Tetrahedron 64 (2008) 8078–8081

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent-free, microwave assisted 1,3-cycloaddition of nitrones with vinyl nucleobases for the synthesis of *N*,*O*-nucleosides

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ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 4 June 2008
Accepted 19 June 2008
Available online 24 June 2008

ABSTRACT

A number of 4′-aza-2′,3′-dideoxy nucleosides have been synthesized in good yields and short reaction times by straightforward microwave assisted 1,3-cycloaddition of vinyl nucleobases with nitrones, in the absence of solvent. The vinyl nucleobases are used, for the first time, in their unprotected form.

1. Introduction

There is an increasing interest in the synthesis of modified nucleosides in connection with their potential applications in antiviral and anticancer therapies. In particular, modified nucleosides have been proved to efficiently inhibit in vitro and in vivo virus infections caused by HIV, HBV, and HTLV-1.[1] In a recent approach to modified nucleosides, the furanose ring was replaced with *N*,*O*-containing five membered heterocycles, in particular isoxazolidine and isoxazoline derivatives.[2] For this reason, new routes for the synthesis of isoxazolidine based compounds are highly desirable, with 1,3-dipolar cycloadditions of nitrones being the most straightforward route to these derivatives.[3] Among the different strategies for the preparation of nucleosides using this protocol, the insertion of the nucleobase via nucleophilic substitution of a suitable leaving group on the isoxazolidinyl cycloadduct[2] or, alternatively, the cycloaddition reaction on an appropriate vinyl nucleobase acting as dipolarophile is the most used.[4] This latter strategy suffers, however, of two major drawbacks: (i) the difficulty in obtaining *N*-vinyl derivatives of all nucleic acid bases and (ii) the drastic experimental conditions necessary to obtain cycloaddition products in satisfactory yields. In recent years these limitations have been successfully overcome, and the whole set of *N*-vinyl nucleobases may now be prepared in a convenient, efficient, and simple way, using trimethylsilyl trifluoromethane sulfonate as catalyst.[5]

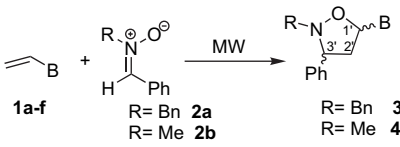
On the other hand, we have shown that 1,3-dipolar cycloadditions between nitrones and vinyl derivatives, including *N*-vinyl thymine, may be carried out at room temperature, in good yields and short reaction times, in ionic liquids, using $Er(OTf)_3$ as catalyst.[6]

We disclose here a further modification of this synthetic strategy consisting of a direct 1,3-dipolar cycloaddition between nitrones and vinyl nucleobases, assisted by microwave irradiation,[7] in the absence of solvent. Notably, no protection is required for the vinyl nucleobases during cycloaddition.

2. Results and discussion

Microwave irradiation (MW) has been used for the rapid synthesis of a variety of compounds[8] and this technique, under solvent-free conditions, is regarded as an environmentally acceptable practice for a number of reasons, including the fact that the reactions are quite often cleaner, faster, and higher yielding than conventional synthesis.[9]

The direct 1,3-dipolar cycloadditions between the model *N*-benzyl- or *N*-methyl-*C*-phenyl nitrone **2a**,**b** and a set of vinyl nucleobases **1a**–**f**, acting as dipolarophiles, in the absence of solvent and under microwave irradiation conditions were carried out according to Scheme 1, and the pertinent results are collected in Table 1. The procedure is simple and straightforward consisting of the co-grinding of the two components in a mortar, further mixing



B= thymine (**1a**); uracil (**1b**); cytosine (**1c**); 5-fluoro cytosine (**1d**); adenine (**1e**); 2-(*N*-trityl) guanine (**1f**)

Scheme 1.

