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Highly enantioselective synthesis and potential biological activity of chiral novel nucleoside analogues containing adenine and naturally phenol derivatives

Lan He,* Yumei Liu, Wei Zhang, Ming Li and Qinghua Chen*

Department of Chemistry, Beijing Normal University, Beijing 100875, China

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Abstract—This paper described an efficient synthetic strategy for chiral acyclic nucleoside analogues containing both the phenoxy components of some bioactive natural compounds and a heterocyclic base. The phenoxy components with adenine moiety were incorporated into the chiral acyclic nucleoside analogues through two key synthetic tactics. Chiron 5-(*R*)-menthyloxy-2(5*H*)-furanone **5** was obtained in good yield from the cheap starting material furfural via a valuable synthetic route. The asymmetric Michael addition of **5** with adenine and the subsequent reduction reaction afforded the key chiral intermediate, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**. The absolute configuration of **8** was established by X-ray crystallography. The intermolecular dehydration reaction between 2-(9′-adeninyl)-1,4-butanediol **8** and phenoxy components **9** on treatment with diethyl azodicarboxylate and triphenylphosphine was carried out to give the chiral acyclic nucleoside analogues **1a**–**1e**. The regioselectivity of the reaction was established by NMR methods, especially through ^{13}C NMR shifts and NOE effect observed in the target molecule **1c**, as well as by HMBC/HMQC experiments. The target compounds were tested for inhibition of cytopathogenicity against different cancer cells and exhibited potential anticancer activity.

1. Introduction

It is well known that the phenoxy group is an important component of some bioactive compounds for their biologic properties.[1] For example, the flavan derivatives[2] as new aromatase inhibitors have been considered as a result of the modulation of flavonoids, which are natural products extensively distributing in the plant kingdom. An appropriately fashioned hybrid drug of galdanamycin and estradiol would offer the ability to induce a selective degradation of the estrogen receptor (ER).[3] Several adenosine nucleosides, such as the antibiotics aristeromycin[4] and neplanocin A[5] (as inhibitor *S*-adenosyl-L-homocyseine hydrolase), are obtained from natural products. Despite of the progress that has been made in this field, efficient synthesis of chiral acyclic nucleoside analogues **1a**–**1e**, which contains both the phenoxy components of some bioactive natural compounds and a heterocyclic base, has not been reported.

Our approach to use a synthetic strategy in which the phenoxy components and the adenine moiety could be incorporated into chiral acyclic nucleoside analogues through two key synthetic tactics: (i) preparation of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** by the asymmetric Michael addition of chiron, (5)-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** with adenine and subsequent reduction reaction; and (ii) the intermolecular dehydration reaction occurring between the 2-(9′-adeninyl)-1,4-butanediol **8** and phenoxy (acidic) components **9** on treatment with diethyl azodicarboxylates (DEAD) and triphenylphosphine under mild conditions[6]. Herein, we report our results on the efficient synthesis of the target chiral acyclic nucleoside analogues containing the phenoxy components of some bioactive natural compounds (Fig. 1).

2. Results and discussion

The synthesis of enantiopure 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** was conveniently achieved starting from 5-hydroxy-2(5*H*)-furanone **3** as shown in Scheme 1. The photooxidation of furfural **2** was probably the most suitable method for the preparation of **3**.[7,8] The improved photosynthetic procedure using 95% C_2H_5OH as a the solvent at room temperature provided 5-hydroxy-2(5*H*)-furanone in good yield.[7] Epimeric mixture of 5-menthyloxy-2(5*H*)-furanone **4** was readily available through acetalization of the

Keywords: Asymmetric synthesis; Enantiopure; Chiral acyclic nucleoside analogue; Phenoxy and adenine components; Potential anticancer activity.
* Corresponding authors. Tel.: +86 010 58802076; fax: +86 010 62206222 (Q.C.); e-mail: cqh6693@bnu.edu.cn

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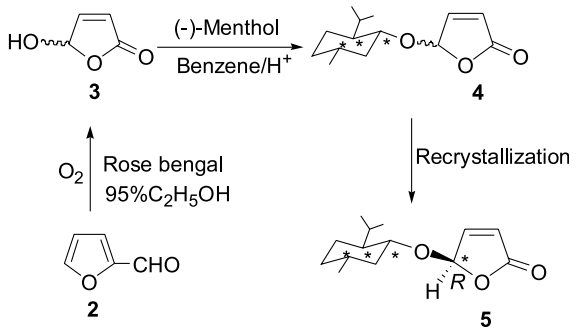
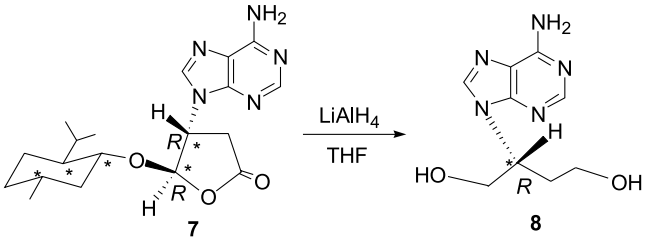


Scheme 1. The synthesis of enantiomerically pure 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5**.

