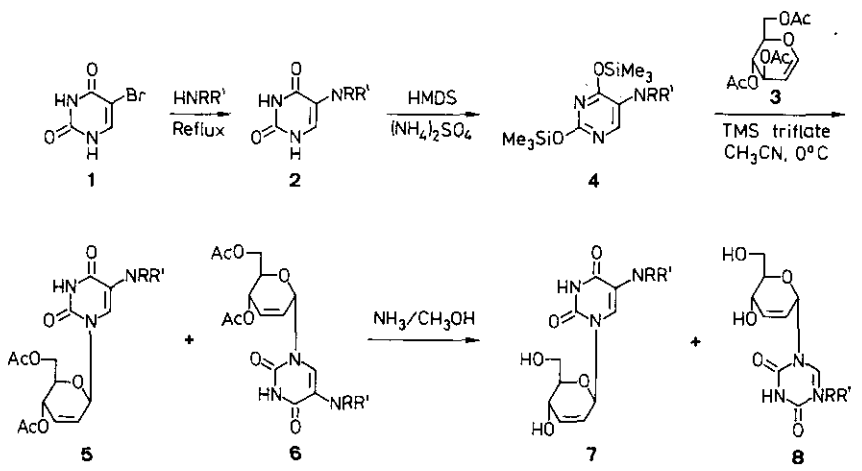
Abstract – Condensation of silylated *N,N*-disubstituted aminouracils (**4**) and 3,4,6-tri-O-acetyl-D-glucal (**3**) in the presence of TMS triflate as catalyst gave anomeric mixtures of 2',3'-dideoxy-D-*erythro*-hex-2'-enopyranosylnucleosides (**5**) and (**6**). The pure β- and α-anomers were separated by chromatography and deprotected with a saturated solution of ammonia in methanol to give 1-(2',3'-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)-5-aminouracils (**7**) and their corresponding α-anomers (**8**), respectively. The anomeric configurations of these nucleosides were assigned by nmr analysis of the dihydro derivatives **9** and **10** obtained by hydrogenation of **7a** and **8a**, respectively. No significant acitivity against HIV–1 was found.

Important advances[1] in virus chemotherapy have been made during the last few years using a variety of compounds with potent and selective antiviral activity.[1,2] This search has been further promoted by the advent of AIDS (acquired immunodeficiency syndrome) and the identification of a retrovirus, now termed human immunodeficiency virus (HIV), as the causative agent.[3] Nevertheless, there is a permanent need for an effective antiviral research towards new and more potent or selective drugs.

Various nucleoside derivatives having double bonds between C–2 and C–3 of the sugar portions are known to have antibiotic acitivity.[4] In AIDS therapy, the main interest of unsaturated compounds has been focused on furanosyl nucleosides,[5] whereas the interest in pyranosyl analogues has been stimulated by Blasticidin S being a 2'-enopyranosylcytosine with antibiotic and antitumoral activity.[6] Another important application of Blasticidin S is its action as fungicide against rice blast disease in Japan.[7] In this paper we describe a series of new *N,N*-disubstituted 5-aminouracils and their corresponding 2',3'-unsaturated pyranosyl nucleosides that may have interesting biological activities.

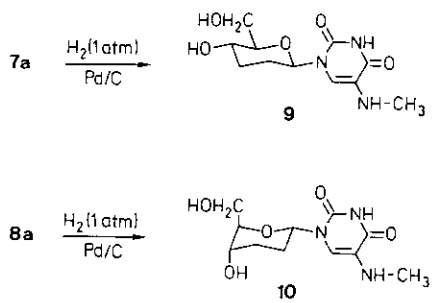


2,4-8	NRR'	2,4-8	
a	$N(CH_3)CH_2C_6H_5$	e	4-Methylpiperazinyl
b	Pyrrolidyl	f	4-Benzylpiperazinyl
c	4-Methylpiperidyl	g	$NHC_6H_4OC_2H_5$-4
d	$NH(CH_2)_5CH_3$		

