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Note

Synthesis of azole nucleoside analogues of D-pinitol as potential antitumor agents

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Abstract—A convenient strategy is reported for the synthesis of azole nucleoside analogues of D-pinitol (=3-*O*-methyl-D-*chiro*-inositol). The key intermediate 3-*O*-methyl-4,5-epoxy-D-*chiro*-inositol was obtained in excellent yield via an epoxidation from monomethanesulfonate of D-pinitol. The process of opening of the epoxy ring by azole-bases appeared strongly regioselective in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. All newly synthesized carbocyclic azole nucleosides were assayed against lung and bladder cancer in vitro. Only the triazole and benzotriazole nucleoside analogues inhibited the growth of human lung cancer cell lines (PG) with EC_{50} of 11.3 and 22.6 μM, respectively, and showed much less inhibitory activity against human bladder cell lines (T_{24}).
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Keywords: Carbocyclic azole nucleoside; D-Pinitol; 1,2,4-Triazole; Benzotriazole; Nitroindazole; Opening of epoxy ring reaction; Antitumor activity

Carbocyclic nucleosides, in which the oxygen atom of the sugar moiety is replaced by a CH_2 group, have emerged as a promising class of nucleosides with interesting antiviral and antitumor activities.[1] Due to the absence of the glycosidic linkage between the heterocycle and the sugar, these compounds have a higher metabolic stability against the nucleoside phosphorylases.[2] Natural as well as synthetic carbocyclic nucleosides such as abacavir[3] and entecavir[4] have shown interesting antitumor activities and antiviral activities against the human cytomegalovirus (HCMV),[5] herpes simplex virus (HSV),[6] hepatitis B virus (HBV),[7] and human immunodeficiency virus (HIV).[8] Based on their notable biological activities, it is not surprising that these targets have drawn substantial synthetic interest.

Another alteration to the nucleoside structure that has resulted in profound biological effects is modification of the heterocyclic base.[9] In this field, azole nucleosides were proven to be a large class of antimetabolites and have attracted considerable attention because of their broad bioactive spectrum.[10] Bredinin shows immunosuppressive properties and inhibits inosine 5′-monophosphate dehydrogenase (IMPDH) and depletes cells of guanine nucleotides.[11] Ribavirin, a broad spectrum antiviral agent, also displays antitumor activity.[12] Pyrazofurin exhibits remarkable anticancer and antiviral properties.[9,13] In addition to the above compounds, numerous other azole nucleoside analogues have also been synthesized and display strong antiviral activities, in which the base involves benzimidazole, indazole, and other azole derivatives.[12b,14] Despite significant progress, there are very few reports on the synthesis and bioactivity of carbocyclic azole nucleoside.[15]

D-Pinitol (=3-*O*-methyl-D-*chiro*-inositol) occurs ubiquitously in plants[16] and is a useful chiral starting material, as illustrated by the asymmetric synthesis of a putative insulin mediator.[17] Its structural features make it perfectly suited for the stereocontrolled synthesis of the title compounds (Scheme 1). For example, a cyclohexane ring is already present and a chiral center at C-4 and C-5 allows stereospecific introduction of the base moiety via transformation of the OH and MsO groups