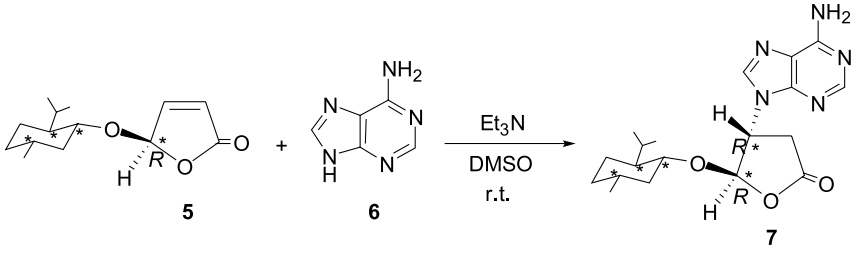
resulting 5-hydroxy-2(5*H*)-furanone with (−)-menthol in refluxing benzene in the presence of a catalytic amount of condensed sulfuric acid.[7,9]

Asymmetric Michael addition of heterocyclic bases with 5-(*R*)-(−)-menthyloxy-2(*5H*)-furanone **5** was studied originally in our laboratory.[7] Basic condition was one of the most important factors for the successful reaction to acquire the main N-9 alkylation product (Scheme 2). The reaction of **5** and adenine **6** in the presence of triethylamine afforded 5-(*R*)-(−)-menthyloxy-4-(*R*)-(9′-adeninyl)-butyrolactone **7** via the asymmetric addition. The important factor was the selection of solvent. Because of the low solubility of adenine, DMSO was chosen as the suitable solvent. The base **6** was dissolved in DMSO at 40 °C, and then triethylamine was added at room temperature. Purification of the products was another key factor. The remaining chiron **5** was washed with petroleum, and the adduct was extracted using acetone due to the solubility difference between the chiron and the product. The optically pure compound **7** was obtained in 64% yield with ≥98% ee by column chromatography. The chemical structures of chiral products were established by element analysis, IR, UV, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography.[7]

As outlined in Scheme 3, 5-(*R*)-(−)-menthyloxy-4-(*R*)-(9′-adeninyl)-butyrolactone **7** was reduced by $LiAlH_4$ in a suspension of THF to give the enantiopure functionalized compound, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** in good yield with ≥98% ee. The chemical structure of **8** was readily confirmed by the spectroscopic data. The stereochemistry and configuration of the molecule were further confirmed by its X-ray crystallography as shown in Figure 2 (CCDC 273580).



Scheme 3. The synthesis of enantiomerically pure 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**.



Scheme 2. The synthesis of enantiomerically pure **7**.

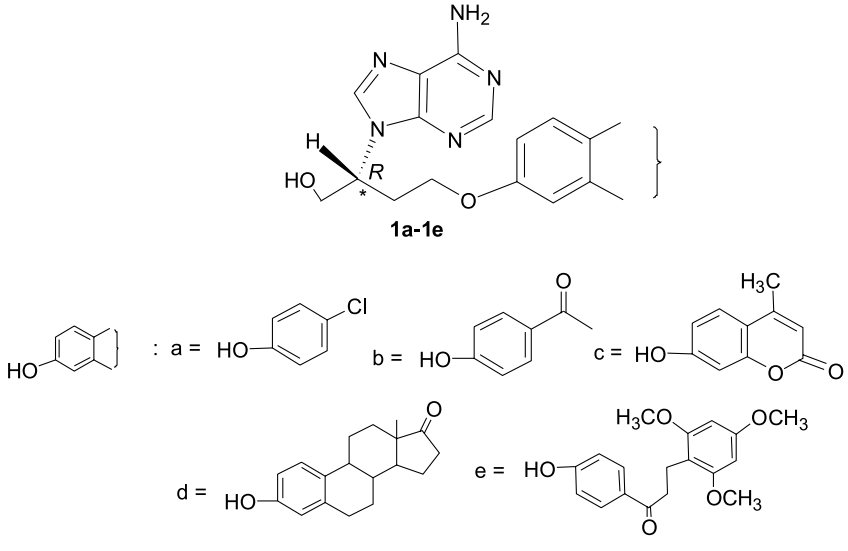


Figure 1. The structures of target molecules.