For synthesis of the 5-aminouracils (**2**) we observed that 5-bromouracil (**1**) reacts rapidly to give moderate yields of **2** when refluxed with excess of the amines according to the procedures of Phillips[8] and Gerns.[9] The corresponding nucleosides were prepared according to the method of Bowles and Robins[10] by Lewis acid-catalysed condensation of **3** with **4** under simultaneous migration of the double bond in the sugar to the 2',3'-position. This reaction resulted in formation of an anomeric mixture of **5** and **6** ($\alpha/\beta \approx 1$), from which pure α- and β-anomers could be isolated in good yields by silica gel column chromatography. Compounds (**5**) and (**6**) were deacetylated with methanolic ammonia at room temperature to give **7** and **8**, respectively.

It is possible to assign anomeric configurations for this type of unsaturated nucleosides from the observed $J_{1',3'}$ and $J_{1',4'}$ coupling constants.[11,12] Lemieux[12] reported these coupling constants for the methyl 4',6'-*O*-benzylidene-2',3'-dideoxy-α- and β-D-*erythro*-hex-2'-enopyranosides as 0.3 and 1.5 Hz and 1.2 and 2.6 Hz, respectively. These two relatively large values, typical of the β-anomers, agree with the corresponding data for **7** (Table 4). To confirm the anomeric structures, we have hydrogenated the sugar double bond in **7a** and **8a** during which debenzylation of the amino group also took place (Scheme 2). The so formed saturated pyranose derivatives (**9**) and (**10**) were easily analyzed by ^1H–^1H homonuclear shift-correlated (COSY) 2D nmr. The nmr data of **9** indicate that the substituents at C–1', C–4' and C–5' are all equatorial with typical axial-axial coupling constants: $J_{1',2'a} = 9.7$ Hz, $J_{3'a,4'} = 11.4$ Hz and $J_{4',5'} = 10.3$ Hz. On the other hand, the α configuration of **10** is evidenced by $J_{1',2'a} = 10.2$ Hz, $J_{3'a,4'} = 2.5$ Hz and $J_{4',5'} = 1.3$ Hz which

are typical coupling constants for (1a,2a), (3a,4e) and (4e,5e) in pyranose rings.[13]



The compounds (**5a,b**), (**6b**), (**7a,e–g**) and (**8a,b,f,g**) were selected for biological evaluation, but no significant activity against HIV was found at sub-toxic concentrations in MT–4 cells. At 100 μM only compound (7e) showed cytotoxicity against MT–4 cells with TD_{50} = 8 μM.

EXPERIMENTAL

The nmr spectra were recorded on a Bruker AC 250 FT NMR spectrometer. Chemical shifts are reported in ppm, and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad). All exchangeable protons were confirmed by addition of D_2O. EI mass spectra were recorded on a Varian MAT 311A spectrometer. Microanalyses were done at NOVO Microanalytical Laboratory A/S, Novo Allé, DK–2880 Bagsvaerd. Column chromatography was performed on Merck silica gel (0.040–0.063 mm).

General method for preparation of **2a–f**.

A mixture of **1** (5.0 g, 26.2 mmol) and the appropriate amine (97 mmol) was heated for 2 to 15 min under reflux. **1** gradually dissolved and a yellowish solid was slowly formed. After cooling, the product was collected by filtration, washed with methanol and dried. Recrystallization from methanol gave **2a–f** as a white or off-white crystalline solid.

5-Pyrrolidyluracil (**2b**).

Yield 3.61 g (76%), mp 288–289°C. EIms: m/z = 181 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 1.56–1.92 (m, 4H, 2xCH_2), 2.96 (t, J = 6.0 Hz, 4H, 2xCH_2), 6.49 (s, 1H, 6–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 23.3 (2xCH_2), 49.3 (2xCH_2), 120.6 (C–5), 125.1 (C–6), 150.0 (C–2), 161.4 (C–4). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.00; H, 6.11; N, 23.31.

Table 1. Preparation of **5** and **6**.