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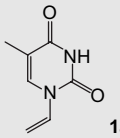
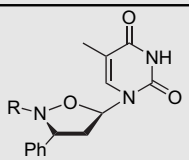
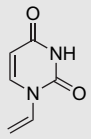
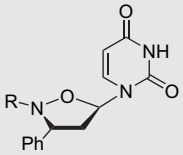
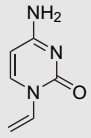
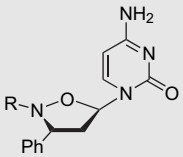
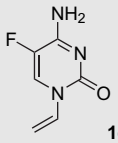
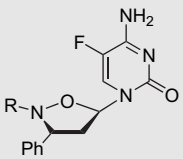
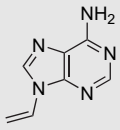
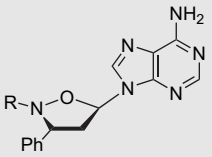
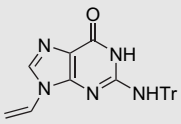
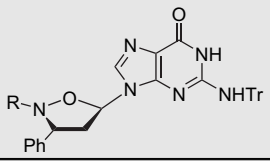
doi:10.1016/j.tet.2008.06.074

Table 1
Solvent-free 1,3-dipolar cycloaddition of unprotected vinyl nucleobases **1a**–**f** with *N*-benzyl-*C*-phenyl nitrone **2a** and *N*-methyl-*C*-phenyl nitrone **2b** under microwave irradiation[a]

Entry	*N*-Vinyl nucleobases	Nitrones	Time (min)	Products		*endo*/*exo* ratio	Yield %[b]
1	 **1a**	**2a**	10		**3a**	80:20	80
2		**2b**	15		**4a**	80:20	80
3	 **1b**	**2a**	12		**3b**	78:22	80
4		**2b**	20		**4b**	70:30	80
5[c]	 **1c**	**2a**	25		**3c**	75:25	50
6[c]		**2b**	25		**4c**	65:35	60
7[c]	 **1d**	**2a**	25		**3d**	84:16	90
8[c]		**2b**	25		**4d**	71:29	90
9	 **1e**	**2a**	20		**3e**	70:30	70
10		**2b**	20		**4e**	72:28	72
11	 **1f**	**2a**	50		**3f**	75:25	20

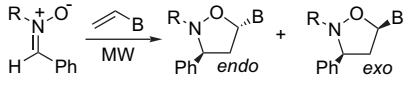
[a] Vinyl nucleobase/nitrone ratio 1:2.
[b] Isolated yields after column chromatography.
[c] Vinyl nucleobase/nitrone ratio 2:1.

of the solids in a vortex, followed by transfer of the mixture in an apposite open vessel, that is placed within a household microwave oven, at 750 W irradiation power, for times ranging from 10 min up to 50 min.

After the appropriate time the reaction mixture, that appeared as a syrup, is dissolved in $CHCl_3$ or MeOH and analyzed by TLC. The product is purified by flash column chromatography and the isolated cycloadducts are subjected to ^1H, ^{13}C NMR spectroscopy and ESI-MS analysis for identification. The unreacted nitrone is equally recovered from the chromatographic separation and may be reused without loss of efficiency or selectivity. As an example, the cycloaddition of *N*-vinyl thymine and nitrone **2a**, as obtained from previous reactions, afforded **3a** in 78% yield in identical reaction times. In the majority of the entries, the cycloaddition products are formed fast and with final yields ranging from acceptable to very good, Table 1.

Worthy of note is the fact that the cycloadditions proceed directly on unprotected vinyl nucleobases, with the only exception being *N*-vinyl guanine. No product is detected using this vinyl derivative, and only modest amounts of cycloadduct are found when employing the protected tritylated derivative **1f**, entry 11. The unnecessary protection of the vinyl nucleobase, and consequent deprotection of the resulting *N*,*O*-nucleoside, represent an interesting improvement characterizing the overall synthetic protocol.

The stereochemical outcome of the reaction showed a certain degree of control that appeared to be very highly regioselective with formation of the 1′-substituted isoxazolidines only.[6] On the other hand, the *endo*/*exo* ratio is satisfactory, in the range 70:30 with a maximum value of 84:16 for the 5-fluoro cytosine derivative, entry 7 of Table 1 and Scheme 2.



Scheme 2.

