Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1749–1752

TETRAHEDRON

An approach to acyclo-3-deazapyrimidine S-nucleosides via 3,5-dicyano-2(1*H*)-pyridinethiones

Adel M. E. Attia[a,*] and Abd El-Hamid A. A. Ismail[b]

[a]*Department of Chemistry, Faculty of Education, University of Tanta (Kafr El-Sheikh Branch) 33516, Egypt*
[b]*Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koom, Egypt*

Received 19 August 2002; revised 20 December 2002; accepted 16 January 2003

Abstract—A series of different acyclo-3-deazapyrimidine nucleosides have been synthesized. The site of glycosylation was confirmed by ^{13}C NMR spectroscopy. © 2003 Published by Elsevier Science Ltd.

Since the discovery of the utility of 3′-azido-3′-deoxythymidine (AZT)[1] and 2′,3′-dideoxyinosine (DDI)[2] as antiretroviral agents in spite of their toxic side effects,[3,4] the synthesis of other drugs has been desirable. Recently, a new class of anti-HIV agents has been identified. These compounds like 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT)[5,6] and 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442),[7,8] show a high selectivity for the HIV-1 reverse transcriptase. As part of our program of research on the synthesis of new thiopyrimidine and thiopyridine cyclic glycosides[9–13] with considerable antiviral activity, we report here the synthesis of a new class of acyclo-3-deazapyrimidine S-nucleosides related to HEPT and MKC-442. As far as we know this is the first coupling reaction of this type to be reported for pyridinethiones.

Thus it has been found that arylidenemalononitriles and arylidenecyanoacetates **1a–d** reacted with 2-cyanothioacetamide **2** in refluxing ethanol containing a catalytic amount of piperidine to give 3,5-dicycano-2(1*H*)-pyridinethiones **3a–d** in good yields after crystallization from absolute ethanol. The structures of the reaction products **3** were supported by their elemental analysis and spectral data (see Section 1). Compounds **3** can be coupled with different classes of acyclo sugars to give a novel series of acyclonucleosides. For example, **3** reacted with (2-acetoxyethoxy) methyl bromide[14] **4** in the presence of sodium hydride in dry dimethylformamide at 0°C to yield the corresponding 3,5-dicyano-2-[(2-acetoxyethoxy) methyl] pyridines **5a–d** after chromatographic purification. For the synthesis of 3,5-dicyano-2-[(ethoxy) methyl] pyridines **7a–d**, compounds **3a–d** were likewise treated with 1.1 equiv. of sodium hydride in dry dimethylformamide followed by 1.1 equiv. of the chloromethyl ethyl ether **6**. In all cases the yields were in the range of 75–82%.

The site of attachment of the alkyl substituent to the heterocyclic bases was concluded from their ^{13}C NMR spectral comparison with known structurally proven pyridine analogues. Thus, the observed shift of C-2 (163.2 ppm) in the ^{13}C NMR spectrum of the pyridine derivative **5a** clearly shown glycosidation on a sulfur atom and not on the nitrogen of 2-thiopyridines when compared with ^{13}C NMR spectra of S-methylated thiopyridine derivatives.[15,16] Deprotection of the hydroxy groups in the nucleosides **5a–d** with ammonia in methanol afforded the free acyclic nucleosides **8a–d** in 85–90% yield after crystallization from methanol. The structure of **8b** has been proved by ^{1}H NMR and ^{13}C NMR spectroscopy in DMSO solution. A strong downfield shift of the C-2 signal (162.8 ppm) is an unequivocal indication of the position of alkylation as well as of the disappearance of the acetoxy protons in its ^{1}H NMR spectrum (see Section 1).

In summary, the alkylation reactions of 3,5-dicyano-2(1*H*)-pyridinethiones with different classes of acyclic sugar halides provides a novel approach for the synthesis of precursors of some pyridine S-nucleosides. The obtained pyridine acyclonucleosides are now under biological evaluation (Scheme 1).