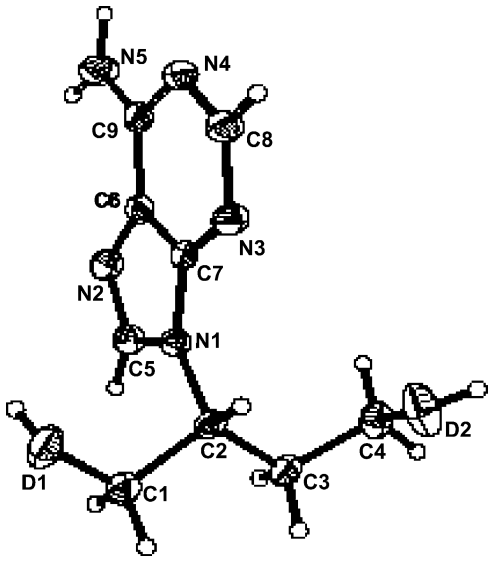
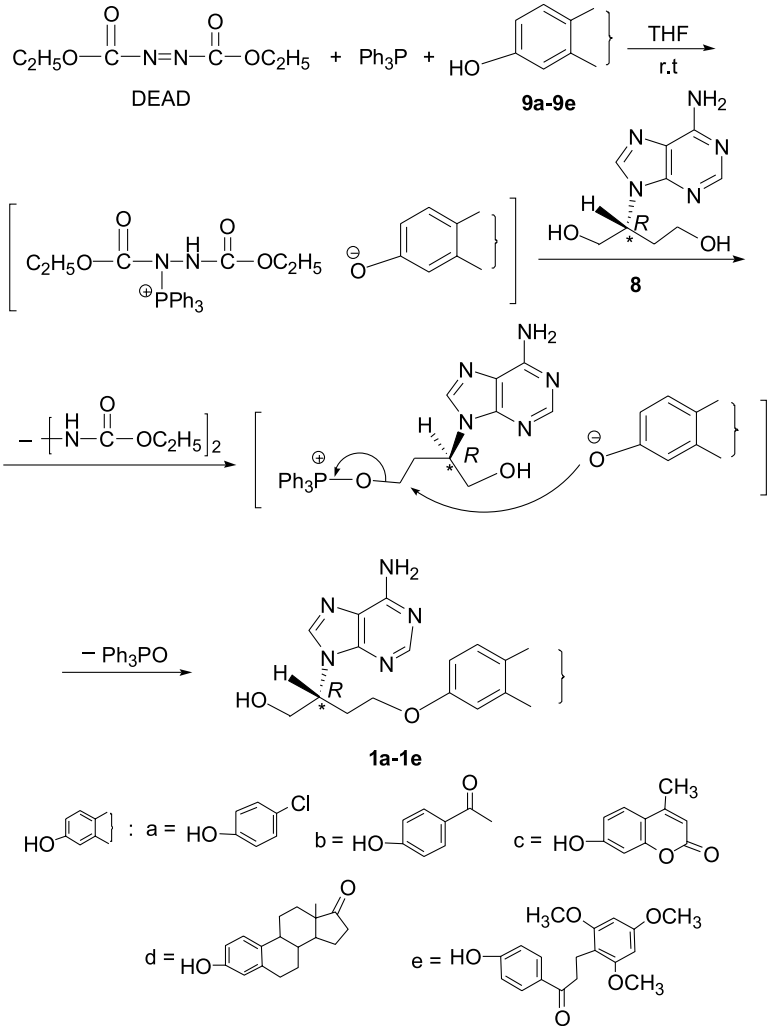


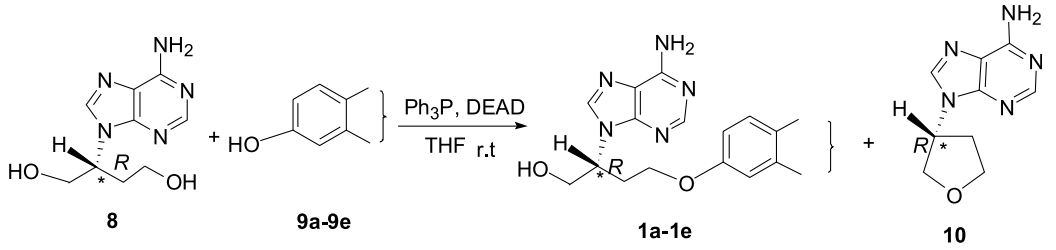
Figure 2. ORTEP drawing of the molecule **8**.