The assigned *endo*/*exo* stereochemical output, as established by accurate ^{1}H NMR spectroscopic analysis, is based on the *J* values measured for the coupling of proton H_a with protons at C2′ and proton H_d with protons at C2′, in the substantiated assumption, applicable to isoxazolidines,[10] that cis vicinal ^{1}H couplings are always higher than the trans.[11] As an example, in the cytosine derivative **3c** the values of coupling constants J_{Ha-Hc}=4.4 Hz and J_{Ha-Hb}=7.5 Hz indicate that H_a is trans to H_c and cis to H_b. Furthermore the values of coupling constants J_{Hd-Hb}=7.6 Hz and J_{Hd-Hc}=9.9 Hz indicate that H_d is trans to H_b and cis to H_c, thereby establishing that H_a and H_d are trans each other (*endo* isomer), Figure 1.

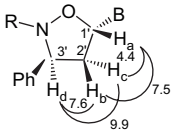


Figure 1. ^{1}H NMR coupling constants expressed in hertz.

Similarly, the most abundant epimer of the *N*-methyl substituted cytosine **4c** has been recognized as the *endo* isomer on the following basis: J_{Ha-Hc}=4.3 Hz, J_{Ha-Hb}=7.6 Hz, J_{Hd-Hb}=7.7 Hz, and J_{Hd-Hc}= 9.9 Hz.

The ESI-MS analysis of **3a**–**f** and **4a**–**e** nucleobases showed the presence of $[MH]^+$ ions and little fragmentation. The protonated molecular ions, submitted to MS/MS experiments, decomposed via cleavage of the nucleosidic bond with preferential formation of the isoxazolidine ion at *m*/*z* 238 (R=Bn) and 162 (R=Me), respectively.

As a final consideration, it should be noted that the 1,3-dipolar cycloaddition protocol presented in this paper is one of the few examples of microwave mediated cycloadditions that proceeded in the absence of solvent,[12] taking into account that from an environmental point of view '*the best solvent is no solvent*'.[13]

3. Conclusions

In summary, we have shown an expeditious, easy-to-handle, and environmentally friendlier approach to the synthesis of a variety of non-easily-available 4′-aza-2′,3′-dideoxy nucleosides prepared for the first time from unprotected vinyl nucleobases. Studies aimed to establish the biological activity of these compounds are currently under way.

4. Experimental

4.1. General

Vinyl nucleobases[5] **1a**–**f** and nitrones[14,15] **2a**,**b** were synthesized according to published procedures. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz). Chemical shifts are given in parts per million from TMS and coupling constants in hertz. The *endo*/*exo* product composition was established by ^{1}H NMR spectroscopy using the *J* values between coupling of proton H_a with protons at C2′ and proton H_d with protons at C2′, Figure 1.[11] The mass spectrometric experiments were carried out on a Finnigan LCQ Deca, equipped with an electrospray ionization source. Standard experimental conditions are as follows: sample concentration 10^{-6} M; elution solvent MeOH; flow rate 8 μL min^{-1}; nebulizing gas 40 units flow rate; spray voltage 4 kV; capillary voltage 14 V; capillary temperature 270 °C. Melting points were obtained on a Kofler apparatus.

4.2. Typical experimental procedure

The selected vinyl nucleobase (0.1 mmol) and the nitrone (0.2 mmol) are co-grinded in a mortar and further mixed in a vortex. The mixture of the two solids is transferred in a 50 mL Pyrex container that is placed within an unmodified household microwave oven, at 750 W irradiation power. For cytosine and 5-fluoro cytosine the molar ratio is overturned, see footnote c of Table 1. After the appropriate time the reaction mixture is submitted to flash chromatographic separation, using variable mixtures of chloroform and methanol. The nitrone in excess is recovered and may be re-used.