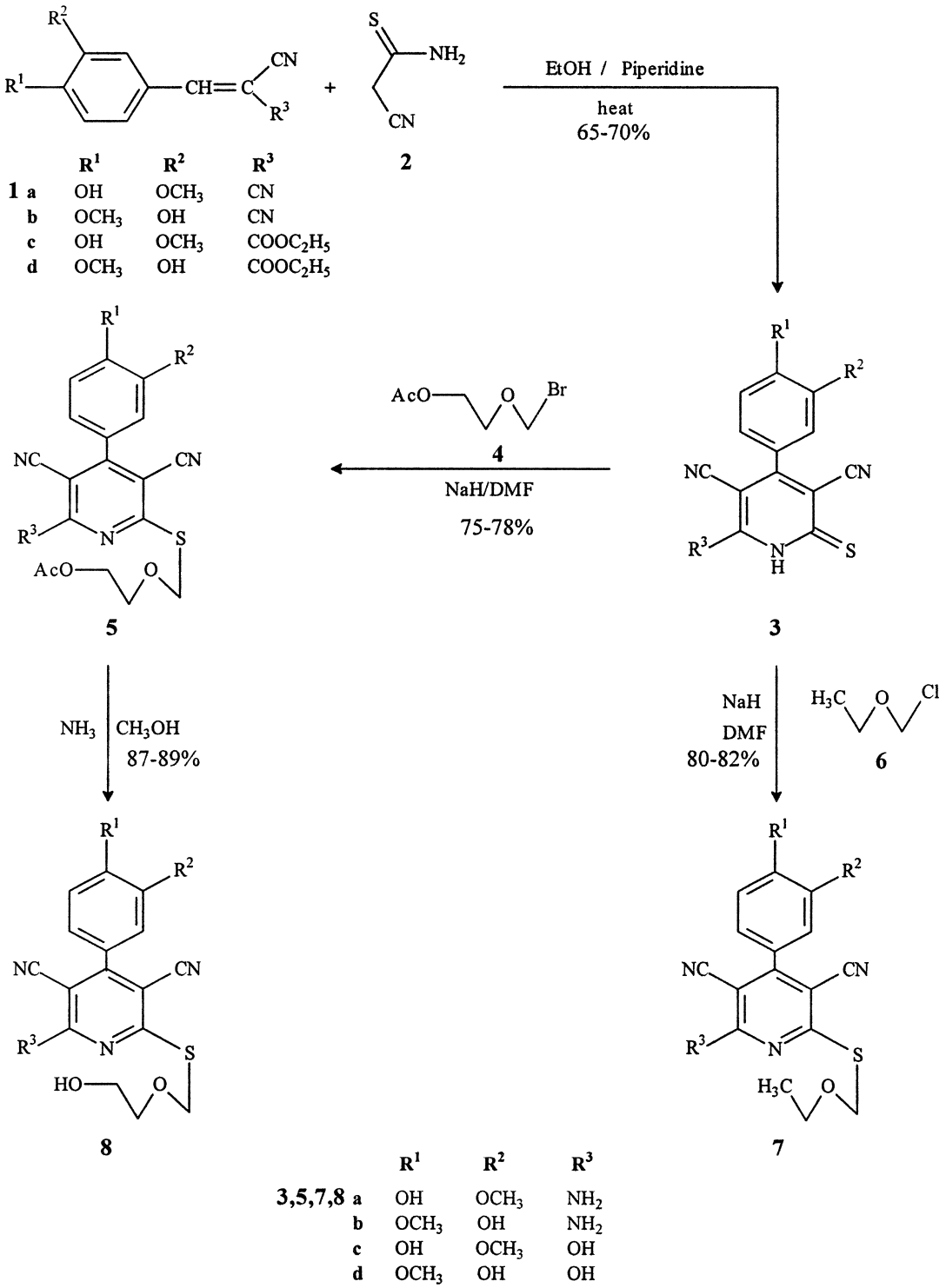
1. Experimental

1.1. General

Melting points are uncorrected. Aluminum-coated silica gel60 F_{254} (Merck) sheets were used for thin layer

Keywords: S-nucleosides; pyridinethiones; acyclonucleoside.
* Corresponding author. Tel./fax: +20-47-223415;
e-mail: adelmattia@hotmail.com; attia-a@edu-kaf.edu.eg

0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00113-3



	R^1	R^2	R^3
1 a	OH	OCH_3	CN
b	OCH_3	OH	CN
c	OH	OCH_3	$COOC_2H_5$
d	OCH_3	OH	$COOC_2H_5$

	R^1	R^2	R^3
3,5,7,8 a	OH	OCH_3	NH_2
b	OCH_3	OH	NH_2
c	OH	OCH_3	OH
d	OCH_3	OH	OH

Scheme 1.

chromatography. IR (KBr) spectra were collected in the transmission mode on a Pye Unicam Spectra-1000 spectrometer. ^1H and ^{13}C NMR spectra were measured in DMSO-d_6 using $SiMe_4$ as internal reference on a Varian 400 MHz spectrometer. Mass spectra were recorded by EI on a Varian Mat 311A spectrometer and FAB on a Kratos MS 50 spectrometer.