The development of mild methods for the synthesis of phenoxy ethers has recently gained increased attention, mainly due to their important roles in natural and unnatural pharmacologically antibiotics and other biologically active compounds.[10] The formation of the C–O bond in ethers can usually be realized by the dehydration of alcohols using sulfuric acid as the catalyst, but this process is not suitable for the synthesis of unsymmetrical ethers partly due to the low selectivity and strong sensitivity of the substrates. The reaction of alcohols and acidic components such as phenoxy group takes place easily to form the condensation products in the presence of organic dehydrating reagents such as the diethyl azodicarboxylate(DEAD)/triphenylphosphine(Ph_3P) system under mild conditions.[6] The condensation reaction of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** with different phenoxy components **9a–9e** was proceeded to afford the corresponding chiral acyclic nucleoside analogues **1a–1e** as shown in Scheme 4. The dehydrating behavior of different phenoxy compounds **9** with alcohol **8** could be explained on the basis of a reaction mechanism including the phenoxy compound as an acidic component and the alcohol containing adenine moiety **8** as a nucleophilic reagent. At first, the adduct of DEAD and Ph_3P by the protonation supported from phenoxy compound was formed as a dipolar system and subsequently the elimination of 1,2-dicarbethoxyhydrazine was easily carried out by the nucleophilic reaction of **8** to afford a new zwitterion. Finally, the target molecules, chiral acyclic nucleoside analogues **1a–1e** were obtained through the nucleophilic substitution of the anion of



Scheme 4. The synthetic route to chiral acyclic nucleoside analogues **1a–1e**.

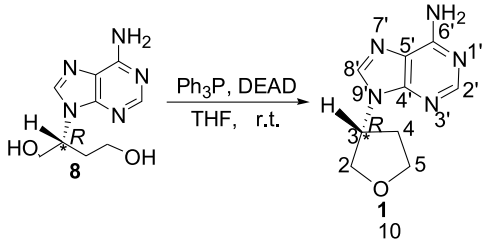
Table 1. Etherification of chiral compond **8** with phenoxy components **9** in the presence of DEAD and Ph_3P[a]



Entry	**1** Yield[b] (mg) (%)	**10** Yield[b] (mg) (%)	**8** Recovered[b] (mg)
1 (**1a**)	130 (43)	86 (42)	22
2 (**1b**)	112 (44)	46 (22)	56
3 (**1c**)	198 (52)	Trace[c]	Trace[c]
4 (**1d**)	251 (75)	—	Trace[c]
5 (**1e**)	279 (53)	Trace[c]	Trace[c]

[a] The etherification was carried out at room temperature for 1–3 days using 1.0 mmol of **8**, 1.2 mmol of **9**, 1.2 mmol of DEAD, 1.2 mmol of Ph_3P in THF.
[b] Yield after flash chromatography based on the amount of **8**.
[c] It was checked by TLC to show the traces of **8**, **9**, and **10**, but did not obtain the pure compounds after the separation by flash chromatography.

phenoxy compound and elimination of triphenylphosphine oxide. The results were summarized in Table 1. The dehydration of alcohol **8** with **9a**–**9e** afforded the corresponding ethers **1a**–**1e** in 43–75% FC yields. When the reactions of **8** with **9a**–**9b** were performed, the corresponding ethers were achieved in 43–44% FC yields (Table 1, entries 1, 2) along with the self-etherification product **10** (Scheme 5) in 42 and 22% FC yields, as well as recovering 22 and 56 mg of starting material **8**, respectively. The unsymmetrical etherification of **8** with **9c** and **9e** gave the corresponding ethers **1c** and **1e** in 52 and 53% FC yields, respectively, (Table 1, entries 3, 5). At the same time, the traces of **8**, **9** and **10** were found by checking TLC, which were not obtained after flash chromatography. The result of the dehydration of alcohol **8** with **9d** under the same condition gave **1d** in 75% FC yield (Table 1, entry 4). Obviously, the aim of our present study would be to propose further groundwork for any future applications on the unsymmetric etherification to the synthesis of more complex molecules containing similar chiral acyclic and cyclic nucleoside skeleton.



Scheme 5. The intramolecular dehydration of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**.