4.3. Product characterization

*4.3.1. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy thymidine (**3a**)*

White solid, mp 71–72 °C. ESI-MS $[MH]^+$ *m*/*z* 364; δ_H ($CDCl_3$) 1.81 (d, *J*=1.2 Hz, 3H, Thy CH_3), 2.36 (ddd, *J*=3.8, 9.8, 13.9 Hz, 1H, H_c), 3.35 (dt, *J*=7.5, 7.6, 13.8 Hz, 1H, H_b), 3.70 (d, *J*=14.0 Hz, 1H, CH_2–Ph), 3.92 (dd, *J*=7.5, 9.8 Hz, 1H, H_d), 4.40 (d, *J*=14.0 Hz, 1H, CH_2–Ph), 6.03 (dd, *J*=3.8, 7.6 Hz, 1H, H_a), 7.21–7.43 (m, 10H, Ph), 7.45 (d, *J*=1.2 Hz, 1H, Thy H_6), 9.19 (br s, 1H, NH); δ_C ($CDCl_3$) 12.5, 48.3, 59.5, 70.5, 83.3, 109.8, 127.6, 127.7, 128.4, 128.6, 128.8, 129.1, 135.8, 136.6, 136.9, 150.4, 164.1; ν_{max} (KBr) 3167 (NH), 3031 (C–H_{Ar}), 1686 (C=O), 1600–1200 (C=C), 963 (C–H). Anal. Calcd (%) for $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56. Found (%): C 69.46, H 5.78, N 11.61.

*4.3.2. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy uridine (**3b**)*

Pale yellow solid, mp 172–173 °C. ESI-MS $[MH]^+$ *m*/*z* 350; δ_H ($CDCl_3$) 2.27 (ddd, *J*=4.0, 10.0, 14.0 Hz, 1H, H_c), 3.27 (dt, *J*=7.5, 7.6, 14.0 Hz, 1H, H_b), 3.64 (d, *J*=14.2 Hz, 1H, CH_2–Ph), 3.90 (dd, *J*=7.6, 10.0 Hz, 1H, H_d), 3.98 (d, *J*=14.2 Hz, 1H, CH_2–Ph), 5.57 (d, *J*=8.1 Hz, 1H, Ura H_5), 6.03 (dd, *J*=4, 7.5 Hz, 1H, H_a), 7.10–7.45 (m, 10H, Ph), 7.64 (d, *J*=8.1 Hz, 1H, Ura H_6), 9.18 (br s, 1H, NH); δ_C ($CDCl_3$) 44.7, 52.8, 64.4, 77.3, 98.2, 120.6, 121.2, 121.9, 124.2, 124.8, 125.3, 128.1, 132.4, 133.8, 143.8, 156.5; ν_{max} (KBr) 3166 (NH), 3031 (C–H_{Ar}), 1685 (C=O), 1600–1200 (C=C), 963 (C–H). Anal. Calcd (%) for $C_{20}H_{19}N_3O_3$: C 68.75, H 5.48, N 12.03. Found (%): C 68.71, H 5.51, N 12.03.

*4.3.3. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy cytidine (**3c**)*

Pale yellow solid, mp 234–235 °C. ESI-MS $[MH]^+$ *m*/*z* 349; δ_H ($CDCl_3$) 2.18 (ddd, *J*=4.4, 9.9, 13.6 Hz, 1H, H_c), 3.31 (dt, *J*=7.5, 7.6, 13.6 Hz, 1H, H_b), 3.72 (d, *J*=14.5 Hz, 1H, CH_2–Ph), 3.92 (d, *J*=14.5 Hz, 1H, CH_2–Ph), 4.10 (dd, *J*=7.6, 9.9 Hz, 1H, H_d), 5.72 (d, *J*=7.4 Hz, 1H, Cyt H_5), 6.16 (dd, *J*=4.4, 7.5 Hz, 1H, H_a), 7.07–7.52 (m, 12H, Ph+NH_2), 7.75 (d, *J*=7.4 Hz, 1H, Cyt H_6); δ_C ($CDCl_3$) 46.5, 58.7, 69.5, 82.0, 93.3, 126.7, 127.1, 127.6, 127.7, 127.8, 128.3, 136.9, 137.1, 139.7, 154.6, 165.1; ν_{max} (KBr) 3333, 3150 (NH_2), 3066 (C–H_{Ar}), 1657 (C=O), 1650–1300 (C=C, C=N). Anal. Calcd (%) for $C_{20}H_{20}N_4O_2$: C 68.95, H 5.79, N 16.08. Found (%): C 68.89, H 5.83, N 16.13.