1.1.1. 3,5-Dicyano-4-aryl-2(1*H*)-pyridinethiones (3). *General procedure*. To a suspension of 2-cyanocinnamonitriles **1** (0.01 mol) and 2-cyanothioacetamide **2** (0.01 mol) in dry ethanol (30 mL), a few drops of piperidine were added. The reaction mixture was refluxed for a variable length of time (8–12 h) until the starting material was exhausted and a solid had been precipitated. It was filtered off and recrystallized from absolute ethanol to afford the title compounds **3a–d**.

Compound **3a**. Yield 68% as yellow crystals, mp 232°C. [Found: C, 56.64; H, 3.59; N, 18.95 $C_{14}H_{10}N_4SO_2$ requires

C, 56.38; H, 3.36; N, 18.79%]; ν_{max} 3450–3180 (OH, NH_2 and NH), 2218 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.92 (3H, s, OCH_3), 7.67–7.74 (3H, m, Ar-H), 7.87 (1H, s, NH), 8.34 (2H, s, NH_2), 9.78 (1H, s, OH); δ_C (DMSO-d_6) 55.6 (OCH_3), 101.8 (C5), 112.6 (C3), 115.2 (CN), 116.1 (CN), 121.4–148.2 (Ar-C), 155.7 (C4), 157.3 (C6), 182.4 (C2); *m/z* 298.

Compound **3b**. Yield 70% as yellow crystals, mp 208°C. [Found: C, 56.71; H, 3.52; N, 19.06 $C_{14}H_{10}N_4SO_2$) requires C, 56.38; H, 3.36; N, 18.79%]; ν_{max} 3470–3200 (OH, NH_2 and NH), 2220 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.96 (3H, s, OCH_3), 7.62–7.71 (3H, m, Ar-H), 7.86 (1H, s, NH), 8.28 (2H, s, NH_2), 9.70 (1H, s, OH); δ_C (DMSO-d_6) 55.5 (OCH_3), 101.9 (C5), 112.2 (C3), 115.4 (CN), 116.1 (CN), 121.8–149.2 (Ar-C), 154.8 (C4), 158.0 (C6), 182.1 (C2); *m/z* 298.

Compound **3c**. Yield 66% as yellow crystals, mp 198°C. [Found: C, 56.61; H, 3.23; N, 14.39 $C_{14}H_9N_3SO_3$ requires C, 56.19; H, 3.01; N, 14.05%]; ν_{max} 3450–3190 (OH and NH), 2215 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.88 (3H, s, OCH_3), 7.10–7.18 (3H, m, Ar-H), 7.68 (1H, s, NH), 8.48 (1H, s, OH), 9.14 (1H, s, OH); δ_C (DMSO-d_6) 55.4 (OCH_3), 101.7 (C5), 111.6 (C3), 115.2 (CN), 116.3 (CN), 119.4–148.7 (Ar-C), 156.0 (C4), 156.8 (C6), 183.4 (C2); *m/z* 299.

Compound **3d**. Yield 65% as yellow crystals, mp 220°C. [Found: C, 56.58; H, 3.24; N, 14.37 $C_{14}H_9N_3SO_3$ requires C, 56.19; H, 3.01; N, 14.05%]; ν_{max} 3430–3180 (OH and NH), 2222 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.90 (3H, s, OCH_3), 7.12–7.21 (3H, m, Ar-H), 7.49 (1H, s, NH), 8.14 (s, 1H, OH), 9.44 (1H, s, OH); δ_C (DMSO-d_6) 55.6 (OCH_3), 101.9 (C5), 112.6 (C3), 115.1 (CN), 116.3 (CN), 121.4–148.1 (Ar-C), 155.9 (C4), 157.1 (C6), 182.5 (C2); *m/z* 299.

1.1.2. 3,5-Dicyano-4-aryl-2-[(2-acetoxyethoxy)methyl] pyridines (5). *General procedure*. To a stirred solution of pyridinethiones **3** (1 mmol) in dry dimethylformamide (25 mL) was added (1.1 mmol) of sodium hydride. After evolution of hydrogen had ceased, the mixture was cooled to −10°C and a solution of (2-acetoxyethoxy) methyl bromide **4** (1.1 mmol) in DMF (5 mL) was added slowly. The stirred mixture was allowed to warm slowly to room temperature over a period of 2 h, 0.5 mL of 1 M $NaHCO_3$ (aq) was added, and volatile materials were evaporated in vacuo. The residue was applied to a silica gel column and elution with chloroform–methanol (19:1) afforded the desired nucleosides as a white solid, which then were recrystallized from chloroform–petroleum ether 40–60 to give the title compounds **5a**–**d**.