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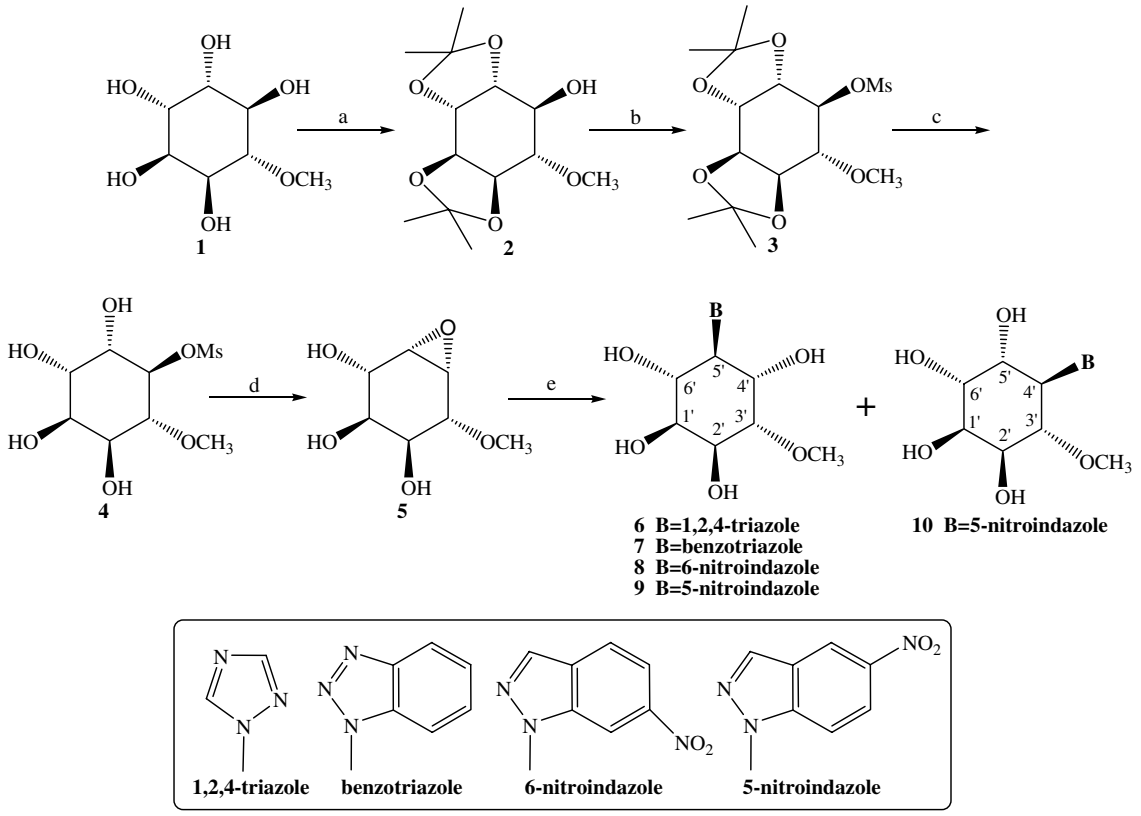

Scheme 1. Reagents and conditions: (a) DMP, acetone, *p*-TsOH, rt, 16 h, 89%; (b) MsC1, Et_3N, CH_2Cl_2, 0 °C, 24 h, 99%; (c) 75% aqueous TFA, 80 °C, 12 h, 81%; (d) anhydrous methanol, K_2CO_3, rt, 6 h, 73%; (e) azole-bases, DBU, DMSO, 90–100 °C, 48 h.

into an epoxy ring, and then regioselective opening of the epoxide by heterocyclic bases. In this paper, a very short and efficient synthetic route to novel azole nucleoside analogues of D-pinitol and their cytotoxicity effects are reported.

Diacetonide derivative **2**, a key intermediate, was synthesized according to an efficient procedure in quantitative yield,[17,18] and then mesylated to obtain methanesulfonate **3** as the glycosyl donor. Subsequently, the common intermediate, diacetonide methanesulfonate **3**, was subjected to 1-methylethylidene deprotection with aqueous CF_3COOH, and afforded mono-methanesulfonate of D-pinitol **4**, which was subsequently converted to epoxide **5** in the presence of K_2CO_3 in anhydrous MeOH[19] in 73% yield. Since most of the reactions gave very high yields, intermediates **2**, **3**, **4**, and **5** involved in the procedure could be subjected directly to the next reaction without further purification. The epoxy ring of **5** was identified from its ^1H NMR spectrum showing an upfield signal for H-4 at 3.58 ppm, a salient feature of the epoxy ring. The regioselective opening of the epoxy ring with various azole-bases was achieved in reasonable yields in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), affording the corresponding carbocyclic azole nucleosides. In the case of the glycose-base coupling reaction, a mixture of C-5′ and C-4′ isomers was theoretically produced. In fact, the reaction of triazole-bases appeared strongly regioselective, giving only the predominant C-5′ isomers **6** and **7**. On the other hand, the reaction of nitroindazole was moderate regioselective, in which the C-5′ isomers were always contaminated with small amounts of C-4′ regioisomers. As a result, the two diastereoisomers **9** and **10** were obtained as a mixture (C-5′/C-4′ = 1.71; see Table 1, entry 4), which was not isolated independently due to their similar chromatographic mobilities on RPC-18 HPLC. These results can be explained by the nucleophilicities of nitroindazole-bases being weaker than those of the triazole base owing to the high electron withdrawing effect of the $-NO_2$ group.[20]