*4.3.4. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy-5-fluoro cytidine (**3d**)*

White solid, mp 213–214 °C. ESI-MS $[MH]^+$ *m*/*z* 367; δ_H ($CDCl_3$) 2.36 (ddd, *J*=3.6, 9.8, 13.9 Hz, 1H, H_c), 3.40 (dt, *J*=7.4, 7.5, 13.9 Hz, 1H, H_b), 3.70 (d, *J*=14.0 Hz, 1H, CH_2–Ph), 3.91 (dd, *J*=7.5, 9.8 Hz, 1H, H_d), 4.04 (d, *J*=14.0 Hz, 1H, CH_2–Ph), 5.73 (br s, 1H, NH_2), 5.99 (dd, *J*=3.6, 7.4 Hz, 1H, H_a), 7.14–7.39 (m, 10H, Ph) 7.62 (d, *J*=6.5 Hz, 1H, FCyt H_6), 8.21 (br s, 1H, NH_2); δ_C ($CDCl_3$) 22.6, 29.7, 48.5, 59.8, 70.7, 84.3, 125.2, 125.7, 127.7, 128.4, 128.5, 128.8, 129.0, 136.8, 154.0, 157.9; ν_{max} (KBr) 3332, 3149 (NH_2), 3066 (C–H_{Ar}), 1657 (C=O), 1650–1300

(C=C, C=N). Anal. Calcd (%) for $C_{20}H_{19}FN_4O_2$: C 65.56, H 5.23, N 15.29. Found (%): C 65.62, H 5.26, N 15.24.

4.3.5. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy adenosine (**3e**)

White solid, mp 244–245 °C. ESI-MS $[MH]^+$ *m*/*z* 373; δ_H (DMSO-d_6) 2.81 (ddd, *J*=4.2, 9.4, 13.5 Hz, 1H, H_c), 3.46 (dt, *J*=7.8, 8.0, 13.5 Hz, 1H, H_b), 3.77 (d, *J*=15.0 Hz, 1H, CH_2–Ph), 3.98 (d, *J*=15.0 Hz, 1H, CH_2–Ph), 4.11 (dd, *J*=7.8, 9.4 Hz, 1H, H_d), 6.50 (dd, *J*=4.2, 8.0 Hz, 1H, H_a), 7.13–7.52 (m, 12H, Ph+NH_2), 8.14 (s, 1H, Ade H_2), 8.29 (s, 1H, Ade H_8); δ_C (DMSO-d_6) 44.5, 69.5, 79.7, 80.6, 118.0, 126.5, 127.3, 127.5, 127.9, 128.2, 128.4, 137.1, 138.1, 139.1, 148.7, 152.3, 155.6; ν_{max} (KBr) 3309, 3144 (NH_2), 3030 (C–H_{Ar}), 1671 (C=N), 1600–1300 (C=C). Anal. Calcd (%) for $C_{21}H_{20}N_6O$: C 67.73, H 5.41, N 22.57. Found (%): C 67.80, H 5.44, N 22.52.

4.3.6. (endo) 4′-Aza-4′-(N-benzyl)-3′-phenyl-2′,3′-dideoxy-2-(N-trityl) guanosine (**3f**)