No.	Reaction time (min)	Yield (%)	mp (°C)
5a	60	35	158–159
6a		32	– [a]
5b	15	40	140–141
6b		34	136–138
5c	60	33	146–148
6c		29	137–140
5d	30	24	145–149
6d		20	– [a]
5e	90	21	145–149
6e		18	– [a]
5f	60	33	161–162
6f		30	152–156
5g	90	23	– [a]
6g		16	– [a]

[a] Amorphous foam.

Table 2. Melting points and elemental analyses of **7** and **8b**[a].

No.	mp (°C)	Molecular formula	Analysis (calcd/found) C	H	N
7a	157	$C_{18}H_{21}N_3O_5 \cdot H_2O$	57.29	6.14	11.13
			57.44	6.21	11.15
7b	143–144	$C_{14}H_{19}N_3O_5 \cdot H_2O$	51.37	6.47	12.84
			51.51	6.50	12.81
7c	147–148	$C_{16}H_{23}N_3O_5 \cdot H_2O$	54.07	7.09	11.82
			54.62	7.17	11.96
7d	150–153	$C_{16}H_{25}N_3O_5 \cdot H_2O$	53.77	7.61	11.76
			53.94	7.64	11.82
7e	146–150	$C_{15}H_{22}N_4O_5 \cdot H_2O$	50.55	6.79	15.72
			51.26	6.62	15.47
7f	158–161	$C_{21}H_{26}N_4O_5 \cdot H_2O$	58.32	6.53	12.95
			57.96	6.56	12.97
7g	– [b]	$C_{18}H_{21}N_3O_6 \cdot H_2O$	54.96	5.89	10.68
			55.63	5.93	10.76
8b	140–141	$C_{14}H_{19}N_3O_5 \cdot H_2O$	51.37	6.47	12.84
			51.07	6.49	12.91

[a] 8a, c–g amorphous.
[b] Amorphous foam.

Table 3. ^{13}C Nmr spectral data ($CDCl_3$/TMS) of **7** and **8**.

No.	Carbohydrate C–1'	C–2'	C–3'	C–4'	C–5'	C–6'	Pyrimidine C–2	C–4	C–5	C–6
7a	78.5	137.5	128.1	61.9	80.1	61.7	149.5	160.7	120.7	126.9
8a	75.9	137.0	126.9	61.8	73.1	61.1	149.8	161.0	121.6	125.6
7b	78.5	137.2	128.6	61.9	80.0	61.7	149.4	160.4	113.2	126.5
8b	76.0	136.3	127.1	61.9	73.7	61.3	149.5	160.5	114.2	125.7
7c	78.5	137.5	128.7	61.9	80.3	61.7	149.5	160.5	120.7	126.4
8c	76.2	136.5	127.2	61.8	74.0	61.3	149.7	160.6	121.9	125.4
7d	78.6	137.3	128.6	61.9	80.1	61.7	148.5	160.4	106.3	126.4
8d	75.9	135.3	126.9	61.9	73.8	61.4	148.7	160.5	107.6	125.9
7e	78.6	137.5	128.1	61.9	80.1	61.6	149.2	160.3	122.4	127.8
8e	76.3	136.5	127.1	61.9	73.7	61.2	149.4	160.4	123.5	127.1
7f	78.6	137.0	128.4	61.8	80.2	61.6	149.5	161.0	120.0	128.0
8f	76.1	136.8	126.7	61.8	73.7	61.2	149.9	160.4	121.0	127.1
7g	78.6	137.4	128.3	61.7	80.1	61.6	149.9	161.0	118.5	133.2
8g	76.1	136.2	127.2	61.7	73.8	61.3	149.9	160.8	119.1	133.0

Table 4. ^{1}H Nmr data ($CDCl_3$/TMS) of **7**[a] and **8**[b].