Structural assignments of products **6**–**10** were accomplished by 1D and 2D NMR spectroscopic methods.

Table 1. Opening of epoxy ring reaction of 4,5-epoxyl-D-pinitol (**5**) with azole-bases[a]

Entry	Azole-bases	Product	Yield[b] (%)	5′/4′ Ratio
1	1,2,4-Triazole	**6**	74	+∞[c]
2	Benzotriazole	**7**	68	+∞[c]
3	6-Nitroindazole	**8**	66	+∞[c]
4	5-Nitroindazole	**9/10**	62	1.71[d]

[a] Reaction was carried out at 100 °C.
[b] Isolated yields.
[c] Isolated yields of two regioisomers.
[d] Ratio was determined by ^1H NMR analysis.

The conformation of **6** at C-5′ was confirmed by the finding of the expected cross-peaks between H-5′ and C-5 in the HMBC spectrum, indicating the coupling in the triazole part at C-5′ and the strong NOE between H-1′, H-5′, and H-2′ in the NOESY.

The newly synthesized compounds **6**, **7**, **8**, and **9/10** were evaluated for their in vitro cytotoxicity by growth-inhibition studies using two human cancer cell lines: human lung (PG cell), human bladder (T_{24} cell).

As shown in Table 2, only triazole nucleoside analogues **6** and **7** exhibited inhibitory activity against human lung cancer cell lines (PG) with EC_{50} of 11.3 and 22.6 μM, respectively, and showed much less activity against human bladder cell lines (T_{24}) with EC_{50} of 78.5 and 83.8 μM, respectively. However, the nitroindazole derivatives **8** and **9/10** did not indicate any inhibition against these two human cancer cell lines up to 100 μM.

1. Experimental

1.1. General methods

The solvents were pretreated, when necessary, according to the appropriate standard procedures before being used. Column chromatography (CC) and thin-layer chromatography (TLC) was performed on precoated silica gel plates F_{254} (Qingdao Marine Chemical Co. Ltd) with visualization under UV light and by H_2SO_4 charring. All reaction mixtures were stirred magnetically. Instrumentation included an X-6 melting-point apparatus (Beijing TECH Instrument Co. Ltd); a Bruker Avance-600 NMR spectrometer (δ in ppm, J in Hz); an ABI-API4000 mass spectrometer (in m/z); a Perkin Elmer 240C elemental analysis apparatus; and a Perkin Elmer 241 polarimeter.

1.2. 3-*O*-Methyl-1,2:5,6-bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (2)

To a suspension of D-pinitol (10.0 g 51.5 mmol) in DMP and acetone (200 mL, 1:3) were added *p*-TsOH (380 mg, 2.0 mmol) and $MgSO_4$ (9 g). The mixture was stirred at room temperature for 16 h, after which a homogeneous solution was obtained. Solid $NaHCO_3$ (1.00 g, 11.9 mmol) was added. The bulk of DMF and acetone was removed under reduced pressure, and the residue was partitioned between saturated $NaHCO_3$ solution and AcOEt. The organic extracts (3 × 100 mL AcOEt) were washed with water and brine, and dried ($MgSO_4$). The organic phase was concentrated under reduced pressure to afford 12.60 g (89%) of **2** as a white crystalline solid. Mp: 95–96 °C, lit.[18] 95–97 °C. ^1H and ^{13}C NMR spectral data matched that reported.[17,18]