Compound **5a**. Yield 78% as white crystals, mp 159°C. [Found: C, 55.39; H, 4.60; N, 13.88 $C_{19}H_{18}N_4SO_5$ requires C, 55.07; H, 4.35; N, 13.53%]; ν_{max} 3450–3220 (OH and NH_2), 2214 (CN), 1736 (CO) cm^{-1}; δ_H (DMSO-d_6) 2.03 (3H, s, CH_3CO), 3.88 (3H, s, OCH_3), 4.32 (2H, t, *J*=4.7 Hz, 2H-3′), 4.93 (2H, t, *J*=4.7 Hz, 2H-4′), 5.67 (2 H, s, 2H-1′), 7.08–7.22 (3H, m, Ar-H), 8.02 (2H, s, NH_2), 9.66 (1H, s, OH); δ_C (DMSO-d_6) 20.6 (CH_3), 55.8 (OCH_3), 61.9 (C4′), 64.6 (C3′), 79.8 (C1′), 94.8 (C5), 112.9 (C3), 115.2 (CN), 115.9 (CN), 121.7–157.5 (Ar-C), 158.1 (C4), 159.7 (C6), 163.2 (C2), 170.1 (CO); *m/z* 414.

Compound **5b**. Yield 76% as white crystals, mp 169°C. [Found: C, 55.46; H, 4.57; N, 13.79 $C_{19}H_{18}N_4SO_5$ requires C, 55.07; H, 4.35; N, 13.53%]; ν_{max} 3480–3240 (OH and NH_2), 2215 (CN), 1738 (CO) cm^{-1}; δ_H (DMSO-d_6) 2.01 (3H, s, CH_3CO), 3.85 (3H, s, OCH_3), 4.25 (2H, t, *J*=5.0 Hz, 2H-3′), 4.84 (2H, t, *J*=5.0 Hz, 2H-4′), 5.80 (2H, s, 2H-1′), 7.05–7.14 (3H, m, Ar-H), 7.98 (2H, s, NH_2), 9.44 (1H, s, OH); δ_C (DMSO-d_6) 20.8 (CH_3), 55.5 (OCH_3), 62.8 (C4′), 67.3 (C3′), 81.4 (C1′), 102.2 (C5), 111.7 (C3), 115.1 (CN), 116.7 (CN), 119.5–149.6 (Ar-C), 154.4 (C4), 158.3 (C6), 163.5 (C2), 170.9 (CO); *m/z* 414.

Compound **5c**. Yield 75% as white crystals, mp 150°C. [Found: C, 55.31; H, 4.36; N, 10.40 $C_{19}H_{17}N_3SO_6$ requires C, 54.94; H, 4.10; N, 10.12%]; ν_{max} 3420–3280 (OH), 2210 (CN), 1740 (CO) cm^{-1}; δ_H (DMSO-d_6) 2.04 (3H, s, CH_3CO), 3.86 (3H, s, OCH_3), 4.31 (2H, t, *J*=4.8 Hz, 2H-3′), 4.94 (2H, t, *J*=4.8 Hz, 2H-4′), 5.70 (2 H, s, 2H-1′), 7.09–7.18 (3H, m, Ar-H), 8.68 (1H, s, OH), 9.46 (1H, s, OH); δ_C (DMSO-d_6) 20.5 (CH_3), 55.6 (OCH_3), 61.9 (C4′), 64.6 (C3′), 87.1 (C1′), 94.9 (C5), 111.8 (C3), 115.0 (CN), 115.4 (CN), 119.9–148.4 (Ar-C), 158.1 (C4), 159.7 (C6), 163.1 (C2), 170.2 (CO); *m/z* 415.