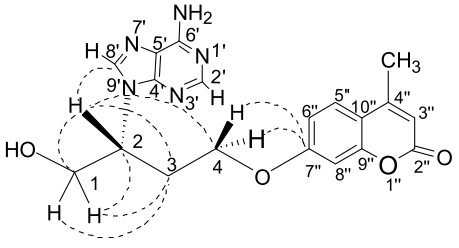


Figure 3. Relevant $^{1}H/^{13}C$ HMBC correlations for structural identification of compound **1c**.

The stereochemistry of the nucleoside **1c** was elucidated by HMQC and HMBC experiment as shown in Figures 3, 4, and 5 as well as Table 2. The result described that H-4 was correlated only with C-2, C-3 and C-7″, which proved the

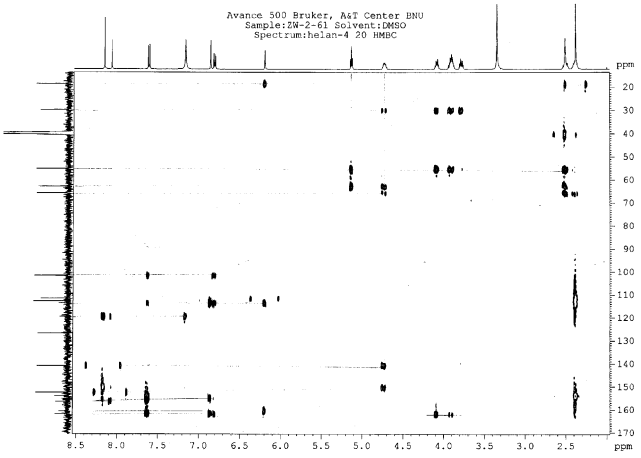


Figure 4. The 500 MHz HMBC spectrum of compound **1c**.

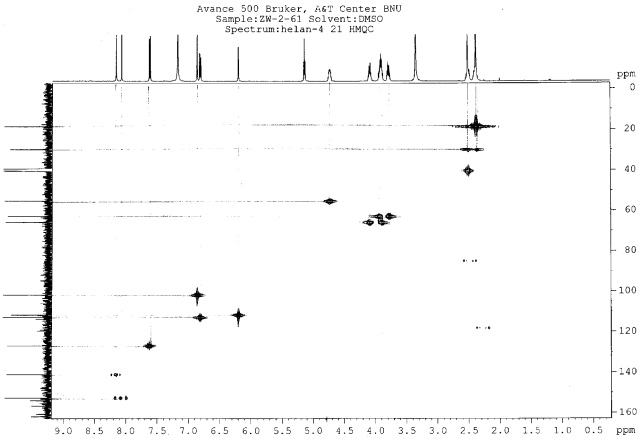


Figure 5. The 500 MHz HMQC spectrum of compound **1c**.

Table 2. ^{1}H NMR, ^{13}C NMR data and HMQC, HMBC correlations for **1c**[a]

Position	δ_H (mult. J in Hz)	δ_C (mult.)	HMQC	HMBC
1	3.77–3.81 (m), 388–3.94 (m)	62.9	C-1	C-3, C-2
2	4.73–4.75 (m)	55.3	C-2	C-1, C-3, C-4, C-8′
3	2.40–2.42 (m), 2.47–2.51 (m)	29.8	C-3	C-1, C-2, C-4
4	3.88–3.94 (m), 4.07–4.11 (m)	65.8	C-4	C-2, C-3, C-7″
2′	8.08 (s)	152.5	C-2′	C-4′, C-5′
4′		155.1	C-4′	
5′		119.5	C-5′	C-10, C-7, C-4
6′		150.2	C-6′	
8′	8.16 (s)	141.0	C-8′	C-5′
2″		161.8	C-2″	
3″	6.20 (s)	111.6	C-3″	C–CH_3
4″		156.4	C-4″	
5″	7.26 (d, 8.8)	126.8	C-5″	C-8″, C-10″
6″	6.82 (d, 8.8)	112.8	C-6″	C-7″, C-8″
7″		160.6	C-7″	
8″	6.87 (s)	101.7	C-8″	C-6″, C-7″, C-9″
9″		153.8	C-9″	
10″		113.6	C-10″	
CH_3	2.37 (s)	18.6	C–CH_3	H-3″
OH	5.13 (t, 5.5)			C-2
NH_2	7.16 (s)			C-5′

[a] ^{1}H NMR and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively. Couling constants (in parentheses) are given in Hz.

ether bond formed between C-4 and C-7″. The long-range correlations of H-2 with C-8′, C-1, C-3, and C-4, respectively, were observed and demonstrated that target molecule **1c** was the N-9′ regioisomer as shown in Figure 3.