Pale yellow solid, mp 217–218 °C. δ_H (DMSO-d_6) 2.08 (ddd, *J*=3.1, 9.2, 12.9 Hz, 1H, H_c), 2.77 (dt, *J*=7.8, 8.0, 13.0 Hz, 1H, H_b), 3.63 (d, *J*=14.4 Hz, 1H, CH_2–Ph), 3.76 (dd, *J*=7.8, 9.2 Hz, 1H, H_d), 4.03 (d, *J*=14.4 Hz, 1H, CH_2–Ph), 5.46–5.63 (dd, *J*=3.1, 8.0 Hz, 1H, H_a), 6.91–7.39 (m, 26H, Ph+Gua H_8), 7.49 (br s, 1H, NHTr), 10.82 (br s, 1H, NH); δ_C (DMSO-d_6) 45.8, 59.2, 69.3, 70.2, 78.9, 116.1, 126.4, 126.8, 127.2, 127.5, 127.9, 128.1, 128.4, 129.2, 129.5, 135.4, 139.2, 143.1, 143.6, 150.9, 155.1, 163.2; ν_{max} (KBr) 3160 (NH), 3060 (C–H_{Ar}), 1680 (C=O), 1650–1300 (C=C, C=N). Anal. Calcd (%) for $C_{40}H_{34}N_6O_2$: C 76.17, H 5.43, N 13.32. Found (%): C 76.22, H 5.39, N 13.29.

4.3.7. (endo) 4′-Aza-4′-(N-methyl)-3′-phenyl-2′,3′-dideoxy thymidine (**4a**)

White solid, mp 74–75 °C. ESI-MS $[MH]^+$ *m*/*z* 288; δ_H ($CDCl_3$) 2.02 (d, *J*=1.2 Hz, 3H, Thy CH_3), 2.36 (ddd, *J*=4.3, 10.2, 13.9 Hz, 1H, H_c), 2.67 (s, 3H, CH_3), 3.31 (dt, *J*=7.4, 7.5, 13.9 Hz, 1H, H_b), 3.67 (dd, *J*=7.4, 10.2 Hz, 1H, H_d), 6.25 (dd, *J*=4.3, 7.5 Hz, 1H, H_a), 7.19–7.42 (m, 10H, Ph), 7.87 (d, *J*=1.2 Hz, 1H, Thy H_6), 9.79 (br s, 1H, NH); δ_C ($CDCl_3$) 12.8, 42.9, 47.9, 73.1, 82.9, 110.7, 127.4, 128.5, 128.9, 135.8, 136.4, 150.6, 164.3; ν_{max} (KBr) 3167 (NH), 3031 (C–H_{Ar}), 1686 (C=O), 1600–1200 (C=C), 963 (C–H). Anal. Calcd (%) for $C_{15}H_{17}N_3O_3$: C 62.71, H 5.96, N 14.62. Found (%): C 62.80, H 5.92, N 14.59.

4.3.8. (endo) 4′-Aza-4′-(N-methyl)-3′-phenyl-2′,3′-dideoxy uridine (**4b**)

Pale yellow solid, mp 164–165 °C. ESI-MS $[MH]^+$ *m*/*z* 274; δ_H ($CDCl_3$) 2.35 (ddd, *J*=4.2, 10.2, 14.1 Hz, 1H, H_c), 2.66 (s, 3H, CH_3), 3.34 (dt, *J*=7.5, 7.6, 14.1 Hz, 1H, H_b), 3.65 (dd, *J*=7.5, 10.2 Hz, 1H, H_d), 5.90 (d, *J*=8.2 Hz, 1H, Ura H_5), 6.21 (dd, *J*=4.2, 7.6 Hz, 1H, H_a), 7.21–7.44 (m, 5H, Ph), 8.18 (d, *J*=8.2 Hz, 1H, Ura H_6), 9.94 (br s, 1H, NH); δ_C ($CDCl_3$) 35.6, 41.2, 65.9, 76.0, 95.1, 120.3, 121.4, 121.8, 129.2, 133.1, 143.5, 156.7; ν_{max} (KBr) 3165 (NH), 3034 (C–H_{Ar}), 1689 (C=O), 1600–1200 (C=C), 965 (C–H). Anal. Calcd (%) for $C_{14}H_{15}N_3O_3$: C 61.53, H 5.53, N 15.38. Found (%): C 61.58, H 5.58, N 15.34.