Compound **5d**. Yield 77% as white crystals, mp 128°C. [Found: C, 55.37, H, 4.29; N, 10.43 $C_{19}H_{17}N_3SO_6$ requires C, 54.94; H, 4.10; N, 10.12%]; ν_{max} 3410–3260 (OH), 2212 (CN) cm^{-1}; δ_H (DMSO-d_6) 2.09 (3H, s, CH_3CO), 3.82 (3H, s, OCH_3), 4.30 (2H, t, *J*=5.2 Hz, 2H-3′), 4.98 (2H, t, *J*= 5.2 Hz, 2H-4′), 5.54 (2H, s, 2H-1′), 7.11–7.21 (3H, m, Ar-H), 8.96 (1H, s, OH), 9.71 (1H, s, OH); δ_C (DMSO-d_6) 20.7 (CH_3), 55.7 (OCH_3), 61.9 (C4′), 68.4 (C3′), 83.0 (C1′), 98.1 (C5), 112.2 (C3), 115.4 (CN), 115.6 (CN), 121.1–147.9 (Ar-C), 157.5 (C4), 158.6 (C6), 163.2 (C2), 170.8 (CO); *m/z* 415.

1.1.3. 3,5-Dicyano-4-aryl-2-[(ethoxy) methyl] pyridines (7). *General procedure*. To a stirred solution of pyridinethiones **3** (1 mmol) in dry dimethylformamide (25 mL) was added (1.1 mmol) of sodium hydride. After evolution of hydrogen had ceased, the mixture was cooled to 0°C and a solution of ethoxymethyl chloride **6** (1.1 mmol) in DMF (5 mL) was added slowly. The stirred mixture was allowed to warm slowly to room temperature over a period of 3 h and then quenched with saturated $NaHCO_3$ (20 mL). The aqueous phase was extracted with $CHCl_3$ (2×20 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The product was purified by silica gel column chromatography (50% EtOAc–PE) to give the title compounds **7a**–**d**.

Compound **7a**. Yield 82% as white crystals, mp 146°C. [Found: C, 57.58; H, 4.73; N, 15.99 $C_{17}H_{16}N_4SO_3$ requires C, 57.30; H, 4.49; N, 15.73%], ν_{max} 3450–3230 (OH and NH_2), 2218 (CN) cm^{-1}; δ_H (DMSO-d_6) 1.13 (3H, t, *J*= 6.8 Hz, CH_3), 3.84 (3H, s, OCH_3), 4.60 (2H, q, *J*=6.8 Hz, OCH_2), 5.52 (2H, s, SCH_2), 7.07–7.20 (3H, m, Ar-H), 7.95 (2H, s, NH_2), 9.73 (1H, s, OH); *m/z* 356.

Compound **7b**. Yield 80% as white crystals, mp 123°C. [Found: C, 57.61; H, 4.70; N, 16.05 $C_{17}H_{16}N_4SO_3$ requires C, 57.30; H, 4.49; N, 15.73%]; ν_{max} 3390–3210 (OH and NH_2), 2215 (CN) cm^{-1}; δ_H (DMSO-d_6) 1.18 (3H, t,

J=7.1 Hz, CH_3), 3.88 (3H, s, OCH_3), 4.54 (2H, q, J= 7.1 Hz, OCH_2), 5.46 (2H, s, SCH_2), 7.06–7.15 (3H, m, Ar-H), 7.90 (2H, s, NH_2), 9.48 (1H, s, OH); δ_C (DMSO-d_6) 13.8 (CH_3), 55.5 (OCH_3), 69.6 (OCH_2), 83.8 (SCH_2), 94.9 (C5), 111.8 (C3), 115.1 (CN), 115.5 (CN), 120.8–149.1 (Ar-C), 155.3 (C4), 157.0 (C6), 162.9 (C2); *m/z* 356.

Compound **7c**. Yield 80% as white crystals, mp 152°C. [Found: C, 57.49; H, 4.38; N, 12.03 $C_{17}H_{15}N_3SO_4$ requires C, 57.14; H, 4.20; N, 11.76%]; ν_{max} 3420–3215 (OH), 2220 (CN) cm^{-1}; δ_H (DMSO-d_6) 1.17 (3H, t, J=7.0 Hz, CH_3), 3.85 (3H, s, OCH_3), 4.62 (2H, q, J=7.0 Hz, OCH_2), 5.53 (2H, s, SCH_2), 7.15–7.24 (3H, m, Ar-H), 8.64 (1H, s, OH), 9.71 (1H, s, OH); *m/z* 357.