Compounds **1a**, **1b**, **1c**, and **1d** were tested for inhibition of cytopathogenicity against different cancer cells such as the colon cancer HCT-8 cell, the cervical cancer HELA cell, the pulmonary cancer A549 cell and the skin cancer A431 cell in pharmacological primary screen model as shown in Table 3. In comparison to the target molecules against the different types of cancer cells, **1d** exhibited higher anticancer activity against skin cancer A431 cell and pulmonary cancer A549 cell. These results probably provided a valuable research route to look for novel types of chiral acyclic nucleoside analogues with new biological activities.

3. Conclusion

An efficient synthetic strategy for chiral acyclic nucleoside analogues containing both the phenoxy components of some bioactive natural compounds and a heterocyclic base was achieved through two key synthetic tactics. One was the asymmetric Michael addition of the chiron 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** with adenine and the subsequent reduction reaction, which provided the key chiral intermediate, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**. The other was the intermolecular dehydration reaction between chiral **8** and phenoxy components **9** to form the target compounds **1**. The enantiopure acyclic nucleoside analogues exhibited potential anticancer activity.

4. Experimental

4.1. General

Infrared spectra were recorded on a Fourier 170-sx spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-500 MHz spectrometer and the chemical shifts were expressed in δ-values using TMS as the internal standard. Mass spectra were determined with a Finnegan GC2000/TRACE TM/MS mass spectrometer. Microanalyses were performed on a Perkin-Elemer 240-C elemental analyzer. Melting point was determined on a XT Digital melting-point apparatus with microscope and uncorrected. All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled.

4.2. Synthesis of 2-(*R*)-(9′-adeninyl)-1,4-butanediol (8)

To a solution of 6 mmol $LiAlH_4$ in dry THF (20 mL) was added **7** (2 mmol) in dry THF (40 mL) under nitrogen atmosphere. The reaction mixture was stirred for 12–24 h until **7** had been consumed. Saturated Na_2SO_4 solution was added to decompose excess $LiAlH_4$, followed by addition of ethanol (20 mL). Then the mixture was filtered, washed with ethanol. The combined organic layer was dried and concentrated in vacuum and purified by flash chromatography to afford 368 mg (82%) of **8** as colorless crystals. Mp 181.3–181.7 °C; $[\alpha]_D^{20}+41.6$ (c 1.0, CH_3OH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02–2.04 (1H, m, H-3), 2.09–2.15 (1H, m, H-3), 3.20–3.23 (1H, m, H-4), 3.31–3.33 (1H, m, H-4), 3.68–3.72 (1H, m, H-1), 3.84–3.88 (1H, m, H-1), 4.60 (1H, t, $J_{HO-CH_2}=5.28$ Hz, OH), 4.62–4.64 (1H, m, H-2), 5.03 (1H, t, OH), 7.19 (2H, s, NH_2), 8.11 (2H, s, H-8′, 2′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 33.4 (C-3), 55.1 (C-2), 57.6 (C-4), 62.8 (C-1), 119.3 (C-5′), 141.1 (C-8′), 150.0 (C-6′), 152.4 (C-2′), 156.2 (C-4′); IR (KBr, cm^{-1}): 3426 (br OH), 1648, 1599, 1575, 1484. Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.37; H, 5.89; N, 31.11.

Table 3. Inhibitory ratio (IR)[a] and corresponding inhibitory concentrations (IC_{50})[b] of chiral acyclic nucleoside analogues on the cytopathogenicity of different cancer cells, in pharmacological primary screen model

Compound	Colon cancer HCT-8 cell IR/IC_{50} (μg/mL)	Cervical cancer HELA cell IR/IC_{50} (μg/mL)	Pulmonary cancer A549 cell IR/IC_{50} (μg/mL)	Skin cancer A431 cell IR/IC_{50} (μg/mL)
1a	9.5/50	7.6/50	23.9/50	58.8/4.10
1b	23.7/50	−1.5/50	31.6/50	78.1/12.0
1c	43.5/61.7	33.0/>50	39.2/>50	42.4/53.1
1d	84.9/9.5	79.3/16.1	82.7/16.8	80.5/5>IC_{50}<50

[a] Inhibitory ratio (IR) was obtained through the use of the concentration of 50 μg/mL.
[b] Inhibitory concentrations (IC_{50}) were determined through the use of an established MTTmethod[11,12] and represent the average of duplicate determinations.