4.3.9. (endo) 4′-Aza-4′-(N-methyl)-3′-phenyl-2′,3′-dideoxy cytidine (**4c**)

Pale yellow solid, mp 252–253 °C. ESI-MS $[MH]^+$ *m*/*z* 273; δ_H (DMSO-d_6) 2.17 (ddd, *J*=4.3, 9.9, 13.6 Hz, 1H, H_c), 2.56 (s, 3H, CH_3), 3.27 (dt, *J*=7.6, 7.7, 13.6 Hz, 1H, H_b), 3.71 (dd, *J*=7.7, 9.9 Hz, 1H, H_d), 5.83 (d, *J*=7.5 Hz, 1H, Cyt H_5), 6.14 (dd, *J*=4.3, 7.6 Hz, 1H, H_a), 7.19 (br s, 2H, NH_2), 7.26–7.45 (m, 5H, Ph), 7.97 (d, *J*=7.5 Hz, 1H, Cyt H_6); δ_C (DMSO-d_6) 43.9, 54.7, 68.2, 82.5, 93.8, 127.6, 127.9, 128.5, 137.3, 139.5, 153.9, 165.4; ν_{max} (KBr) 3332, 3150 (NH_2), 3066 (C–H_{Ar}), 1657 (C=O), 1650–1300 (C=C, C=N). Anal. Calcd (%) for $C_{14}H_{16}N_4O_2$: C 61.75, H 5.92, N 20.57. Found (%): C 61.81, H 5.89, N 20.53.

4.3.10. (endo) 4′-Aza-4′-(N-methyl)-3′-phenyl-2′,3′-dideoxy 5-fluoro cytidine (**4d**)

White solid, mp 234–235 °C. ESI-MS $[MH]^+$ *m*/*z* 291; δ_H ($CDCl_3$) 2.36 (ddd, *J*=3.9, 9.9, 13.9 Hz, 1H, H_c), 2.92 (s, 3H, CH_3), 3.41 (dt, *J*=7.5, 7.7, 13.9 Hz, 1H, H_b), 3.65 (dd, *J*=7.7, 9.9 Hz, 1H, H_d), 5.78 (br s, 1H, NH_2), 6.13 (ddd, *J*=1.2, 3.9, 7.5 Hz, 1H, H_a), 7.24–7.38 (m, 5H, Ph), 8.07 (d, *J*=6.4 Hz, 1H, FCyt H_6), 8.40 (br s, 1H, NH_2); δ_C ($CDCl_3$) 21.5, 28.8, 47.2, 57.3, 68.9, 82.5, 125.3, 127.8, 128.8, 136.1, 153.2, 157.8; ν_{max} (KBr) 3331, 3148 (NH_2), 3068 (C–H_{Ar}), 1658 (C=O), 1650–1300 (C=C, C=N). Anal. Calcd (%) for $C_{14}H_{15}FN_4O_2$: C 57.92, H 5.21, N 19.30. Found (%): C 57.87, H 5.18, N 19.34.

4.3.11. (endo) 4′-Aza-4′-(N-methyl)-3′-phenyl-2′,3′-dideoxy adenosine (**4e**)

White solid, mp 213–214 °C. ESI-MS $[MH]^+$ *m*/*z* 297; δ_H (DMSO-d_6) 2.53 (s, 3H, CH_3), 2.88 (ddd, *J*=4.3, 9.8, 13.9 Hz, 1H, H_c), 3.41 (dt, *J*=7.4, 7.6, 13.9 Hz, 1H, H_b), 3.79 (dd, *J*=7.6, 9.8 Hz, 1H, H_d), 6.49 (dd, *J*=4.2, 7.4 Hz, 1H, H_a), 7.22–7.61 (m, 7H, Ph+NH_2), 8.17 (s, 1H, Ade H_2), 8.39 (s, 1H, Ade H_8); δ_C (DMSO-d_6) 43.4, 45.6, 78.6, 81.7, 119.8, 126.7, 128.4, 128.8, 137.2, 140.5, 149.2, 152.1, 156.6; ν_{max} (KBr) 3309, 3144 (NH_2), 3030 (C–H_{Ar}), 1671 (C=N), 1600–1300 (C=C). Anal. Calcd (%) for $C_{15}H_{16}N_6O$: C 60.80, H 5.44, N 28.36. Found (%): C 60.74, H 5.41, N 28.41.

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