Compound **7d**. Yield 81% as white crystals, mp 170°C. [Found: C, 57.53; H, 4.42; N, 11.99 $C_{17}H_{15}N_3SO_4$ requires C, 57.14; H, 4.20; N, 11.76%]; ν_{max} 3460–3280 (OH), 2216 (CN) cm^{-1}; δ_H (DMSO-d_6) 1.20 (3H, t, J=6.9 Hz, CH_3), 3.80 (3H, s, OCH_3), 4.68 (2H, q, J=6.9 Hz, OCH_2), 5.56 (2H, s, SCH_2), 7.08–7.17 (3H, m, Ar-H), 8.96 (1H, s, OH), 9.46 (1H, s, OH); δ_C (DMSO-d_6) 13.9 (CH_3), 55.7 (OCH_3), 68.4 (OCH_2), 82.3 (SCH_2), 98.4 (C5), 112.6 (C3), 115.4 (CN), 116.1 (CN), 119.9–149.2 (Ar-C), 154.4 (C4), 158.1 (C6), 163.3 (C2); *m/z* 357.

1.1.4. 3,5-Dicyano-4-aryl-2-[(2-hydroxyethoxy) methyl] pyridines (8). *General procedure*. Saturated ammonia in methanol (20 mL) was added with stirring to a solution of **5** (2 mmol) in methanol (10 mL) at 0°C. The mixture was stirred at 0°C for 4 h and then at room temperature for 12 h (monitored by TLC analysis). Volatile materials were evaporated in vacuo and the resulting solid was recrystallized from methanol to give analytically pure compounds **8a–d**.

Compound **8a**. Yield 88% as white crystals, mp 199°C. [Found: C, 55.23; H, 4.51; N, 15.39 $C_{17}H_{16}N_4SO_4$ requires C, 54.84; H, 4.30; N, 15.05%]; ν_{max} 3380–3220 (OH and NH_2), 2213 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.58 (2H, t, J= 4.8 Hz, 2H-3′), 3.86 (3H, s, OCH_3), 4.12 (2H, t, J=4.8 Hz, 2H-4′), 4.60 (1H, s, OH), 5.78 (2H, s, 2H-1′), 7.13–7.22 (3H, m, Ar-H), 8.08 (2H, s, NH_2), 9.49 (1H, s, OH); *m/z* 372.

Compound **8b**. Yield 87% as white crystals, mp 226°C. [Found: C, 55.19; H, 4.44; N, 15.36 $C_{17}H_{16}N_4SO_4$ requires C, 54.84; H, 4.30; N, 15.05%]; ν_{max} 3400–3210 (OH and NH_2), 2215 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.66 (2H, t, J= 4.9 Hz, 2H-3′), 3.90 (3H, s, OCH_3), 4.05 (2H, t, J=4.9 Hz, 2H-4′), 4.82 (1H, s, OH), 5.74 (2H, s, 2H-1′), 7.19–7.28 (3H, m, Ar-H), 8.12 (2H, s, NH_2), 9.40 (1H, s, OH); δ_C (DMSO-d_6) 55.2 (OCH_3), 59.9 (C4′), 70.5 (C3′), 76.8 (C1′), 101.8 (C5), 110.3 (C3), 115.3 (CN), 116.4 (CN), 120.6–146.8 (Ar-C), 155.4 (C4), 158.0 (C6), 162.8 (C2); *m/z* 372.

Compound **8c**. Yield 89% as white crystals, mp 190°C. [Found: C, 54.96; H, 4.27; N, 11.55 $C_{17}H_{15}N_3SO_5$ requires C, 54.69; H, 4.02; N, 11.26%]; ν_{max} 3420–3230 (OH), 2212 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.68 (2H, t, J=5.2 Hz, 2H-3′), 3.88 (3H, s, OCH_3), 4.08 (2H, t, J=5.2 Hz, 2H-4′), 4.56 (1H, s, OH), 5.82 (2H, s, 2H-1′), 7.18–7.25 (3H, m, Ar-H), 8.64 (1H, s, OH), 9.42 (1H, s, OH); *m/z* 373.

Compound **8d**. Yield 88% as white crystals, mp 188°C. [Found: C, 55.04; H, 4.20; N, 11.49 $C_{17}H_{15}N_3SO_5$ requires C, 54.69; H, 4.02; N, 11.26%]; ν_{max} 3410–3200 (OH), 2214 (CN) cm^{-1}; δ_H (DMSO-d_6) 3.74 (2H, t, J=5.4 Hz, 2H-3′), 3.85 (3H, s, OCH_3), 3.98 (2H, t, J=5.4 Hz, 2H-4′), 4.55 (1H, s, OH), 5.80 (2H, s, 2H-1′), 7.23–7.34 (3H, m, Ar-H), 8.72 (1H, s, OH), 9.51 (1H, s, OH); *m/z* 373.

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