Table 2. Cytotoxicity of the final compounds **6**, **7**, **8**, and **9/10** in two cancer cell lines (PG, T_{24})

Compound	EC_{50}[a] (μM)	
	PG[b]	T_{24}[c]
6	11.3	78.5
7	22.6	83.8
8	>100	⩾200
9/10	>100	>100
Sangivamycin	0.012	0.008

[a] 50% effective concentration.
[b] Human lung cells.
[c] Human bladder cells.

1.3. 3-*O*-Methyl-1,2:5,6-bis-*O*-(1-methylethylidene)-4-[(methylsulfonyl)oxy]-D-*chiro*-inositol (3)

A cold (0–5 °C) solution of diacetonide **2** (3.0 g, 11.58 mmol) in dry pyridine (15 mL) was stirred with MsCl (0.41 g, 2.14 mmol) for 24 h at the same temperature. The reaction mixture was poured into 200 mL ice-water containing 50 mL HCl. The resulting aqueous suspension was filtered under reduced pressure, and the residue was washed with anhydrous EtOH to neutral. Then the residue was crystallized to afford **3** (4.04 g, 99%). White solid. Mp: 120–122 °C. $[\alpha]_D^{30}$ +72.5 (*c* 0.3 $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ 4.51 (dd, 1H, $^3J_{3,4} = 8.4$, $^3J_{4,5} = 11.16$ Hz, H-4), 4.44 (dd, 1H, $^3J_{1,6} = 3.06$, $^3J_{5,6} = 6.06$ Hz, H-6), 4.41 (m, 1H, H-2), 4.30 (dd, 1H, $^3J_{1,6} = 6.42$, $^3J_{1,2} = 8.04$ Hz, H-1), 4.24 (t, 1H, $^3J_{2,3} = {}^3J_{3,4}$ 6.86 Hz, H-3), 3.60 (s, 3H, OMe), 3.26 (dd, 1H, $^3J_{4,5} = 7.56$, $^3J_{5,6} = 11.16$ Hz, H-5), 3.14 (s, 3H, OMs), 1.53 (s, 3H, Me), 1.52 (s, 3H, Me), 1.37 (s, 3H, Me), 1.36 (s, 3H, Me). ^{13}C NMR (150 MHz, $CDCl_3$): δ 110.29 ($C(Me)_2$), 109.77 ($C(Me)_2$), 82.66 (C-3), 80.07 (C-5), 79.15 (C-4), 76.73 (C-1), 75.82 (C-2), 75.43 (C-6), 60.53 (OMe), 39.49 (OMs), 28.17 (Me), 27.83 (Me), 25.85 (Me), 25.80 (Me). Anal. Calcd for $C_{14}H_{24}O_8S$: C, 47.72; H, 6.86. Found: C, 47.88; H, 6.79. ESI-MS: (MH^+) 353.6.

1.4. 3-*O*-Methyl-4-[(methylsulfonyl)oxy]-D-*chiro*-inositol (4)

A solution of fully protected compound **3** (7.2 g, 20.46 mmol) in 80% AcOH (60 mL) was heated at 80 °C for 10 h. The solvent was removed under reduced pressure, and the residue was purified by CC (SiO_2, MeOH/$CHCl_3$ 1:8) to afford pure alcohol **4** (4.49 g, 80.68%). Colorless solid. Mp: 144–146 °C. $[\alpha]_D^{30}$ +55.8 (*c* 0.3 MeOH). ^1H NMR (600 MHz, DMSO-d_6): δ 5.14 (d, 1H, $J = 3.93$ Hz, OH), 5.04 (d, 1H, $J = 2.1$ Hz, OH), 5.03 (d, 1H, $J = 0.82$ Hz, OH), 4.88 (d, 1H, $J = 6.72$ Hz, OH), 4.43 (t, 1H, $^3J_{4,5} = 9.53$ Hz, H-4), 3.67–3.72 (m, 2H, H-2 and H-5), 3.64 (dd, 1H, $^3J_{3,4} = 3.7$, $^3J_{2,3} = 7.1$ Hz, H-3), 3.60 (m, 1H, H-1), 3.44 (s, 3H, MeO), 3.24 (t, 1H, $J = 9.5$ Hz, H-6), 3.15