No.	1'–H	2'–H	3'–H	4'–H	5'–H	6'–H	4'–OH	6'–OH	N^3–H	6–H
7a	6.44(dd)	5.52(dt)	6.19(dt)	4.33(m)	3.65(ddd)	3.87(m)	4.88(d)	4.55(t)	8.62(br)	6.40(s)
8a	6.29(dd)	5.52(dt)	6.31(dt)	4.31(m)	3.30(ddd)	3.72(m)	4.94(d)	4.53(t)	8.66(br)	6.86(s)
7b	6.50(dd)	5.50(dt)	6.18(dt)	4.35(m)	3.70(ddd)	3.86(m)	4.90(d)	4.57(t)	8.77(br)	6.22(s)
8b	6.37(dd)	5.77(dt)	6.29(dt)	4.25(m)	3.35(ddd)	3.78(m)	4.95(d)	4.53(t)	8.85(br)	6.61(s)
7c	6.46(dd)	5.99(dt)	6.20(dt)	4.37(m)	3.64(ddd)	3.95(m)	4.86(d)	4.55(t)	8.64(br)	6.51(s)
8c	6.34(dd)	6.03(dt)	6.29(dt)	4.23(m)	3.31(ddd)	3.73(m)	4.94(d)	4.52(t)	8.85(br)	6.83(s)
7d	6.32(dd)	5.51(dt)	6.04(dt)	4.34(m)	3.69(ddd)	3.88(m)	4.83(d)	4.51(t)	7.93(br)	6.08(s)
8d	6.11(dd)	5.57(dt)	6.16(dt)	4.11(m)	3.30(ddd)	3.74(m)	4.90(d)	4.51(t)	8.07(br)	6.44(s)
7e	6.47(dd)	5.71(dt)	6.24(dt)	4.39(m)	3.73(ddd)	3.86(m)	4.87(d)	4.55(t)	8.46(br)	6.18(s)
8e	6.33(dd)	5.76(dt)	6.31(dt)	4.18(m)	3.24(ddd)	3.74(m)	4.95(d)	4.54(t)	8.74(br)	6.73(s)
7f	6.45(dd)	5.67(dt)	6.19(dt)	4.38(m)	3.74(ddd)	3.87(m)	4.96(d)	4.61(t)	8.62(br)	6.49(s)
8f	6.33(dd)	5.77(dt)	6.28(dt)	4.23(m)	3.25(ddd)	3.70(m)	4.95(d)	4.52(t)	8.69(br)	6.85(s)
7g	6.44(dd)	5.53(dt)	6.14(dt)	4.40(m)	3.66(ddd)	3.82(m)	4.89(d)	4.55(t)	8.34(br)	6.45(s)
8g	6.27(dd)	5.69(dt)	6.26(dt)	4.19(m)	3.32(ddd)	3.72(m)	4.94(d)	4.51(t)	8.62(br)	6.82(s)

[a] Coupling constants in **7a–g**: J(Hz) = (1',2') = 1.5–1.8, (1',3') = 1.9–2.1, (1',4') = 2.2–2.4, (2',3') = 10.3, (2',4') = 1.6–1.7, (3',4') = 1.8–2.0, (4',5') = 8.5–9.1, (4',4'–OH) = 6.3–6.6, (6',6'–OH) = 5.8–5.9.

[b] Coupling constants in **8a–g**: J(Hz) = (1',2') = 2.1–2.5, (1',3') = 1.5–1.8, (1',4') = 1.2–1.4, (2',3') = 10.2–10.3, (2',4') = 1.4–1.9, (3',4') = 1.7–2.5, (4',5') = 7.3–8.6, (4',4'–OH) = 6.3–6.5, (6',6'–OH) = 5.3–5.8.

5-(4-Methylpiperidyl)uracil **(2c).**

Yield 4.44 g (81%), mp > 300° C. EIms: m/z = 209 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 0.91 (d, 3H, CH_3), 1.05–1.75 (m, 5H, 2xCH_2 and CH), 2.78 (t, J = 6.2 Hz, 4H, 2xCH_2), 6.47 (s, 1H, 6–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 21.7 (CH_3), 29.9 (CH), 33.7 (2xCH_2), 50.1 (2xCH_2), 125.8 (C–5), 126.9 (C–6), 150.2 (C–2), 161.4 (C–4). Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.34; H, 7.23; N, 20.14.