4.3. General procedure for the preparation of (1a–1e)

To a mixture of compound **8** (1 mmol), ROH **9** (1.2 mmol), Ph_3P (1.2 mmol) in 1 mL THF, DEAD (1.2 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at room temperature under N_2 atmosphere for 1–3 days. The solvent was removed in vacuum and the crude product was obtained and further purified by flash chromatography to afford the target compounds **1a**–**1e**.

4.3.1. 2-(*R*)-(9′-Adeninyl)-4-(4″-chlorophenoxy)-butan-1-ol (1a). One hundred and thirty milligrams, yield 43%; mp 185.7–186.3 °C; $[\alpha]_D^{20}+80.0$ (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.34–2.37 (1H, m, H-3), 2.44–2.49 (1H, m, H-3), 2.44–2.49 (2H, m, H-1), 3.88–3.95 (2H, m, H-4), 4.70–4.73 (1H, m, H-2), 5.11 (1H, t, OH), 6.83 (2H, d, $J=9.0$ Hz, H-2″, 6″), 7.16 (2H, s, NH_2), 7.26 (2H, d, $J=9.0$ Hz, H-3″, 5″), 8.08 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.0 (C-3), 55.2 (C-2), 62.8 (C-1), 65.3 (C-4), 116.6 (C-2″, 6″), 119.4 (C-5′), 124.7 (C-4″), 129.6 (C-3″, 5″), 141.0 (C-8′), 150.1 (C-6′), 152.5 (C-2′), 156.3 (C-4′), 157.6 (C-1″); IR (KBr, cm^{-1}): 3442 (br OH), 1678, 1605, 1492; HRMS (FAB^+) *m/z* calcd for $C_{15}H_{17}ClN_5O_2$ $(M+H)^+$334.1071, found 334.1070.

4.3.2. 2-(*R*)-(9′-Adeninyl)-4-(4″-acetophenyl)-butan-1-ol (1b). One hundred and twelve milligrams, yield 44%; mp 233.8–235.0 °C; $[\alpha]_D^{20}+85.9$ (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.09 (3H, s, CH_3), 2.37–2.40 (1H, m, H-3), 2.50–2.51 (1H, m, H-3), 3.76–3.79 (1H, m, H-1), 3.86–3.92 (2H, m, H-1, 4), 4.03–4.06 (1H, m, H-4), 4.72–4.75 (1H, m, H-2′), 5.14 (1H, t, OH), 6.89 (2H, d, $J=8.8$ Hz, H-2″,6″), 7.21 (2H, s, NH_2), 7.86 (2H, d, $J=8.8$ Hz, H-3″,5″), 8.08 (1H, s, H-2′), 8.17 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.8 (CH_3), 30.0 (C-3), 55.2 (C-2), 62.8 (C-1), 65.3 (C-4), 114.7 (C-2″,6″), 119.0 (C-5′), 130.4 (C-4″), 130.8 (C-3″,5″), 141.0 (C-8′), 150.1 (C-6′), 152.4 (C-2′), 156.2 (C-4′), 162.6 (C-1″), 196.7 (C=O); IR (KBr, cm^{-1}): 3307 (br OH), 1677 (C=O). Anal. Calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.51. Found: C, 59.22; H, 5.80; N, 20.02.

4.3.3. 2-(*R*)-(9′-Adeninyl)-4-[7″-(4″-menthylumbelliferonyl)]-butan-1-ol (1c). One hundred and ninety three milligrams, yield 52%; mp 202.3–202.4 °C; $[\alpha]_D^{20}+85.6$ (*c* 0.9, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.37 (3H, s, CH_3), 2.40–2.42 (1H, m, H-3), 2.47–2.51 (1H, m, H-3), 3.77–3.81 (1H, m, H-1), 3.88–3.94 (2H, m, H-1, 4), 4.07–4.11 (1H, m, H-4), 4.73–4.75 (1H, m, H-2), 5.13 (1H, t, OH), 6.20 (1H, s, H-3″), 6.82 (1H, d, $J=8.8$ Hz, H-6″), 6.87 (1H, s, H-8″), 7.16 (2H, s, NH_2), 7.26 (1H, d, $J=8.8$ Hz, H-5″), 8.08 (1H, s, H-2′), 8.16 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.6 (CH_3), 29.8 (C-3), 55.3 (C-2), 62.9 (C-1), 65.8 (C-4), 101.7 (C-8″), 111.6 (C-3″), 112.8 (C-6″), 113.6 (C-10″), 119.5 (C-5′), 126.8 (C-5″), 141.0 (C-8′), 150.2 (C-6′), 152.5 (C-2′), 153.8 (C-9″), 155.1 (C-4′), 156.4 (C-4″), 160.6 (C-7″), 161.8 (C-2″); IR (KBr, cm^{-1}): 3424 (br OH), 1711 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{19}H_{20}N_5O_4$ $(M+H)^+$382.1515, found 382.1514.