(s, 3H, MsO). ^{13}C NMR (150 MHz, DMSO-d_6): δ 39.14 (MsO), 59.83 (MeO), 68.63 (C-2), 70.40 (C-1), 72.03 (C-6), 72.37 (C-4), 81.27 (C-5), 85.41 (C-3). Anal. Calcd for $C_8H_{16}O_8S$: C, 35.29; H, 5.92. Found: C, 35.25; H, 5.90. ESI-MS: (MH^+) 273.3.

1.5. 3-*O*-Methyl-4,5-epoxyl-D-*chiro*-inositol (5)

A solution of mono-methylsulfonate **4** (1.088 g, 4 mmol) in 30 mL of anhydrous MeOH was treated with 0.72 g of K_2CO_3 and the solution was stirred at room temperature for 8 h. TLC analysis showed that compound **8** disappeared, and the reaction mixture was then neutralized with a HCl in MeOH. Potassium salt was filtrated, and the filtrate was concentrated to afford **5** (0.514 g, 73%). Mp: 192–196 °C. $[\alpha]_D^{30}$ −16.0 (*c* 0.2 MeOH). ^{1}H NMR (600 MHz, D_2O): δ 4.04 (dd, 1H, $^3J_{1,6} = 3.16$, $^3J_{5,6} = 5.84$ Hz, H-6), 3.72–3.75 (m, 2H, H-2 and H-5), 3.62 (t, 1H, $^3J_{1,6} = 3.22$ Hz, H-1), 3.58 (dd, 1H, $^3J_{3,4} = 1.78$, $^3J_{4,5} = 5.86$ Hz, H-4), 3.50 (t, 1H, $^3J_{2,3} = 3.54$ Hz, H-3), 3.44 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 53.61 (epoxy), 56.02 (epoxy), 56.85 (MeO), 67.86 (C-1), 69.28 (C-2), 71.04 (C-6), 77.41 (C-3). Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.70; H, 6.82. ESI-MS: (MH^+) 177.4.

1.6. Typical procedure for the preparation of azole nucleoside analogues of D-pinitol

1.6.1. (1′*S*,2′*S*,3′*S*,4′*S*,5′*R*,6′*R*)-3′-*O*-Methyl-5′-deoxy-5′-(1,2,4-triazole-1-yl)-D-*chiro*-inositol (6). To a stirred suspension of **5** (544 mg, 2 mmol) and dry 1,2,4-triazole (1.5 equiv) in dry DMSO (4 mL), DBU (0.5 mL, 3.3 mmol) in 2 mL dry DMSO was added dropwise. The clear solution was stirred at 100 °C for 48 h. After removal of DMSO in vacuo, the resulting brown residue was diluted with anhydrous MeOH. Silica gel was added, and the mixture was evaporated to dryness. The dry powder was applied to silica gel CC ($CHCl_3$/MeOH) to afford **6** (363 mg, 74%) as an amorphous foam. Mp: 235–236 °C. ^{1}H NMR (600 MHz, D_2O): δ 8.38 (s, 1H, H-5), 8.04 (s, 1H, H-3), 4.31 (dd, 1H, $^3J_{2',3'} = 3.22$, $^3J_{1',2'} = 10.77$ Hz, H-2′), 4.25 (m, 1H, H-5′), 4.23 (t, 1H, $^3J_{1',6'} = {}^3J_{5',6'} = 3.60$ Hz, H-6′), 4.01 (t, 1H, $^3J_{3',4'} = 9.92$ Hz, H-4′), 3.73 (dd, 1H, $^3J_{1',6'} = 3.26$, $^3J_{1',2'} = 9.83$ Hz, H-1′), 3.66 (t, 1H, $^3J_{2',3'} = 3.59$ Hz, H-3′), 3.41 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 61.22 (MeO), 67.31 (C-5′), 70.19 (C-2′), 70.39 (C-6′), 72.23 (C-4′), 73.35 (C-1′), 83.63 (C-3′), 148.43 (C-5), 154.51 (C-3). Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 43.96; H, 6.24; N, 17.21. ESI-MS: (MH^+) 246.5.