5-Hexylaminouracil **(2d).**

Yield 3.99 g (72%), mp 273–274° C. EIms: m/z = 211 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 0.89 (t, J = 6.6 Hz, 3H, CH_3), 1.09–1.66 (m, 8H, 4xCH_2), 2.79 (q, J = 6.5 Hz, 2H, CH_2), 4.17 (t, 6.5 Hz, 1H, NH), 6.31 (s, 1H, 6–H), 10.18 (s, 1H, N^1–H), 11.16 (s, 1H, N^3–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 14.0 (CH_3), 22.1 (CH_2), 26.4 (CH_2), 28.2 (CH_2), 31.1 (CH_2), 43.5 (CH_2), 112.3 (C–5), 124.1 (C–6), 149.4 (C–2), 161.4 (C–4). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.74; H, 8.13; N, 19.92.

5-(4-Methylpiperazinyl)uracil **(2e).**

Yield 3.58 g (65%), mp 275° C. EIms: m/z = 210 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 2.18 (s, 3H, CH_3), 2.39–2.51 (br, 4H, 2xCH_2), 2.81–2.99 (br, 4H, 2xCH_2), 6.72 (s, 1H, 6–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 45.6 (CH_3), 49.3 (2xCH_2), 54.4 (2xCH_2), 125.7 (C–5), 126.2 (C–6), 150.2 (C–2), 161.4 (C–4). Anal. Calcd for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.36; H, 6.70; N, 26.71.

5-(4-Benzylpiperazinyl)uracil **(2f).**

Yield 5.25 g (70%), mp > 300° C. EIms: m/z = 286 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 2.44 (s, 4H, 2xCH_2), 2.82 (s, 4H, 2xCH_2), 3.49 (s, 2H, CH_2), 6.71 (s, 1H, 6–H), 7.21–7.37 (m, 5H, Ar–H), 10.50 (s, 1H, N^1–H), 11.06 (s, 1H, N^3–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 49.5 (2xCH_2), 52.4 (2xCH_2), 62.0 (CH_2), 125.7 (C–5), 126.2 (C–6), 126.8 (Ph), 128.1 (Ph), 128.8 (Ph), 138.0 (Ph), 150.2 (C–2), 161.4 (C–4). Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 62.77; H, 6.37; N, 19.36.

5-(4-Ethoxyanilino)uracil **(2g).**

A solution of 1 (5.0 g, 26.2 mmol) and 4-ethoxyaniline (12.6 g, 91.7 mmol) (distilled from zinc) in ethylene glycol (75 ml) was heated under reflux for 2 h at 190–200° C in the presence of hydroquinone (200 mg). The crude product precipitated on cooling to room temperature. It was collected by filtration, washed with water and acetone, and dried. The product was recrystallised from glacial acetic acid with the aid of charcoal. Yield 5.44 g (84%), mp > 300° C. EIms: m/z = 247 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 1.28 (t, J =

6.9 Hz, 3H, CH_3), 3.92 (q, J = 6.9 Hz, 2H, CH_2), 6.58 (s, 1H, 6–H), 6.72–6.82 (m, 4H, Ar–H), 7.08 (s, 1H, NH), 10.46 (s, 1H, N^1–H), 11.25 (s, 1H, N^3–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 14.6 (CH_3), 63.2 (CH_2), 115.0 (Ar), 117.1 (Ar), 117.8 (C–5), 126.6 (C–6), 138.5 (Ar), 150.0 (C–2), 151.8 (Ar), 162.1 (C–4). Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.21; H, 5.30; N, 17.01.

General procedure for preparation of **5** *and* **6**.

2 (15.0 mmol) was silylated by heating with excess of hexamethyldisilazane (HMDS) (20 ml, 95 mmol) at 160° C for 3–4 h in the presence of ammonium sulphate (50 mg).[14] The excess HMDS was removed by co-distillation with 2 x 50 ml portions of dry toluene leaving a colorless liquid (**4**). To a solution of **3** (10.0 mmol) and **4** in dry acetonitrile (100 ml) at 0° C was added trimethylsilyl triflate (2.7 ml, 15.0 mmol). The resulting solution was stirred for 15–90 min until the glucal had completely disappeared on silica tlc with CH_3OH/CH_2Cl_2 (1:30). The reaction mixture was diluted with 250 ml of CH_2Cl_2 and washed with saturated sodium bicarbonate (200 ml) and with H_2O (200 ml), dried with Na_2SO_4, and evaporated *in vacuo* to give an anomeric mixture of **5** and **6**. Silica gel column chromatography (2 x 50 cm) with CH_2Cl_2/CH_3OH (50:1) of the residue afforded two pure anomers.