4.3.4. 2-(*R*)-(9′-Adeninyl)-4-(3″-estronyl)-butan-1-ol (1d). Two hundred and fifty one milligrams, yield 75%; mp 242.4–244.5 °C; $[\alpha]_D^{20}+141.1$ (*c* 0.9, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (3H, s, H-18″), 2.43–2.46 (2H, m, H-3), 2.75–2.78 (2H, m, H-16″), 3.70–3.77 (2H, m, H-4), 3.87–3.91 (2H, m, H-1), 4.69–4.71 (1H, m, H-2), 5.11 (1H, t, OH), 6.48 (1H, s, H-4″), 6.57 (1H, dd, $J=2.5$, 8.6 Hz, H-2″), 7.11 (1H, d, $J=8.6$ Hz, H-1″), 7.20 (2H, s, NH_2), 8.10 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.0 (C-18″), 29.5 (C-3), 55.3 (C-2), 62.8 (C-1), 64.7 (C-4), 112.6 (C-4″), 114.6 (C-2″), 119.2 (C-5′), 126.6 (C-1″), 132.3 (C-10″), 137.8 (C-5″), 141.0 (C-8′), 150.1 (C-6′), 152.5 (C-2′), 156.6 (C-4′), 220.2 (C-17″); IR (KBr, cm^{-1}): 3437 (br OH), 1732 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{27}H_{34}N_5O_3$, $(M+H)^+$476.2662, found 476.2650.

4.3.5. 2-(*R*)-(9′-Adeninyl)-4-[4″-(2‴,4‴,6‴-trimethoxyldihydrochalcony1)]-butan-1-ol (1e). Two hundred and seventy nine milligrams, yield 53%; mp 100.1–102.0 °C; $[\alpha]_D^{20}+12.0$ (*c* 0.2, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.36–2.41 (1H, m, H-3), 2.48–2.51 (1H, m, H-3), 2.74–2.77 (2H, m, H-β), 2.88–2.91 (2H, m, H-α), 3.73 (6H, s, 2× OCH_3), 3.76 (3H, s, OCH_3), 3.78–3.79 (1H, m, H-1), 3.88–3.90 (2H, m, H-1,4), 4.03–4.06 (1H, m, H-4), 4.71–4.73 (1H, m, H-2), 5.14 (1H, t, OH), 6.21 (2H, s, H-3‴,5‴), 6.89 (2H, d, $J=8.8$ Hz, H-3″,5″), 7.18 (2H, s, NH_2), 7.86 (2H, d, $J=8.8$ Hz, H-2″,6″), 8.08 (1H, s, 2′), 8.17 (1H, s, H-8′); ^{13}C NMR (125 MH_Z, DMSO-d_6) δ 18.8 (C-β), 30.0 (C-3), 38.5 (C-α), 55.2 (C-2), 55.6 (OCH_3), 56.1 (OCH_3), 62.8 (C-1), 65.3 (C-4), 91.2 (C-3‴,5‴), 109.0 (C-1‴), 114.7 (C-3″, 5″), 129.9 (C-1″), 130.6 (C-2″, 6″), 141.0 (C-8′), 150.2 (C-6′), 152.5 (C-2′), 156.4 (C-4′), 158.7 (C-2‴, 6‴), 159.8 (C-4‴), 162.5 (C-4″), 198.8 (C=O); IR (KBr, cm^{-1}): 3437 (br OH), 1670 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{27}H_{32}N_5O_6$, $(M+H)^+$522.2353, found 522.2348.

4.3.6. 3-(*R*)-(9′-Adeninyl)-tetrahydrofuran(10). Mp 202.3–203.1 °C; $[\alpha]_D^{20}-2.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29–2.30 (1H, m, H-4), 2.47–2.50 (1H, m, H-4), 3.84–3.89 (1H, m, H-5), 3.96–3.97 (2H, m, H-2, 5), 4.08–4.11 (1H, m, H-2), 5.15–5.19 (1H, m, H-3), 7.25 (2H, s, NH_2), 8.14 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 32.3 (C-4), 54.4 (C-3), 67.0 (C-5), 72.2 (C-2), 119.3 (C-5′), 139.3 (C-8′), 149.8 (C-6′), 152.8 (C-2′), 156.4 (C-4′); IR (KBr, cm^{-1}): 3341.9, 3180.9, 1652.0. Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.78; H, 5.30; N, 33.59.

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