1.6.2. (1′*S*,2′*S*,3′*S*,4′*S*,5′*R*,6′*R*)-3′-*O*-Methyl-5′-deoxy-5′-(benzotriazole-1-yl)-D-*chiro*-inositol (7). The procedure was carried out as described above. Corresponding compound **7** (401 mg, 68%) was obtained as an amorphous foam. Mp: 222–226 °C. ^{1}H NMR (600 MHz, D_2O): δ 7.83 (m, 2H, arom., H-6 and H-7), 7.43 (m, 2H, arom., H-4 and H-9), 4.78 (t, 1H, $^3J_{1',2'} = 10.64$ Hz, H-1′), 4.57 (dd, 1H, $^3J_{2',3'} = 3.26$, $^3J_{1',2'} = 10.91$ Hz, H-2′), 4.28 (m, 2H, H-4′ and H-3′), 3.83 (dd, 1H, $^3J_{5',6'} = 3.21$, $^3J_{1',6'} = 9.82$ Hz, H-6′), 3.71 (t, 1H, $^3J_{4',5'} = {}^3J_{5',6'} = 3.66$ Hz, H-5′), 3.45 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 61.29 (MeO), 70.45 (C-5′), 71.71 (C-2′), 73.37 (C-6′), 73.65 (C-4′), 74.33 (C-1′), 83.83 (C-3′), 120.10 (C-5 and C-8), 130.16 (C-6 and C-7), 146.26 (C-4 and C-9). Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 51.96; H, 5.76; N, 14.18. ESI-MS: (MH^+) 296.6.

1.6.3. (1′*S*,2′*S*,3′*S*,4′*S*,5′*R*,6′*R*)-3′-*O*-Methyl-5′-deoxy-5′-(6-nitroindazole-1-yl)-D-chiro-inositol (8). The procedure was carried out as described above. Corresponding compound **8** (448 mg, 66%) was obtained as an amorphous yellow foam. Mp: 273–274 °C. ^{1}H NMR (600 MHz, D_2O): δ 8.71 (s, 1H, H-7), 8.49 (s, 1H, H-3), 7.95 (dd, 2H, $^4J_{3,4\text{ or }5,7} = 9.15$, $^3J_{4,5} = 25.31$ Hz, arom., H-4, and H-5), 4.62 (d, 1H, $^3J_{3',4'} = 10.90$ Hz, H-4′), 4.56 (t, 1H, $^3J_{4',5'} = 10.57$ Hz, H-5′), 4.38 (d, 1H, $^3J_{2',3'} = 2.94$ Hz, H-2′), 4.33 (t, 1H, $^3J_{1',6'} = 9.89$ Hz, H-6′), 3.91 (dd, 1H, $^3J_{1',6'} = 3.11$, $^3J_{1',2'} = 6.68$ Hz, H-1′), 3.82 (d, 1H, $^3J_{3',4'} = 2.87$ Hz, H-3′), 3.56 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 61.44 (MeO), 70.63 (C-2′), 71.28 (C-4′), 71.64 (C-5′), 73.28 (C-6′), 73.65 (C-1′), 83.97 (C-3′), 117.23 (C-1), 118.24 (C-4), 125.40 (C-5), 126.48 (C-6), 130.87 (C-2), 130.87 (C-8), 149.62 (C-3). Anal. Calcd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.71; H, 4.99; N, 12.44. ESI-MS: (MH^+) 340.5.