General procedure for preparation of **7** *and* **8**.

5 or 6 (200 mg) was added to a saturated solution of ammonia in methanol (25 ml) and stirred at room temperature overnight. The solvent was evaporated *in vacuo*. Silica gel chromatography with CH_2Cl_2/CH_3OH (10:1) to eluate the impurities was followed by eluation with methanol to afford the pure product **7** or **8**.

1-(2',3'-Dideoxy-β-D-erythro-hexopyranosyl)-5-methylaminouracil (**9**).

7a (200 mg) was hydrogenated in a hydrogen atmosphere at room temperature in methanol (15 ml) in the presence of 10% palladium on charcoal (200 mg) for 2 h. The catalyst was removed by filtration and the solvent was evaporated to leave **9** as a white crystalline solid. Yield 190 mg (96%), mp 220–223° C. EIms: m/z = 271 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 1.47–1.70 (m, 2H, 2'–H), 1.84–2.05 (m, 2H, 3'–H), 2.56 (d, J = 4.1 Hz, 3H, CH_3), 3.31 (m, 2H, 6'–H), 3.48 (ddd, J = 11.4 Hz, 10.3 Hz and 5.2 Hz, 1H, 4'–H), 3.70 (dd, J = 10.3 Hz and 2.0 Hz, 1H, 5'–H), 4.55 (t, J = 5.6 Hz, 1H, 6'–OH), 4.68 (d, J = 4.7 Hz, 1H, NH), 4.88 (d, J = 5.1 Hz, 1H, 4'–OH), 5.58 (d, J = 9.7 Hz, 1H, 1'–H), 6.37 (s, 1H, 6–H), 11.42 (br, 1H, N^3–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 28.2 (C–3'), 30.1 (CH_3), 31.5 (C–2'), 61.0 (C–6'), 64.0 (C–4'), 80.9 (C–1'), 83.4 (C–5'), 109.7 (C–5), 125.9 (C–6), 148.1 (C–2), 160.0 (C–4). Anal. Calcd for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.32; N, 15.49. Found: C, 48.26; H, 6.30; N, 15.52.

1-(2',3'-Dideoxy-α-D-erythro-hexopyranosyl)-5-methylaminouracil (**10**).

The same procedures as above for **9** are used to obtain the product (**10**) as an amorphous compound. Yield 180 mg (91%). EIms: m/z = 271 (M^+). ^{1}H–Nmr (DMSO–d_6/TMS): δ 1.49–1.75 (m, 2H, 2'–H), 1.88–2.19 (m, 2H, 3'–H), 2.57 (d, J = 4.5 Hz, 3H, CH_3), 3.60 (m, 2H, 6'–H), 3.78 (ddd, J = 5.1 Hz, 2.5 Hz and 1.3 Hz, 1H, 4'–H), 4.16 (d, J = 2.0 Hz, 1H, 5'–H), 4.65 (d, J = 5.1 Hz, 1H, NH), 4.81 (t, J = 5.3 Hz, 1H, 6'–OH), 5.01 (d, J = 5.5 Hz, 1H, 4'–OH), 5.76 (dd, J = 10.2 Hz and 2.8 Hz, 1H, 1'–H), 6.51 (s, 1H, 6–H), 11.35 (br, 1H, N^3–H). ^{13}C–Nmr (DMSO–d_6/TMS): δ 23.3 (C–3'), 26.3 (C–2'), 30.1 (CH_3), 60.0 (C–6'), 62.1 (C–4'), 77.1 (C–1'), 80.7 (C–5'), 109.9 (C–5), 125.8 (C–6), 148.1 (C–2), 160.0 (C–4). Anal. Calcd for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.32; N, 15.49. Found: C, 47.96; H, 6.36; N, 15.60.

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