1.6.4. (1′*S*,2′*S*,3′*S*,4′*S*,5′*R*,6′*R*)-3′-*O*-Methyl-5′-deoxy-5′-(5-nitroindazole-1-yl)-D-chiro-inositol (9) and (1′*S*,2′*S*,3′*S*,4′*R*,5′*R*,6′*R*)-3′-*O*-methyl-4′-deoxy-4′-(5-nitroindazole-1-yl)-D-chiro-inositol (10). The procedure was carried out as described above. A mixture of more polar **9** and less polar **10** (423 mg, 62%, **9/10** = 1.71 by ^{1}H NMR) was obtained as an amorphous yellow foam. Anal. Calcd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.67; H, 5.08; N, 12.29. ESI-MS: (MH^+) 340.5.

1.6.4.1. Data for 9. ^{1}H NMR (600 MHz, D_2O): δ 8.86 (d, 1H, $^4J_{4,6\text{ or }4,7} = 1.75$ Hz, H-4), 8.66 (s, 1H, H-3), 8.14 (dd, 1H, $^4J_{4,6} = 2.22$, $^3J_{6,7} = 9.51$ Hz, H-6), 7.76 (d, 1H, $^3J_{6,7} = 9.52$ Hz, H-7), 4.62 (m, 1H, H-2′), 4.54 (m, 1H, H-5′), 4.38 (t, 1H, $^3J_{4',5'} = 3.59$ Hz, H-4′), 4.32 (m, 1H, H-6′), 3.91 (dd, 1H, $^3J_{1',6'} = 3.22$, $^3J_{1',2'} = 9.75$ Hz, H-1′), 3.82 (m, 1H, H-3′), 3.55 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 61.44 (MeO), 70.63 (C-4′), 71.09 (C-2′), 71.50 (C-5′), 73.08 (C-6′), 73.65 (C-1′), 83.96 (C-3′), 119.98 (C-1), 123.61

(C-4), 123.78 (C-3), 124.82 (C-6), 134.40 (C-7), 145.31 (C-5), 152.80 (C-2).

1.6.4.2. Data for 10. ^{1}H NMR (600 MHz, D_2O): δ 8.84 (d, 1H, $^4J_{4,6\text{ or }4,7} = 1.94$ Hz, H-4), 8.47 (s, 1H, H-3), 8.31 (dd, 1H, $^4J_{4,6} = 2.15$, $^3J_{6,7} = 9.37$ Hz, H-6), 7.71 (d, 1H, $^3J_{6,7} = 9.38$ Hz, H-7), 4.60 (m, 1H, H-1′), 4.57 (m, 1H, H-5′), 4.40 (t, 1H, $^3J_{4',5'} = 3.62$ Hz, H-4′), 4.29 (m, 1H, H-2′), 3.96 (dd, 1H, $^3J_{5',6'} = 3.25$, $^3J_{1',6'} = 9.82$ Hz, H-6′), 3.83 (m, 1H, H-3′), 3.57 (s, 3H, MeO). ^{13}C NMR (150 MHz, D_2O): δ 61.31 (MeO), 70.63 (C-4′), 71.01 (C-1′), 71.50 (C-5′), 73.28 (C-2′), 73.77 (C-6′), 83.96 (C-3′), 112.72 (C-1), 122.11 (C-4), 122.61 (C-3), 124.84 (C-6), 140.49 (C-7), 144.91 (C-5), 147.02 (C-2).

1.7. Cytotoxicity assays

Growth inhibition of the synthetic compounds to various tumor cells was determined by MTT assays.[21] Briefly, tumor cells ($3–5 \times 10^4$ cells mL^{-1}) were inoculated in 96-well culture plates (100 μL/well). After 24 h culture, 50 μL of culture medium containing synthetic compound of various concentrations was added to the wells, and BCS-1640 medium in control cells, then the cells were incubated for 48 h. The absorbance of each well was measured using a microculture plate reader at 490 nm.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.01.004.

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